CHAPTER 2

Physiological changes in pregnancy

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Physiological changes during pregnancy facilitate the adaptation of the cardiovascular system to the increased metabolic needs of the mother, thus enabling adequate delivery of oxygenated blood to peripheral tissues and the fetus. Changes occur in circulating blood volume (affecting preload), peripheral vascular compliance and resistance (affecting afterload), myocardial function and contractility, heart rate, and sometimes heart rhythm and the neurohormonal system (Table 2.1). Women without heart disease adapt well and adverse cardiac events are rare. In some women, heart disease may first be detected during pregnancy when inadequate adaptation exposes previously unrecognized limitations of cardiac reserve. In the presence of important maternal structural heart disease, increased cardiovascular demands of pregnancy can result in cardiac decompensation, arrhythmias, and, rarely, maternal death. This chapter examines the physiologic changes of pregnancy as they occur in the antepartum period, at the time of labour and delivery (peripartum), and in the postpartum period.

Changes in the antepartum period

An increase in blood volume and heart rate as well as a reduction in systemic vascular resistance bring about the increase in cardiac output necessary to sustain pregnancy.

Circulating blood volume

An increase in blood volume has been documented in a number of studies; however, there is variability among studies with regard to the magnitude and timing of this increase. The increased blood volume delivered to the ventricle during pregnancy increases the preload (the distending force on the ventricular wall) and can be estimated by examining ventricular diastolic volume and pressure.

Blood volume begins to increase in week 6 of gestation and by the end of pregnancy it will have reached approximately 50% more than in the pre-pregnant state (Figure 2.1).[1,2] Individuals differ considerably; one study demonstrated individual increases from 20% to 100% above pre-pregnant

Table 2.1 Hemodynamic changes during pregnancy, peripartum and post partum

	Pregnancy	Peripartum	Post partum
Blood volume	↑	↑	↓
Systolic blood pressure	↓	↑	↑
Diastolic blood pressure	↓	↑	↑
Systemic vascular resistance	↓	↑	↑
Heart rate	↑	↑	↓
Stroke volume	↑	↑	↓
Cardiac output	↑	↑	↓

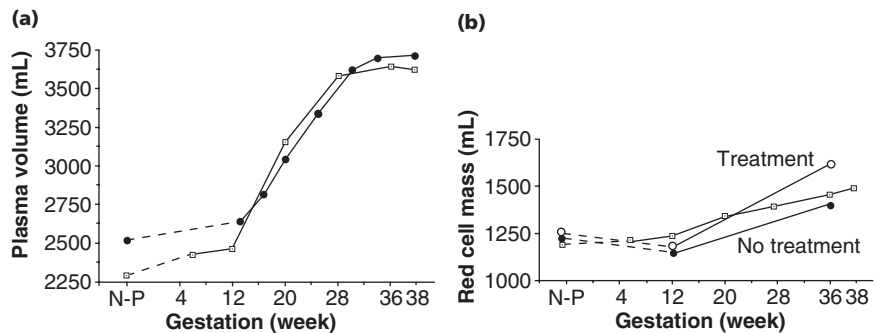Hemodynamic changes are discussed in more detail in the text.

Figure 2.1 Changes in plasma volume and red cell mass during pregnancy. N-P, not pregnant. (Plasma volume data reproduced from Lind[1] and Pirani et al.[2] Red cell mass reproduced from Lind[1] and Taylor and Lind.[5]) (b) The treatment group (white circles) included women treated with folic acid and iron. Women in the no-treatment group (black circles) were not given any supplements.

blood volume.[3] All studies have shown that blood volume progressively increases, at least until mid-pregnancy; some studies have found that it plateaus in the third trimester,[4,5] whereas others suggest that it increases continuously until term.[6] The increase in blood volume is more pronounced in twin pregnancies.[7] Red cell mass increases as much as 40% above pre-pregnancy levels.[2,5] The plasma volume increase is proportionally greater than the increase in red blood cell mass, and the resulting hemodilution explains the so-called 'physiological anemia of pregnancy'. Reduced plasma volume expansion has been associated with low birthweight and intrauterine growth retardation.[8]

In normal pregnancies, there is an increase in the left ventricular end-diastolic volume (assessed echocardiographically), which can be noted by 10 weeks' gestation and peaks during the third trimester. There are also increases in the left atrial, right atrial and right ventricular diastolic dimensions (Table 2.2).[9]

Preload is influenced by maternal position: the supine position results in compression of the inferior vena cava and consequent obstruction of venous return and decreased cardiac output. The effect is more profound in twin

Table 2.2 Cardiac chamber dimensions (measured by echocardiography) during pregnancy and post partum in pregnant women ($n = 18$)

Chamber	Weeks 8–12	Weeks 20–24	Weeks 30–34	Weeks 36–40	Puerperium	Control
LVd (mm)	41.1 ± 3.1	42.7 ± 2.2	43.0 ± 1.7	43.6 ± 2.5	41.8 ± 1.8	40.1 ± 3.0
LA (mm)	29.6 ± 2.1	31.5 ± 2.4	33.1 ± 2.4	32.8 ± 3.0	29.9 ± 3.1	27.9 ± 2.4
RVd (mm)	30.1 ± 2.0	31.9 ± 2.1	35.5 ± 3.2	35.5 ± 2.3	31.1 ± 2.1	28.5 ± 3.0
RA (mm)	42.8 ± 2.3	47.4 ± 2.4	50.8 ± 2.7	50.9 ± 2.8	46.6 ± 3.3	43.7 ± 4.4

LVd, left ventricular diastolic dimension; LA, left atrial dimension; RVd, right ventricular diastolic dimension; RA, right atrial dimension.

Values represent the mean value ± standard deviation (SD).

Reproduced from Campos.[38]

compared with singleton pregnancies. A paravertebral collateral circulation can develop that allows blood to bypass the obstructed inferior vena cava.

A number of mechanisms are postulated for the hypervolemia of pregnancy. Estrogen increases renin levels and causes sodium retention and an increase in total body water. Other hormones, such as prolactin, placental lactogen, prostaglandins and growth hormone, are increased during pregnancy and may contribute to fluid retention.

Despite increasing blood volume and atrial and ventricular distension, cardiac filling pressures (central venous pressure and pulmonary capillary wedge pressure) have not been shown to be higher in women at term compared with women 11–13 weeks' postpartum (Table 2.3).[10] The ability of a normal heart to adapt to chronic volume overload probably prevents pressures from increasing in women without heart disease.

Women with dilated cardiomyopathy, obstructive valve lesions such as mitral stenosis or pulmonary hypertension may not be able to adapt to the increased blood volume. In such patients, increased preload can result in decompensation. In contrast, in patients with hypertrophic obstructive cardiomyopathy, increased preload and larger ventricular dimensions may diminish the degree of left ventricular outflow tract obstruction, improving the hemodynamics during pregnancy.

Peripheral vascular compliance and resistance

Afterload is the force against which the ventricular muscle contracts; typically it is reduced during pregnancy. In the absence of outflow tract obstruction, systemic ventricular afterload can be approximated by either measuring the arterial systolic pressure or calculating the systemic vascular resistance.

During pregnancy, there is a fall in systemic (peripheral) vascular resistance beginning in week 5 of gestation with a nadir between weeks 20 and 32. After week 32 of gestation, the systemic vascular resistance slowly increases until term. There is a corresponding initial decrease in the systemic arterial pressure, which begins in the first trimester and reaches its nadir at mid-pregnancy.[11,12] Thereafter, systemic pressure begins to increase again and ultimately reaches or

Table 2.3 Hemodynamic changes at term and post partum (measured by cardiac catheterization)

Measurement	Post partum (mean $\pm$ SD)	At term (mean $\pm$ SD)	Percentage change	*P*
Cardiac output (L/min)	4.3 ± 0.9	6.2 ± 1.0	44	0.0003
Heart rate (beats/min)	71 ± 10	83 ± 1.0	17	0.015
Mean arterial pressure (mmHg)	86.4 ± 7.5	90.3 ± 5.8	4.5	0.210
Systemic vascular resistance (dyn cm/s^{-5})	1530 ± 520	1210 ± 266	-21	0.100
Pulmonary vascular resistance (dyn cm/s^{-5})	119 ± 47	78 ± 22	-34	0.022
Central venous pressure (mmHg)	3.7 ± 2.6	3.6 ± 2.5	-2.7	0.931
Pulmonary capillary wedge pressure (mmHg)	6.2 ± 2.1	7.5 ± 1.8	19	0.187
Left ventricular stroke work index (g m/m^{-2})	41 ± 8	48 ± 6	17	0.040

Reproduced from Clark et al.[10]

SD, standard deviation.

exceeds the pre-pregnancy level. The overall fall in systemic vascular resistance is a result of changes in resistance and flow in multiple vascular beds. During pregnancy, blood flow increases in the low impedance uteroplacental circulation, reaching up to 500 mL/min at term, measured in the supine position, and even higher in the left lateral decubitus position.[13] Placental flow increases until week 25 of gestation and then remains unchanged. In addition there is a fall in resistance caused by increased levels of peripheral vasodilators, in particular prostacyclin (PGI_2).

Renal blood flow increases during pregnancy, peaking in the third trimester at about 60–80% above pre-pregnancy levels. This coincides with a 50% increase in the glomerular filtration rate.[14] Changes in renal blood flow are primarily caused by renal vasodilatation and are also altered by positional changes. Supine recumbency and sitting result in lower glomerular filtration rates. The blood flow to the hands and feet increases during pregnancy, with an increase in cutaneous flow that results in warm erythematous extremities. Nasal congestion results from increased flow to the nasal mucosa. Mammary blood flow increases, causing breast engorgement, dilatation of superficial veins and a continuous murmur known as the mammary souffle. No changes have been shown to occur in cerebral or hepatic blood flow. Coronary blood flow has not been studied in pregnancy.

Not only is the inferior vena cava compressed in the supine position, but the uterus may obstruct the abdominal aorta and the iliac arteries.[15] This compression is relieved by shifting to the left lateral decubitus position. The decreased

cardiac output that occurs in the supine position is usually compensated by an increase in supine systemic vascular resistance. The 'supine hypotensive syndrome of pregnancy' occurs when there is inferior vena caval obstruction, possibly further exacerbated by an underdeveloped paravertebal collateral system, and insufficient increase in the systemic vascular resistance or heart rate.

Generally a decrease in afterload will not exacerbate cardiac dysfunction; in fact, the decreased afterload in women with regurgitant valve lesions helps to attenuate the severity of the regurgitation. However, in specific situations, decreases in afterload can be detrimental, e.g. in women with Eisenmenger syndrome and also in other types of cyanotic heart disease, a decrease in afterload facilitates an increase in right-to-left intracardiac shunting, leading to increased cyanosis and hypoxemia. As another example, changes in renal blood flow impacting on drug excretion and changes in the volume of distribution of drugs together explain in large part the need for modified drug dosing during pregnancy.

Anatomical changes during pregnancy

The physiological changes in preload and afterload are accompanied by remodeling of the ventricles and atria. All four cardiac chambers increase in size from the first trimester to the end of the third trimester. The dimensions decrease to baseline levels in the postpartum period (see Table 2.2). Left ventricular remodeling also manifests as increases in left ventricular wall thickness and mass.[16–20] Structural changes also occur at the level of the valve annulus: increases in mitral, tricuspid and pulmonic annular diameters lead to increasing degrees of mitral, tricuspid and pulmonic regurgitation. Small pericardial effusions are frequently found, which usually resolve after delivery.[21]

Increases in atrial size may contribute to atrial arrhythmias during pregnancy. Other changes, such as small pericardial effusion, may have little clinical significance. Although the prognostic significance of changes such as ventricular remodeling are well described in non-pregnant women, their magnitude and direction, and their long-term prognostic significance, have not yet been well studied in pregnant women with structural heart disease.

Myocardial function and contractility

Both systolic and diastolic function contribute to overall cardiac performance. Contractility is the ability of the heart to generate force and shorten, and is usually approximated by surrogate assessments of systolic myocardial function such as cardiac output (index), velocity of circumferential fiber shortening and ejection fraction. Left ventricular diastolic function, which influences the ability of the heart to fill effectively, is assessed most commonly by examining echocardiographic Doppler-filling patterns.

Cardiac output has been the most extensively studied measure of cardiac performance during pregnancy and is dependent on heart rate and stroke volume, both of which increase during pregnancy (Figure 2.3). Cardiac output increases by about 30–50%,[10,11,16,17,22] with the first increase noted as early as week 5 of gestation and reaching a peak at approximately the end of the second trimester
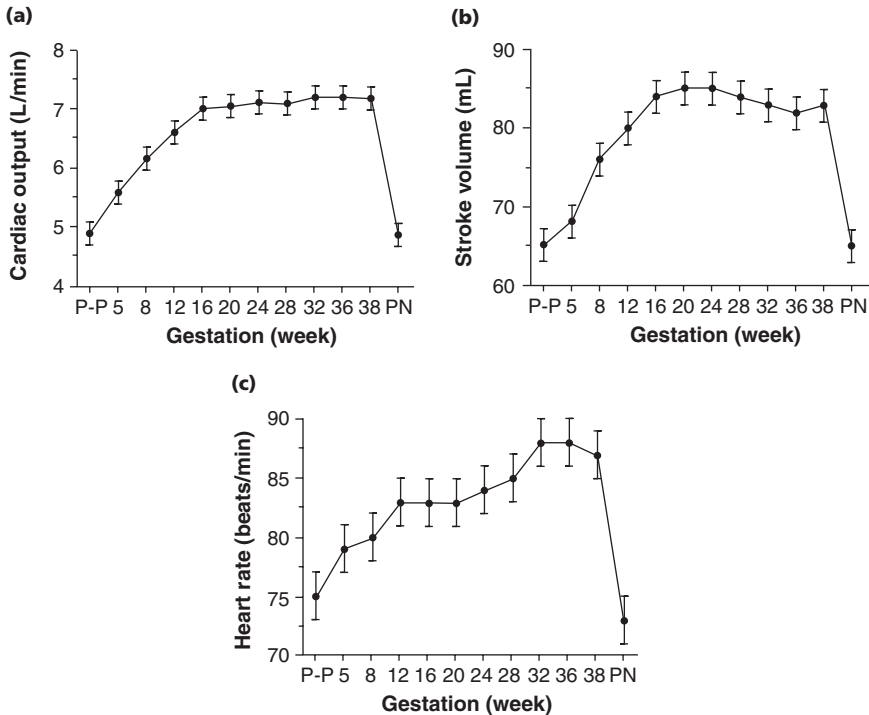
Figure 2.2 Changes in cardiac output, stroke volume and heart rate during pregnancy. P-P, prior to pregnancy; PN, postnatal – 6 months after delivery. (Adapted from Robson et al.[11])

according to some (see Figure 2.2)[11] and later in the third trimester, according to others.[23] Thereafter, cardiac output remains unchanged till term, or decreases slightly near term. Although most of the increase in cardiac output results from increase in stroke volume, increased heart rate also contributes; this becomes more important later in the pregnancy when the stroke volume plateaus while the heart rate continues to rise.[11,24] Although less information is available about the cardiac response to pregnancy of women with heart disease, Ueland et al. showed that pregnant women with underlying cardiac disease have lower cardiac output than pregnant women with normal cardiac function.[25]

Studies vary with regard to the effect of pregnancy on left ventricular ejection fraction. Some studies have demonstrated increases in ejection fraction,[11] whereas others have shown no significant change.[17,26,27] Ejection fraction is sensitive to changes in both preload and afterload, and differences in study results may be related to differences in loading conditions. In one study, an afterload-adjusted and preload-insensitive index of contractility (afterload-adjusted velocity of circumferential fiber shortening) decreased during pregnancy and returned to normal 2–4 weeks postpartum.[27]

Diastolic function has been studied less than systolic function during pregnancy. Using echocardiography, the ratio of early to late diastolic flow velocity

(*E/A* ratio) has been shown to be lower during the third trimester compared with post partum.[28] The mechanism and significance of this finding are not known.

As a result of increased fetal and maternal tissue mass and cardiac and respiratory work, maternal peak oxygen consumption can increase by 20–30% at term.[29] Whereas most of the increase in cardiac output occurs early, the increase in oxygen consumption occurs progressively throughout the pregnancy.

The increased demands and stresses of pregnancy may be detrimental to women with limited cardiac reserve. Women who are unable to increase cardiac output or who require elevated filling pressures to do so may develop evidence of right- or left-sided heart failure. Fixed stenotic valvular lesions, such as aortic stenosis, may limit the ability of the heart to provide the increased cardiac output necessary, resulting in adverse maternal and fetal events. For women with coronary disease, increased cardiac work during pregnancy, and hence increased myocardial oxygen consumption, may trigger ischaemia. In women with Marfan syndrome the increased cardiac output and hypervolemia of pregnancy, as well as the changing hormonal milieu, contribute to the observed increase in risk of aortic dissection.

Heart rate and rhythm

Mean heart rate usually increases by 10–20 beats over the course of pregnancy, peaking in the late second trimester or early third trimester (see Figure 2.3), although there is wide individual variation. Most women remain in sinus rhythm during pregnancy; however, premature atrial and ventricular complexes may become more frequent. The frequency of new-onset supraventricular arrhythmias and even ventricular tachycardia has been shown to increase during preg-
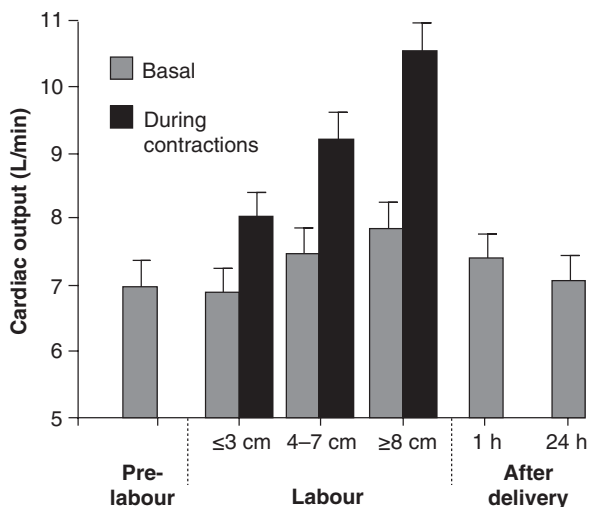

Figure 2.3 Changes in cardiac output during labour and delivery. (Reproduced from Robson et al.[37])

nancy. Furthermore, pregnancy may increase the frequency of supraventricular and ventricular arrhythmias in women with a prior history of such arrhythmias. Women with a history of arrhythmias before pregnancy are at increased risk for adverse cardiac events during pregnancy.

Neurohormonal factors

An alternative method of exploring the hemodynamic changes is to examine the neurohormonal response to pregnancy. Nitric oxide and the prostaglandins are vasodilators that may be responsible for the observed drop in peripheral resistance and for changes in uterine and renal blood flow. These hemodynamic changes initiate additional baroreceptor-mediated neurohormonal events, including activation of the renin–angiotensin–aldosterone and sympathetic nervous systems, and release of natriuretic peptides.

The renin–angiotensin system regulates salt and water hemostasis in the body. There is an increase in both renin and angiotensin levels during pregnancy.[30] This paradoxical increase in renin secretion occurs despite the normal expansion of extracelluar volume during pregnancy.

Activation of the sympathetic nervous system typically occurs in response to a decrease in peripheral vascular resistance and arterial pressure. Conversely, plasma volume expansion suppresses catecholamine levels. During pregnancy, both opposing influences are active and the findings in the literature vary with regard to the extent and nature of net sympathetic activation during normal pregnancy and in patients with hypertensive disorders of pregnancy.[31,32]

The natriuretic peptides are involved in integration of cardiovascular and renal function. Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are released in response to volume overload states. Release of ANP and BNP occurs in response to atrial and ventricular distension, respectively. In healthy pregnant women, ANP and BNP levels increase during the course of pregnancy.[33] Among pregnant women with pre-eclampsia, increased levels of ANP and BNP are related to changes in left ventricular mass and left ventricular volume.[34]

Overactivity of the autonomic nervous and the renin–angiotensin systems, and impairment in production or activity of vasodilators such as nitric oxide and PGI_2, have all been implicated in the pathogenesis of pre-eclampsia. Plasma catecholamine and neurohormone levels have not been examined in pregnant women with structural cardiac disease, and the role and behavior of these systems in pregnant women who develop cardiac decompensation are unknown.

Respiratory changes

Minute ventilation increases during pregnancy because of increases in tidal volume; the respiratory rate does not change. The increase in minute ventilation is greater than the increase in oxygen consumption and this results in both hyperventilation and an increased ventilatory equivalent for oxygen (the ventilation in liters required for each 100 mL of oxygen consumed). Subjective awareness of increased ventilation is one explanation for the sensation of dyspnea in

pregnant women without cardiopulmonary limitation. Functional residual capacity decreases and, along with the increased oxygen consumption described earlier, results in less oxygen reserve. Exercise can further deplete this reserve in women with little ability to compensate.

Changes in the peripartum period

Pain, anxiety and uterine contractions all alter the hemodynamics at the time of labour and delivery. Increases in cardiac output, tachycardia and hypertension may stress the marginally compensated woman with heart disease and also lead to decompensation.

During the first stage of labour uterine contractions can increase central blood volume by as much as 500 mL, a so-called 'autotransfusion'.[35] On average, vaginal delivery results in the loss of 10% and cesarean delivery in 29% of total blood volume, although there is wide individual variation in the magnitude of blood loss.[36] Placental separation does not usually cause any significant change to the circulation. The basal blood pressure increases during labour and further increases with each uterine contraction; this is thought to result partly from the increasing cardiac output. In addition, compression of the lower limb vessels may redistribute blood to the upper limbs and add to upper body hypertension. Heart rate increases during labour secondary to increased circulating catecholamines. Reports vary with regard to the effect of uterine contractions on heart rate; some investigators have demonstrated increasing heart rate and others no significant change or a decrease.

Heart rate changes are variable among individuals, dependent on position and attenuated by anesthesia. Basal cardiac output increases during labour by about 10%.[37] The increased cardiac output is the result of increased heart rate and stroke volume. There is an additional 7–15% increase in cardiac output with each uterine contraction (see Figure 2.3). The increase in cardiac output is more pronounced during the second stage of labour and in the left lateral decubitus position compared with the supine position. Early after delivery, cardiac output may continue to increase to as much as 80% above pre-labour values, as a result of the relief of inferior vena cava compression and autotransfusion from the placenta. Cardiac output returns to pre-labour levels about 1 hour post partum. Immediately post partum, cardiac output can continue to increase and women need to be monitored closely during this time period. Appropriate anesthesia and careful monitoring can help to prevent serious adverse events.

Anesthesia and analgesia can significantly alter the hemodynamics during the peripartum period, e.g. epidural anesthesia can help to alleviate pain and anxiety, thereby reducing increases in heart rate, blood pressure and oxygen consumption. However, epidural anesthesia may cause significant hypotension as a result of venous pooling and decreased venous return. Compared with pudendal or paracervical anesthesia, caudal anesthesia results in less increase in cardiac output during labour, and thus limits the absolute increase in cardiac output at the

time of delivery. Induction of general anesthesia can exacerbate hypertension and tachycardia. Anesthetic issues are discussed in more detail in Chapter 20.

Women at high risk during labour and delivery include women unable to accommodate to increases in preload, such as those with mitral stenosis, and women unable to accommodate to the increased cardiac output, such as those with dilated cardiomyopathy. Women with Marfan syndrome are at risk for aortic dissection especially if there are significant blood pressure elevations.

Changes in the postpartum period

Hemodynamic parameters slowly return to baseline values, but full resolution may take as long as 6 months after delivery. Thus, hemodynamic studies that used early postpartum values as surrogates for pre-pregnancy baseline values, when the latter were unavailable, may underestimate the actual changes that occur during pregnancy.

The blood volume decreases by 10% within the first 3 days after delivery. The hemoglobin level and the hematocrit increase progressively for the first 2 weeks after delivery and stabilize thereafter. Systolic and diastolic blood pressures remain unchanged from late pregnancy values until about 12 weeks post partum, after which they increase. Within 2 weeks post partum, systemic vascular resistance increases by 30%.[18] After the initial tachycardia associated with labour and delivery, a bradycardia often develops in the early puerperium. The heart rate slowly returns to baseline levels over the next 2 weeks. There is an immediate increase in cardiac output after delivery (within the first hour) by as much as 80%.[35] After this there is a decrease over the next 24 weeks.[18] Similarly, stroke volume decreases for the first 24 weeks after delivery. Most studies have demonstrated regression towards a baseline of left atrial and left ventricular dimensions and left ventricular mass by 24 weeks post partum (Table 2.3).[38] The left ventricular ejection fraction and rate of circumferential fiber shortening decrease following pregnancy. There has been concern that the anatomical changes in left ventricular mass and the function associated with pregnancy may not all ultimately return to pre-pregnancy values.[18]

Conclusion

During pregnancy and post partum, changes occur in the circulating blood volume, peripheral vascular compliance and resistance, myocardial function, heart rate and the neurohormonal system. These changes allow the cardiovascular system to meet the increased metabolic demands of pregnancy. Although these changes have been examined in normal pregnancies, less well understood is how these changes may differ in women with structural heart disease compared with women without heart disease and the mechanisms responsible for the differences that may exist.

References

1 Lind T. Hematologic system. Maternal physiology. *Washington: CREOG* 1985;**25**:7–40.

2 Pirani BB, Campbell DM, MacGillivray I. Plasma volume in normal first pregnancy. *J Obstet Gynaecol Br Commonw* 1973;**80**:884–7.

3 Pritchard JA, Rowland RC. Blood volume changes in pregnancy and the puerperium. III. Whole body and large vessel hematocrits in pregnant and nonpregnant women. *Am J Obstet Gynecol* 1964;**88**:391–5.

4 Rovinsky JJ, Jaffin H. Cardiovascular hemodynamics in pregnancy. I. Blood and plasma volumes in multiple pregnancy. *Am J Obstet Gynecol* 1965;**93**:1–15.

5 Taylor DJ, Lind T. Red cell mass during and after normal pregnancy. *Br J Obstet Gynaecol* 1979;**86**:364–70.

6 Lund CJ, Donovan JC. Blood volume during pregnancy. Significance of plasma and red cell volumes. *Am J Obstet Gynecol* 1967;**98**:394–403.

7 Thomsen JK, Fogh-Andersen N, Jaszczak P. Atrial natriuretic peptide, blood volume, aldosterone, and sodium excretion during twin pregnancy. *Acta Obstet Gynecol Scand* 1994;**73**:14–20.

8 Salas SP, Rosso P, Espinoza R, Robert JA, Valdes G, Donoso E. Maternal plasma volume expansion and hormonal changes in women with idiopathic fetal growth retardation. *Obstet Gynecol* 1993;**81**:1029–33.

9 Campos O. Doppler echocardiography during pregnancy: physiological and abnormal findings. *Echocardiography* 1996;**13**:135–46.

10 Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of normal term pregnancy. *Am J Obstet Gynecol* 1989;**161**:1439–42.

11 Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989;**256**:H1060–5.

12 Duvekot JJ, Cheriex EC, Pieters FA, Menheere PP, Peeters LH. Early pregnancy changes in hemodynamics and volume homeostasis are consecutive adjustments triggered by a primary fall in systemic vascular tone. *Am J Obstet Gynecol* 1993;**169**:1382–92.

13 Jurkovic D, Jauniaux E, Kurjak A, Hustin J, Campbell S, Nicolaides KH. Transvaginal color Doppler assessment of the uteroplacental circulation in early pregnancy. *Obstet Gynecol* 1991;**77**:365–9.

14 Davison JM. Kidney function in pregnant women. *Am J Kidney Dis* 1987:**9**: 248–52.

15 Bieniarz J, Yoshida T, Romero-Salinas G, Curuchet E, Caldeyro-Barcia R, Crottogini JJ. Aortocaval compression by the uterus in late human pregnancy. IV. Circulatory homeostasis by preferential perfusion of the placenta. *Am J Obstet Gynecol* 1969;**103**:19–31.

16 Rubler S, Damani PM, Pinto ER. Cardiac size and performance during pregnancy estimated with echocardiography. *Am J Cardiol* 1977;**40**:534–40.

17 Katz R, Karliner JS, Resnik R. Effects of a natural volume overload state (pregnancy) on left ventricular performance in normal human subjects. *Circulation* 1978;**58**: 434–41.

18 Robson SC, Hunter S, Moore M, Dunlop W. Haemodynamic changes during the puerperium: a Doppler and M-mode echocardiographic study. *Br J Obstet Gynaecol* 1987;**94**:1028–39.

19 Vered Z, Poler SM, Gibson P, Wlody D, Perez JE. Noninvasive detection of the morphologic and hemodynamic changes during normal pregnancy. *Clin Cardiol* 1991;**14**:327–34.

20 Mone SM, Sanders SP, Colan SD. Control mechanisms for physiological hypertrophy of pregnancy. *Circulation* 1996;**94**:667–72.

21 Abduljabbar HS, Marzouki KM, Zawawi TH, Khan AS. Pericardial effusion in normal pregnant women. *Acta Obstet Gynecol Scand* 1991;**70**:291–4.

22 Ueland K, Novy MJ, Peterson EN, Metcalfe J. Maternal cardiovascular dynamics. IV. The influence of gestational age on the maternal cardiovascular response to posture and exercise. *Am J Obstet Gynecol* 1969;**104**:856–64.

23 Bader RA, Bader ME, Rose DF, Braunwald E. Hemodynamics at rest and during exercise in normal pregnancy as studies by cardiac catheterization. *J Clin Invest* 1955;**34**:1524–36.

24 Mabie WC, DiSessa TG, Crocker LG, Sibai BM, Arheart KL. A longitudinal study of cardiac output in normal human pregnancy. *Am J Obstet Gynecol* 1994;**170**:849–56.

25 Ueland K, Novy MJ, Metcalfe J. Hemodynamic responses of patients with heart disease to pregnancy and exercise. *Am J Obstet Gynecol* 1972;**113**:47–59.

26 Mashini IS, Albazzaz SJ, Fadel HE, et al. Serial noninvasive evaluation of cardiovascular hemodynamics during pregnancy. *Am J Obstet Gynecol* 1987;**156**:1208–13.

27 Geva T, Mauer MB, Striker L, Kirshon B, Pivarnik JM. Effects of physiologic load of pregnancy on left ventricular contractility and remodeling. *Am Heart J* 1997;**133**: 53–9.

28 Sadaniantz A, Kocheril AG, Emaus SP, Garber CE, Parisi AF. Cardiovascular changes in pregnancy evaluated by two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 1992;**5**:253–8.

29 Elkus R, Popovich J Jr. Respiratory physiology in pregnancy. *Clin Chest Med* 1992;**13**:555–65.

30 August P, Lenz T, Ales KL, et al. Longitudinal study of the renin–angiotensin–aldosterone system in hypertensive pregnant women: deviations related to the development of superimposed preeclampsia. *Am J Obstet Gynecol* 1990;**163**:1612–21.

31 Natrajan PG, McGarrigle HH, Lawrence DM, Lachelin GC. Plasma noradrenaline and adrenaline levels in normal pregnancy and in pregnancy-induced hypertension. *Br J Obstet Gynaecol* 1982;**89**:1041–5.

32 Davey DA, Macnab MF. Plasma adrenaline, noradrenaline and dopamine in pregnancy hypertension. *Br J Obstet Gynaecol* 1981;**88**:611–18.

33 Yoshimura T, Yoshimura M, Yasue H, et al. Plasma concentration of atrial natriuretic peptide and brain natriuretic peptide during normal human pregnancy and the postpartum period. *J Endocrinol* 1994;**140**:393–7.

34 Borghi C, Esposti DD, Immordino V, et al. Relationship of systemic hemodynamics, left ventricular structure and function, and plasma natriuretic peptide concentrations during pregnancy complicated by preeclampsia. *Am J Obstet Gynecol* 2000;**183**: 140–7.

35 Ueland K, Hansen JM. Maternal cardiovascular dynamics. 3. Labour and delivery under local and caudal analgesia. *Am J Obstet Gynecol* 1969;**103**:8–18.

36 Ueland K. Maternal cardiovascular dynamics. VII. Intrapartum blood volume changes. *Am J Obstet Gynecol* 1976;**126**:671–7.

37 Robson SC, Dunlop W, Boys RJ, Hunter S. Cardiac output during labour. *Br Med J (Clin Res Ed)* 1987;**295**:1169–72.

38 Campos O. Doppler echocardiography during pregnancy. *Echocardiography* 1996;**13**: 135–146.