GYNECOLOGY

FOR

POSTGRADUATES,

THEORY AND PRACTICE

Mamdouh M. Shaaban

Professor of Obstetrics and Gynecology

Assiut University

Volume II

لماذا .....؟

هذا الكتاب إفراغ للجعبة، وابراء للذمة.

ولعله يكون آخر فسيلة أبتغي به عند الله وسيله.

فيه استقراء للخبرة والخبر، ومراجعة لما نشر

وكل أمر مستطر في الدوريات والزبر،

واستبعاد لما كان ونكر،أو ما فيه الخلاف مستعر

وإثبات لكل أمر مستقر.

Preface

With the rapid increase of medical graduates in Egypt, there has been a great demand on specialization. Postgraduate training has become to form a good part of the academic responsibility of the faculty of medical schools. The postgraduate studies in Obstetrics and Gynecology presently involve three degrees: Diploma, Master and Doctorate. Lack of definition of the syllabuses of these three degrees has been, for many years, a matter of concern to me. This book is a trial to define what is required from postgraduate students.

The logarithmic expansion of basic science foundation and the many innovations in Gynecological practice have urged me to put together a summary of them in one text. The book covers the needs for the Master and gives a description of the practical skills required from the Diploma candidates. The book also gives most of the knowledge that should be required in Doctorate examinations and equivalent degrees. It can be a reference text for undergraduates. The relevance to the Egyptian practice is emphasized as has been amassed during forty-year experience in clinical practice and teaching. Practicing gynecologists can find in this text many helpful hints, and guidance to their clinical work.

I acknowledge the help I received from Omar M. Shaaban, M.D., in preparing the book. I also acknowledge the secretarial help of Mr. Abdel-Haleem A. Aly and Ms. Meiral A. Fayez.

Mamdouh M. Shaaban

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CHAPTER 20

INFERTILITY

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I. Definition and Causes of Infertility

Infertility is defined as the inability of a couple to conceive after one year of sexual intercourse without using any type of contraception. This definition has been based on the following classical estimation of the chances of conception:

Table 1: Time Required for Conception in Couple to attain pregnancy

Months of Exposure	% Pregnant
3 Months	57%
6 months	72%
1 Year	85%
2 Years	93%

The term infertility is generally used to indicate that the couple has a reduced capacity to conceive as compared with the mean capacity of the general population.

- ***Infertility is not exactly synonym to sterility.*** The term *sterility* is generally reserved to the inability of the couple to conceive without treatment as found after clinical evaluation, e.g., as when having tubal block or azoospermia.
- ***Fecundability*** is generally used to indicate the probability of achieving a pregnancy within one menstrual cycle. *This is about 25% in a normal couple*.
- ***Fecundity*** is the ability to achieve a live birth within one menstrual cycle.
- ***Impaired fecundity*** is generally defined as impaired ability of the couple in achieving pregnancy and carrying it to live birth.

  Some of the above terms are sometimes interchangeably used in the medical literature.
- The terms *primary or secondary infertility* are used depending upon whether the couple has not or have previously achieved a pregnancy respectively.

Infertility will be considered under three headings:

I. ***Prevalence and causes of infertility***
II. ***Diagnosis***
III. ***Treatment modalities***

Prevalence

Infertility affects approximately 10–15% of the couples in the reproductive age group, which makes it an important component of gynecological practice. The estimation of the prevalence vary depending upon the following:

1. The definition of infertility used.
2. The inclusion of couples with a history of experiencing a previous period of infertility besides those who are currently infertile.
3. The inclusion of unsuccessful pregnancy in the definition.
4. The type of population studied. The prevalence of infertility may be influenced by factors as the usual age of marriage, and prevalence of reproductive tract infections. Most probably, ethnic difference does not influence prevalence of infertility.

The concern about infertility varies in different cultures. In communities that are more primitive, the concern about infertile marriage is intense. Infertility in these communities is taken as a mark of divine displeasure; as a cause of divorce; in our culture, as a reason for a second marriage; or even rarely for suicide. Infertile individual in Upper Egypt is described as functionless person. For the male it is a disgrace and a stigma of inferior of masculinity; he is equated to a female.

Infertility forms an important sector of the work of a gynecologist.

Causes of Infertility

The exact incidence of the various factors causing infertility varies among different populations, and cannot be precisely determined. The relative contribution of different causes to infertility varies among different populations. In general, however, 10% to 15% of infertility results from anovulation; 30% to 40% is caused by tubal or peritoneal factors interfering with ovum pickup and transport, and fertilization; about 30% to 40% is associated with a male factor; and an additional 10% to 15% of infertility is associated with cervical mucus factor interfering with ascent of sperm. The contribution of uterine abnormalities to failure of conception is small; but they may result in abortions. Other abnormalities such as antisperm antibodies, luteal phase deficiency, subclinical endocrine abnormalities like disturbed thyroid function, or diabetes, and subclinical genital tract infections may contribute to infertility to an extent which is difficult to estimate because of frequent association with other abnormalities mentioned above, and because of variability in the diagnostic criteria of these conditions.

Infertility is frequently multifactorial, i.e. contributed to by more than one factor in the couple. This fact should indicate completing a certain scheme of investigation before starting the treatment. It is useless to go on in attempts of induction of ovulation in a woman with blocked tube or severely defective husband.

With the current techniques of investigation, it is impossible to diagnose the cause of infertility in about 10% to 15% of couples, and they are considered to have idiopathic or *unexplained infertility.*

The following is ***a summary of causes of infertility*** (certain causes receive detailed discussion elsewhere):

A. Female factors:

1. *Anovulation*

Anovulation represents 10% to 15% of cases of infertility. Generally, failure to ovulate is associated with amenorrhea, oligomenorrhea or occasionally dysfunctional uterine bleeding, and has the same causes detailed elsewhere; as hypothalamic, pituitary and ovarian causes. (See under these headings). In women menstruating regularly, anovulation is rare and accounts for less than 5% of cases of infertility. ***Frequent anovulation in menstruating women can be caused by****:*

- *Middle age (≥35) or premature failure of the ovaries;* this can be diagnosed by high serum FSH level (>20 mIU/ml) during the early follicular phase. It is also suggested by high serum estradiol in early follicular phase. The clomiphene challenge test also indicates an exaggerated FSH response (see later). These three parameters indicate reduced numbers of follicles in the ovaries and reduced inhibin production. In addition, middle-aged women (above 40 years) have less fertilizable ova. This is generally considered to be resulting from aging of ova.

  Induction of ovulation is less likely to be successful in middle-aged women and results of IVF are generally poor.
- *Minimal hyperprolactinemia:* prolactin level >20 ng, or rise during luteal phase.
- *Subclinical hypothyroidism.*
- *Early polycystic-ovary syndrome.*
- *Effect of drugs* e.g. corticosteroids, phenothiazin, antihypertensives, tranquilizers and antihistaminics.
- *Diabetes mellitus.*
- *Luteinized unruptured follicles (LUF)* (diagnosed by repeated VUSG).

- *Indulgence in athletic activity, or extremes of dieting*.
- *Anxiety or other psychological disturbance.* This is a questionable cause for infertility.
- *Some cases of anovulation are unexplainable.*

2. *Luteal Phase Defects (LPD)*

Luteal phase defects are defined as abnormalities of corpus lutetium function with insufficient progesterone production. This entity reportedly occurs in 1% to 2% of infertile couples, but more commonly is present in women with recurrent abortions. The condition may be suspected from BBTC recordings and is diagnosed by low progesterone level (<10 ng/mL) during mid luteal phase, and by a dated premenstrual biopsy. Better dating can be obtained through detecting of LH surge or repeated sonographic assessment that can identify the day of ovulation. LPD may be associated with short luteal phase.

The etiology of LPD is not clear. It has been ascribed to 1) decreased secretion of FSH during the early follicular phase, 2) decreased level of LH and FSH at the time of ovulation surge or, 3) decreased response of the endometrium to progesterone. 4) Elevated prolactin levels may be associated. 5) The condition is commoner in clomiphene stimulated cycles, and when Gn RH analogues are used as adjutant to HMG therapy (i.e iatrogenic LPD).

3. *Tubal and/or peritoneal factors*

Physiological considerations

The ovum crosses a small potential space in the peritoneal cavity between the ovum and the abdominal ostium of the tube. Its pick up by the infundibulum of the tube is ensured by close proximity of the fimbria to the ovary. A special long fimbria is usually seen on the surface of the ovary; fimbria ovaricum. There is a tiny musculo-fascial band between the two layers of the mesovaruim stretching between the ovary and infundibulum. This infundibulo-ovarian muscle undergoes frequent contraction under the effect of the preovulatory estrogen surge. The ovum pick-up is also ensured by the ciliary currents, which beats towards the uterus. The ovum is fertilized in the ampulla and traverses it in 72 hours. There, it is maintained by the tubal secretion. The transport of the ovum is determined by peristaltic contractions of myosalpinx and by the cilias of the endosalpinx. The cilia are most abundant in the lateral part of the tube and diminish as the uterine end is approached. The mucosal folds or plicae determine a combination of permissive and restrictive effects on the passage of the ovum. The ovum takes also about 12 hours in the isthmo-interstitial portion of the tube. This ±4 day journey ensures that the fertilized ovum will develop into a blastocyst, which acquires an invasive trophoblast by the time at

reaches, the uterus. If there is delay in the tube until the trophoblast is developed tubal pregnancy will result. Any kink in the tube or narrowing of its lumen can result in this delay.

Abnormality in the fallopian tubes or pelvic peritoneum account to infertility in 30% to 40% of couples. *These are commonly associated together and result from:*

a) ***Pelvic inflammatory disease*** (PID). This can be secondary to:
   - STDs mainly gonorrheal and chlamydial infections; these reach the tube along the lumen. They cause variable degrees of destruction of the endosalpinx; the affection is severer with gonorrhea. Infection with these two STDs may pass unnoticed, particularly in case of chlamydial infection.
   - Puerperal or postabortive infections. The infection reaches the tube via lymphatics and usually causes perisalpingitis.
   - Direct spread form appendicitis and other peritoneal infections.
   - Tuberculoses; this is usually a post-primary affection. It reaches the tube in blood and destroys any or all layers of the tube. This usually happen in young age and may pass unnoticed.
   - Bilharziasis: is usually a cause of perisalpingitis-rarely causing hydrosalpinx.

   The pathology in PID is usually bilateral. They can result in complete or partial obstruction of the tubes; however, the tubes may remain patent. The peritoneal adhesions can interfere with the ovum pick-up and its transport through the tubes.

b) Adhesions in the pelvic peritoneum can result from ***endometriosis.*** After the advent of laparoscopy in investigation of infertility, endometriosis is more commonly diagnosed. However, in absence of significant anatomic distortion of the tubo-ovarian anatomy the cause and effect relationship between endometriosis and infertility cannot be ascertained. Endometriosis is suspected however, to cause, in addition to mechanical effect, other changes, which interfere with fertility. Examples might include that the retrograde menstruation responsible for eliciting large population of inflammatory cells into the peritoneal cavity, or the altered cell mediated immune response reported in women with endometriosis (See under Endometriosis). Alternatively, endometriosis can be a consequence of infertility rather than the cause.

4. *Cervical Factor*

Abnormal midcycle cervical mucus-spermatozoa interaction has been estimated to be the cause of infertility in 5% to 10% of couples. However, abnormalities in cervical factor can be caused by abnormalities in ovarian factors. Mucus, produced by the endocervical epithelium undergoes preovulatory changes that serve to facilitate sperm transport. Moreover, viable sperm

can stored for some time in the cervical mucus. The preovulatory rise in estrogen stimulates an increase in the production of *thin, watery, alkaline, acellular* cervical mucus. The water content of mucus increases from 85% to 98%. Glycoproteins form a sort of parallel, longitudinal arrangement allowing the sperm to swim up the channels in-between. The cervix also softens, and there is slight dilation of the external os. After ovulation, the cervix gets firm, the os closes, and the mucus becomes thick, cellular and scanty due to the rise of the progesterone. These changes diminishes the ability of sperm to penetrate the cervical mucus.

Infertility can be caused by abnormalities in the cervical factors like:

a. Abnormal, impenetrable cervical mucus or poorly penetrable mucus, due to 1) abnormal hormonal mileau, 2) effect of certain treatments, e.g. antiestrogens like clomiphene used in treatment of anovulation or 3) poor response of the cervical epithelium to normal estrogen levels. Consequently, the mucus is viscid, or has a low pH. 4) Poor receptivity of the cervical mucus can result from presence in it of sperm antibodies that immobilize the sperm (see later).
b. Loss of mucus resulting from amputation of the cervix; overenthusiastic cervical cauterization; or cone biopsy. The frequently unnecessary cervical cauterization can result in poor function of the cervix and infertility.
c. Faulty direction of the cervix such as is found is cochleate uterus, retroversion – flexion or severe prolapse has been blamed for causing infertility, but without real evidence.
d. Cervicitis or cervical erosion (ectopy) are most doubtful causes of infertility. Most of the cautaries done on the basis of this assumption are unnecessary and can be harmful.

5. *Uterine factor*

This should be an uncommon cause for infertility: the exact incidence of endometrial factor in infertile couple is difficult to know, but is thought to be in the region of 5%. Endometrial abnormalities may be associated with tubal pathology. The uterine factor can cause repeated abortion rather than failure of conception.

Uterine defects include:

a. Uterine hypoplasia or failure of fusion of its two mullerian halves, e.g. bicornuate or septate uterus. This are causes for abortion rather than infertility.
b. Uterine fibroids are frequently associated with infertility. However, they are usually a consequence of infertility rather than a cause for it. Myomas can sometimes cause infertility when they distort the tubes or interfere with implantation or placentation. They can cause abortion particularly when they are encroaching upon the uterine cavity.

c. Uterine synechias can cause infertility and/or abortion. They frequently result from excessive curettage of the endometrium in presence of an infection. The possibility arises most commonly in the treatment of septic abortion or postabortive bleeding. Uterine adhesions can arise after manual removal of retained unseparated placenta. Amenorrhea or hypomenorrhea may result from removal of basal endometrium (amenorrhea traumatica). The amenorrhea can result from replacement of part of the endometrium by fibrosis tissue, without the fibrosis tissue bridging the uterine cavity. Obliteration of the isthmic part of the uterine cavity results in inhibition of upper spared endometrium, i.e. cryptomenorrhea does not result from isthmic obliteration.
d. Destruction of the endometrium by tuberculosis or severe puerperal infection.
e. Obliteration of uterine cavity rarely occurs during cesarean section or myomectomy as a result of the grave mistake of suturing the anterior to the posterior walls of the uterine cavity.
f. Failure of the endometrium to respond to hormonal preparation can result in conceptionless fertilization. The various factors influencing endometrial receptivity to fertilized ovum is receiving now intense investigation. However, this possibility is still a hypothetical one.

6. *Vaginal factor*

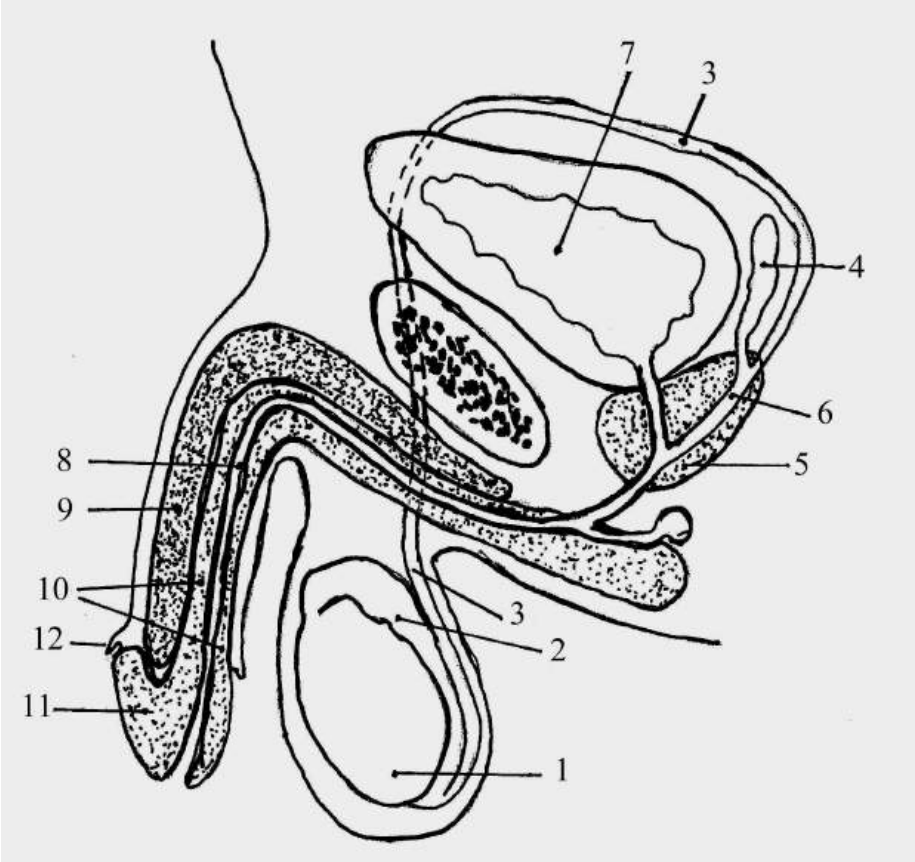
a. Vaginitis is a doubtful cause of infertility. Clinical observations go to show that many women with chronic cervicitis, trichomonas and monilial vaginitis or bacterial vaginosis conceive repeatedly without difficulty.
b. Congenital septa may rarely prevent sperm from reaching the cervix.

Immunological factors:

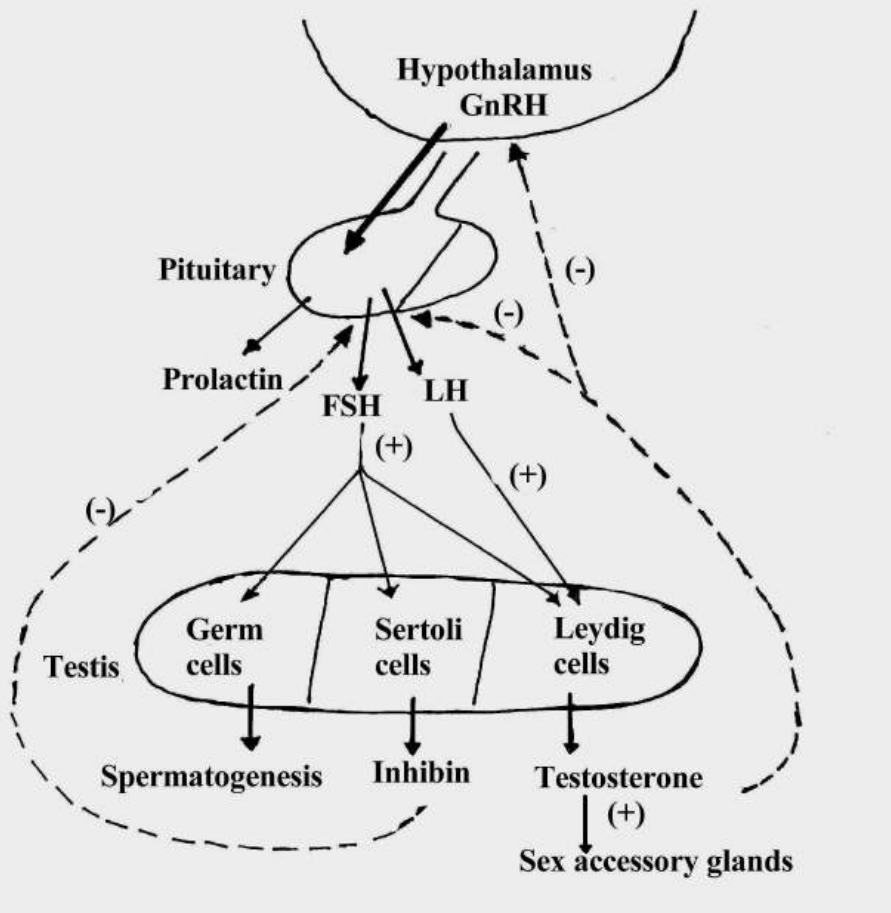
Antibodies to sperm can be either locally generated in different parts of the genital tract or are circulating in the woman's on the man's blood. Antibodies can be formed to particular part of the sperm or to the sperm as a whole. They can immobilize the sperm or interfere with their fertilizing capability. Antibodies to zona-located antigens can interfere with sperm penetration. Immunological factors can interfere with a later phase of reproduction by interfering with implantation of the fertilized ovum, or development and of the supply of the placenta. The role of systemic antisperm antibodies in infertility is most questionable. Immunological factor are also involved in repeated pregnancy wastage (See under abortion).

B. Male Factors

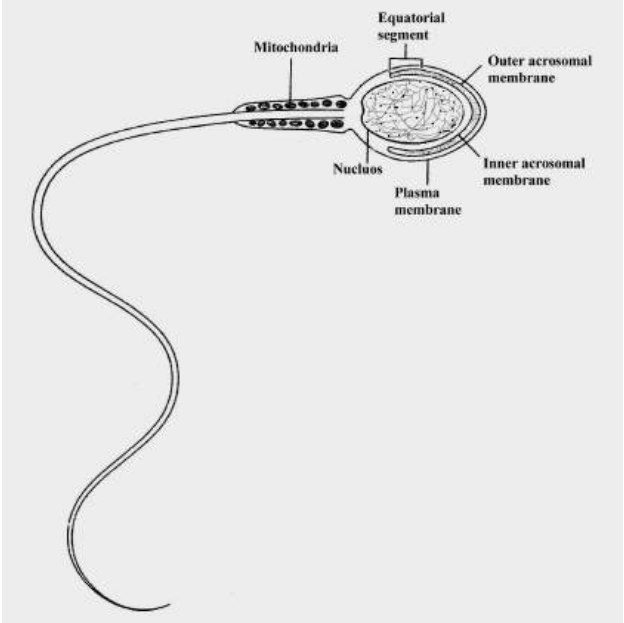
Salient anatomical and physiological features in the male reproductive system are shown in figure 1-3



Infertility; Figure 1: Diagram of the male genital system; *1. Testis; 2. Epididymis; 3. Vas deferens; 4. Seminal vesicle; 5. Prostate; 6. Ejaculatory duct; 7. Urinary bladder; 8. Urethra; 9. Corpus cavernosus of the penis; 10. Corpus spongeousus of the penis; 11. Glans penis; 12. Remnant of the prepuce in circumcised male.*



Infertility; Figure 2: Diagrammatic representation of endocrine relationship among the hypothalamus, pituitary and testis.



Infertility: Figure 3: Structure of a sperm length 0.05 mm. The acrosomal vesicle contains enzymes to help fertilization.

Male factors are present in 30% to 40% of infertile couples. Abnormalities can comprise:

1. ***Defective spermatogenesis*** (failure to produce spermatozoa in sufficient numbers and with the capacity to fertilize):

In most cases of azoospermia, oligospermia and asthenaspermia the cause is not clear. It is now well recognized that defective sperm motility and morphology are as important, if not more important, than reduced number of spermatozoa. Established and postulated causes of defective spermatogenesis include the following:

- Incomplete development of the testes. This comprises:
    - *a.* Chromosomal abnormalities e.g. Klinefelter syndrome with 47 XXY karyotype or less commonly XX/XY mosiacism.
    - *b.* Recently Y chromosome deletions have been found in a good proportion of men with nonobstructive azoospermia. This deletion is inherited in male siblings, if the case is successfully treated through ICSI.
    - *c.* Idiopathic spermatogenic arrest. Maturation arrest can occur at any stage of the spermatogenic process, most frequently at one of the two spermatocytic stages. The extreme form is the absence of germinal cells in the seminiferous tubules *(Sertoli cell-only syndrome)*.
- *Late (after puberty) descent, or non-descent, of the testes.* The spermatogenic function of the testis depends on its extraabdominal site, probably because of the bad effect of heat on the seminiferous tubules. The tissue temperature of the scrotal testes is 2°C lower than that of the rest of the body.
- *Previous orchitis* due to mumps or other severe viral infection (even influenza) occurring after puberty. Orchitis complicates 25 – 50% of cases of adult mumps.
- *Destruction of testicular tissue by infective disease* like tuberculosis or severe nonspecific orchitis. Severe crushing trauma can cause testicular atrophy.
- *Damage to the testes* resulting from accidents, operation, or exposure to X rays. The injury may be in the blood supply rather than in the gonad itself.
- *Varicocele* is not uncommonly found in subfertile men (and in the general population as well). It can raise the scrotal temperature or lead to hypoxemia of testicular tissue, particularly when marked. *However, the beneficial effect of ligation of varicocele has been recently disputed*.
- *Exposure of testes to heat impairs spermatogenesis,* at least temporarily. This can result from wearing of non-porous nylon underwear and suspensory garmet, this may keep the testicular temperature to near the body temperature. Certain occupations exposing the

groin region to high temperatures (e.g. bakers or truck drivers) may depress spermatogenesis.

- *Heavy smoking* is associated with poor sperm quality.
- *Vitamin deficiencies* particularly folate and vitamin B12 has been suggested. Recently excess of free oxygen radicals has also been blamed.
- *Endocrine disorder particularly of the hypothalamopituitary axis* can cause secondary hypogonadism. These are associated with low, or low normal FSH or LH levels or high prolactin level. These can be managed by specific hormone treatment. *Unfortunately, secondary hypogonadism is much less common than primary hypogonadism*.
- *Accessory glands defects*. Bacteria, toxins and pus cells present in the seminal fluid in cases of prostatitis and seminal vesiculitis can influence the motility of sperm as well as their capacity to fertilize the ovum. These factors can cause high viscosity of semen, poor postcoital test, or high percentage of sperm agglutination.
- *Sperm agglutinins and antibodies* may result from operative or severe crushing trauma to the testes. They can result from vasal occlusion for sterilization. These influences can cause break down of the testicular-blood barrier and escape of sperm genes to the general circulation where they elicit formation of antisperm antibodies. The presence of these antibodies may be the cause of failure of operation for reversal of sterilization to achieve pregnancy in spite of reestablishment of potency. Other local and circulatory antibodies may form in the testes or are present in the circulation or in the ejaculate; and can cause sperm agglutination.
- *Old age:* Male fertility tends to decline after the age of 40 years; although spermatogenesis usually continues to some extent until old age. It is frequently quoted that 40% of men above 40 years, 50% above 50 years, and 60% above 60 years are infertile; the basis for this assumption is however, not solid.

2. *Bilateral obstruction of the epididymis, the vas deference or ejaculatory duct:*

This can result from:

- *Congenital absence of the vasa deferentia.* This may be associated with cystic fibrosis or sickle cell anemia. This syndrome is inherited by both male and female siblings. Screening for cystic fibrosis mutation should be considered in males with bilateral absence of vas deferens that is embarking on ICSI. It is sufficient to demonstrate that the wife is not having the mutation.

- *Infections:* of which gonorrhea and chlamydia are the most important. Tuberculosis and bilharzial lesions may cause obstruction.
- *Postoperative epididimo-orchatis* may complicate urological surgery particularly when done in presence of infection. This is common in Egyptian practice due high prevalence of complicated bilharzial lesions in the urinary tract.

3. *Abnormalities in the seminal fluid*

- Presence of pus cells in big amounts.
- Big (>7 ml or small <1 ml) volume of the ejaculate.
- High viscosity of semen. Failure of semen to liquefy after 1 hour is considered abnormal.
- Presence of antibodies, which are fixed to sperm (see later).

4. *Failure to deposit spermatozoa in the vagina*

1. Impotence, or failure to maintain the erection.
2. Failure to achieve orgasm.
3. Premature ejaculation-before penetration.
4. Abnormalities of the penis such as marked hypospadias and phimosis.
5. Retrograde ejaculation into the bladder. This results from certain types of prostatectomies, excision of ulcers near the bladder neck or certain nerve resection operation. The condition is also rarely congenital when the ejaculatory ducts open and empty into the bladder; while prostatic fluid empties normally.

C. Coital Problems

1. **Apareunia and dyspareunia**: Occasionally couples seeking advice for infertility are found to have not consummated their marriage. Many of these couples do not realize the fact. They are contented with interlabial intercourse.
2. **Vaginismus** can be the cause of apareunia or severe dyspareunia that can make intercourse too infrequent.
3. **Infrequent intercourse**: Absence of the husband for long times or irregular visits to his home can be the cause of infertility. Coitus needs to take place every second day during the fertile period to offer the optimal chance of conception. Some couples have wrong information about the fertile period. Some husbands fail to have erection; or to maintain it when pressed to do so during the fertile period. Too infrequent intercourse may result from marital disharmony or old age of the husband or the couple.
4. **Lubricants:** when coitus is difficult and the vagina is dry many couples resort to using lubricants. These include saliva, proprietary jellies, Vaseline, or K-Y gel. These enmesh the spermatozoa and interfere with the chance of conception.

D. Other factors

Some factors are popularly believed to contribute to reduce chances of conception. These beliefs are commonly wrong. These include:

1. Coital positions. There is no particular coital position that contributes to higher chances of conception. Women with extreme retroversion flexion are frequently advised to has intercourse in a special position that favors deposition of the semen in the anterior fornix. There is however no evidence to support the value of this advice.
2. Too frequent intercourse does not seem to contribute to infertility.
3. **Failure of the women to achieve orgasm** at the same time as the man, or not at all is rarely associated with failure or diminished chances of conception. Female circumcision may reduce sexual pleasure but very rarely contribute to infertility.
4. **Effluvium seminis:** Immediately after coitus most of the semen escapes from vagina with the superaddition of the orgasmic secretions of the female. Frequently infertile couples are worried about this occurrence. They should be assured that effluvium seminis is a normal phenomenon. Only the small portion of the sperm, which enters the cervix, are capable of fertilizing the ovum and the loss of the remainder is irrelevant. Spermatozoa only account for

about 10% of the seminal fluid volume. In a normal ejaculate of 200 to 300 million sperm, less than 200 reach the distal end of the fallopian tube.

5. **Anxiety and apprehension:** It is commonly believed that anxiety particularly about getting pregnant is commonly believed to reduce the chances of conception. This is usually not true.
6. **Familial disposition; or genetic factors in infertility**: Some families appear to have a high and others a low conception rate but the explanation is generally not clear.
7. **Obesity,** unless it is a manifestation of an endocrine imbalance, is not a cause of infertility.
8. Women in an ***athletic career*** or who indulge in repetitive physical exercise like running or cyclic are recognized to have lower fertility because of anovulation, hyperprolactinemia and frequently amenorrhea.
9. **Diet** plays no part, provided that is not very deficient.
10. The practice of **contraception** does not reduce the subsequent chances of conception. The exception is the use of progestogen-only injectable which may delay resumption of fertility for only few months (see under Contraception).
11. **Alcohol consumption** if heavy, or drugs as opium or cocaine may reduce fertility and potency.
12. **Coffee consumption** does not interfere with fertility.

II. Investigation of an infertile couple

The diagnostic workup covers the following five items:

1. ***Clinical assessment of the couple*** **through history taking and office examination**. This detects gross abnormalities like problems with sexual intercourse, menstrual irregularities, and ***gross abnormalities*** in the genital organs like inflammatory adnexal masses, amenorrhea, undescended testes, or absent vasa deferentia.
2. Evaluation of ***male factor*** which begins with semen analysis and may proceed to other tests whenever necessary.
3. Evaluation of the ***tubal and peritoneal factors***. This usually begins by hysterosalpingography (or an alternative test), and proceeds to endoscopy.
4. Evaluation of the ***ovarian factor*** to assess its two relevant functions of 1) ovulation and 2) adequate hormone production. There is a multitude of tests for this purpose that are complementary to each other.
5. Evaluation of the ***cervical factor***. This is primarily done through the postcoital test (PCT). Other *in vitro* tests can be done when necessary.

After covering these five basic items, one proceeds to other items like evaluation of other subtle endocrine disorders; uterine and endometrial factors, immunological abnormality, or subclinical reproductive tract infections.

It is generally advisable to proceed in the order given above or with all the items evaluated at the same time. However, deviations from the basic scheme can suite the special needs of a particular couple e.g. reluctance of the husband to be involved early in the diagnostic workup or indication for presence of an abnormality in the tuboperitoneal factor e.g. prior peritonitis.

***Since infertility can be multifactorial the whole scheme should be covered*;** one should not stop at finding an abnormality and start treating it. This is unless the abnormality disclosed needs treatment for its own, e.g., uterine bleeding, inflammatory conditions. However, the scheme needs to be completed early during giving this treatment.

***When to begin investigation infertility**:* Other than the first item of clinical office evaluation, it is advisable to convince the couple to delay specific investigations until the lapse of one years of unprotected intercourse. Assurance is an effective remedy of these couples presenting early. This is unless there is an abnormality that needs direct treatment e.g. infections or amenorrhea. Women approaching their menopause (>35 years old) should be directly evaluated without long delay.

Premarital assessment of fertility is occasionally requested, particularly if one partner has had an unsuccessful marital experience or is having an evident abnormality or strong suspicion of having an abnormality. There are a number of ethical problems in requiring routine premarital assessment. Confidentiality of information is one. The lack of a parallelism in investigating the couple; there is no test in case of the female which is as revealing as the semen appraisal.

1. Clinical Assessment

It is advantageous to have the husband involved from beginning, important historical points should be elicited from him. The gynecologist must always be satisfied that he is receiving a parallel and equal attention of an andrologist, particularly if there are indication that he is contributing to the problem. A good rapport is essential between the two specialists managing the couple.

Instigation and management of infertility can be a lengthy and demanding process needing patience and sympathy on the part of the specialist. It is not to be carried out in a busy, impartial practice.

a. History

The following points need to be covered:

- Ages and occupations.
- Duration of previous marriage, the number of pregnancies that occurred during the previous experience(s), the duration in which contraception was used, and the number of living children from previous marriage. The fact that the husband is responsible for one or two pregnancies should not always preclude the need for his investigation. He can be subfertile or might have acquired a diseased condition after the last pregnancy of his wife.
- Duration of consummation of present marriage and if there have been periods of separation, or contraceptive use, or infrequent intercourse.
- Consumption of cigarettes, alcohol or drugs.
- Detailed **menstrual history**. Many infertile couple may complain of menstrual irregularity when the month-to month variability is within the normal range.
- **Obstetric history:** Particular attention should be given to induction of abortion, septic abortion, and puerperal and postoperative complications. History and nature of operative deliveries should be known. The physician should always respect the desire of the couple of having more children regardless of the number of their living children.
- **Previous illnesses** *on the female side*: Particularly appendicitis, peritonitis tuberculosis (systemic or local), abdominal surgery, uretheritis or purulent discharge. *On the part of the male*: history of orchitis, bilharziasis, significant urinary tract infections, urological operations, symptoms suggestive of gonorrhea or other STDs, tuberculosis. *On both sides*: history suggestive of diabetes or thyroid disease or operations, and use of drugs like antihypertensives, antipeptics and sedatives and tranquilizers, and corticosteroids.
- **Sexual history**: whether intercourse is normal and painless; and frequency of intercourse, particularly during the fertile period. More detailed questions may be indicated with certain couples like difficulty of maintaining erection, adequate penetration, retrograde ejaculation, use of lubricants. The questions should be direct and clear and the answer should help the physician to identify any contributing problem in

the sexual relation. The possibility of prior exposure to STDs needs consideration. It is a delicate part of the interview.

- **Previous investigation carried out for the couple**. The physician should himself revise the documents and do not depends on verbal reports.
- Previous attempts at treatment: reports are required.

b. Examination

This should cover all the systems with particular attention to the reproductive systems. General examination should exclude all possible contributing problems. The women are examined for evidence of reproductive tract infection, position, size, normality and mobility of the uterus, any adnexal tenderness or swelling and its possible nature. Occasionally the cervix needs to be sounded if it looks abnormally narrow. The cervical mucus should be observed and correlated to the stage in the menstrual cycle.

The gynecologist may, either himself examine the husband or have a report from the husband's treating physician, covering the following items: the size and consistency of the testes, epidermal mass, varicocele, hydrocele, precence and normalcy of the vasa deferentia and any prostatic abnormality. Many times, unsuspected abnormalities, e.g., undescended testes, varicocele, epidimoarchitis, absent or grossly abnormal vasa deferentia, and prostatitis are discovered. These might have been concealed from the wife.

2. Investigation of Male Factor

A. Semen analysis.

B. Sperm function tests.

C. Sperm antibodies.

D. Special tests-for certain etiological factors.

After fulfilling the above clinical assessment, semen analysis should be an early part of the infertility diagnostic workout. This is because of 30% to 40% possibility of the male contributing to the problem, and because it is the least invasive and least expensive item in the investigation.

A. Semen Analysis

Semen appraisal is an essential part of the infertility workup. It should never be substituted by the postcoital test; the later does not reliably assess the morphology and motility of the spermatozoa.

An abstinence period of 2–3 days before semen collection is adequate. Shorter period may reduce the volume and count, but should have no effect on motility and morphology of sperm. The specimen is better collected by masturbation into a clean dry container. The condom is not suitable for receiving the specimen because it frequently contains greasing material and may contain spermicidal preparations that interfere with sperm motility. The man who cannot get the specimen by masturbation can collect it by coitus interrupts. However, this runs the risk of losing the first part of the specimen that contains the highest concentration of sperm. The specimen should be protected from cold and delivered to the laboratory *within 1 hour of collection*.

Semen rapidly coagulates after ejaculation but should liquefy again within 20 – 30 minutes after ejaculation. This is a necessary prerequisite for doing an accurate analysis. On occasions, a specimen does not undergo normal liquefaction or is abnormally viscid, and if this is associated with a poor postcoital test, it may be a factor in infertility. If the postcoital test is normal, however, high viscosity probably is not an infertility factor. Techniques used to break up a viscid specimen in preparation for doing a proper semen analysis or for artificial insemination include mechanically dispersing the gel-like specimen by repeatedly running the specimen through a number 19 gauge needle, collecting the specimen as a split ejaculate because the first part is usually less viscid, or treating the semen with a drop of a proteolytic enzyme.

The main parameters assessed in seminalysis include the number, percent motile and morphology. Measurement of sperm density is conventionally done utilizing a hemocytometer or a Makler chamber. Sperm motility is usually assessed subjectively rating the motility in four grades: A) rapid forward (progressive) motility, B) slow forward motility, C) Non forward motility or D) Immotility. This is a subjective attempt to assess the vigor of motion (how fast the sperm swim) and the pattern of sperm motion (how straight the sperm swim). There is no real need to reassess the motility later than one hour from ejaculation. The automated method for assessment of motility allows qualitative measurement of speed of movement. The curvilinear velocity for the spermatozoon is the average distance per unit time between successive positions along its pathway.

Sperm morphology assessment is also done subjectively. Human semen usually contains many abnormal sperm. The spermatozoon is classified as having a normal shape if its head is oval, with approximately a length of 3 to 5 um and a width of 2 to 3 um.

The andrologist and gynecologist are frequently overwhelmed by the difference in techniques for judging and reporting upon the various features of semen, difference in the rating of the specimens and the great difference between laboratories. Confidence in any figure is limited by the inaccuracies inherent in the methods used for counting sperm, assessing the motility or judging the morphology. For example, the between laboratory variation of one pooled specimen of semen can be as great as between the concentrations of 10 and 90 million /ml. The situation has not much improved by introduction of new technologies like the **computer assisted semen analysis (CASA),** automated method of motility analysis which objectively measure the pattern and vigor of sperm movement, or the automated sperm dimension measurement for morphology assessment. The way-out of this problem is to require at least two or preferably three appraisals from different reliable labs before an individual can be categorized as potentially fertile, subfertile or infertile. Because it can take 2.5 months (75 days) for the testes to recover from an insult, it is reasonable to space the assessments over longer period. Passage of this time is also required to assess effect of any therapy.

The following table classify the parameters of semen quality into one of three categories: semen quality within normal limit, no evidence for infertility; marginal semen quality, i.e. infertility is possible; and abnormal semen quality, i.e. infertility is likely. It is based on the manual *of laboratory standards* generated by the World Health Organization (WHO):

Table 2 Classification of semen quality (Modified from WHO standards)

Semen Parameter	Normal*	Marginal	*Abnormal*
- Volume (mL)	**2-5**	**1**	**< 1**
- Sperm concentration (x 10^6 /mL)	**≥ 20**	**10–20**	**< 10**
-% Forward progressive **• Motility within 60 minutes of ejaculation (% of both rapid+ slow).** **Or** **• % Rapid progression only.**	**≥ 50%** **≥ 25%**	**40–50%** **10–25%**	**< 40%** **< 10%**
- Normal morphology *** (Of the head)**	**> 50%**	**40–50%**	**< 40%**

* All features should be fulfilled to classify the specimen as normal.

** This figure has been reduced to 15 X 10^6

Categories 2 or 3 needs reassessment after 2.5 months isolated abnormalities if sperm motility or numbers are abnormal, but abnormalities of sperm morphology are sometimes seen in association with normal numbers and motility.

Other parameters assessed in semen analysis

Whereas the count, motility, and morphology of the specimen constitute the major parameters on which the male's fertility is categorized, there are other characteristics of the semen that may influence fertility potential:

1) A ***volume*** of less than 1 ml may be too small to allow the adequate contact with the cervix, and a volume greater than 7 mL may dilute sperm concentration so that insufficient number are in close proximity to the cervix.
2) ***Round cells*** in the specimen can be either white blood cells (pus cells) or immature spermatogenic cells. The WHO standards manual states that a normal ejaculate should not contain more than 5 million round cells per ml (5 per high power field); while the number of leukocytes (if identified as such) should not exceed 1 million per ml. It is reasonable to ask for a culture of specimen (better obtained by prostatic massage), when the report states that there are 5 or more round cell per high power field, even though some of these may represent immature spermatogenic cells.
3) Repetitive reporting of ***agglutination of sperm*** is suggestive of the presence of an immunological effect or an infection.
4) Although it is common practice to report the ***pH*** of semen, but in practice this is of little value.
5) ***Seminal fructose assay*** is needed for patient with azoospermia. Fructose is produced in the seminal vesicles; and its production is androgen dependent. It should be present in all semen, with the exception of 1) individuals with bilateral ejaculatory duet obstruction, and 2) those with congenital absence of the vasa deferentia who also have no seminal vesicles. Fructose assay is a simple laboratory lest.

B. Sperm function tests

These in vitro tests are rarely used in practice. They are not well standardized and their diagnostic value is not high. They are particularly used in assessing the prognosis for IVF in marginal (category 2) men when choice is made between utilizing husband semen or donor semen for IVF (in centers using the latter). Their value has markedly diminished after advent of intracytoplasmic sperm injection (ICSI).

They include 1) sperm penetration assay using Zona-free hamster oocytes and 2) In vitro test of sperm penetration into bovine cervical mucus.

C. Sperm antibodies

Sperm are very antigenic due to alteration of chromosomal complement during meiosis. They can elicit formation of antisperm antibodies both in the male and female; usually of the IgA, IgG and IgM types. This does not normally occur in the male because sperm antigenic materials are normally isolated by a blood-testis barrier that results from tight junctions between Sertoli cells. Disruption of this anatomic and functional barrier in the seminiferous tubules can lead to antibody formation; hence, antibodies can follow vasectomy, testicular crushing trauma, or torsion and infections. In addition, women can develop antisperm antibodies. These categories of antibodies were suspected to interfere with fertility in a small proportion of couples. These antibodies react to certain antigenic sites on the sperm head, acrosome or tail, causing sperm agglutination, or interfering with their motility or their ability to penetrate into the ovum. *Antibodies circulating in the blood of the wife or husband carry little significance, while those fixed to sperm are important.*

Two tests done on the semen are now in clinical use to detected antibodies on the sperm. Both utilize immunologically mediated attachment of particles or beads (immunoplotting techniques) to the affected sperm, which are, assessed directly under the microscope; to identify the sperm carrying on their surface the antibodies.

1. The *immunobead test* has beads carrying on them sperm anti IgG, anti-IgA, or anti-IgM; the beads will bind to the sperm carrying such immunoglobulins. The test provides identification of the location of these classes of antibodies on the surface of spermatozoa i.e., the site on the sperm where the beads are adherent (head or tail) can also be noted.
2. The *SpermMar test* is an agglutination reaction utilizing an antiserum to IgG (the commonest antibody) to couple the IgG on the sperm surface to latex particles coated with human Ig G. The endpoint is agglutination of the latex particles when the sperm have on their body Ig G. This test cannot localize the site of the antibodies on the spermatozoon surface as it the case with the immunobead test. The SpermMar test can be done on unprepared semen as opposed to the immunobead test where sperm washing is required in order to remove seminal fluid debris. Therefore SpermMar is suitable as a screening test; and if it is positive, the immunobead can be used to determine which antibody is present, and where it is localized. Anti – Ig A usually localizes to the tail and anti – Ig G to the head of the spermatozoon. Antibodies on the tail may interfere with motility, while antibodies on the head can cause failure of fusion with the ovum.

For the SpermMar test the diagnosis of immunologic infertility is suggested when more than 10% of motile sperm are attached to latex particles, and for the immunobead test when more than 20% of motile sperm are covered with beads (WHO standards).

A high percentage of positive sperm antibody test is associated with poor postcoital test, and it would be cost-effective to initially perform this test, and examine with the antibody sperm tests only those individuals whose postcoital tests show no sperm, all dead sperm, a high percentage of "sperm with shaking heads" or less than 3 motile sperm per high power field. In IVF programmes, it is usually advisable to perform antibody tests on all cases.

D. Special testes for etiological factors for male factor infertility

These tests are not routinely requested but are done to investigate possible etiological factors for oligospermia or azoospermia. They comprise:

1. ***Seminal fructose***. The presence of fructose in the semen rules out obstruction or atresia of the ejaculatory duct or congenital absence of the seminal vesicles, which is commonly associated with absence of the vasa deferentia.
2. ***Endocrine evaluation***: including serum testosterone, FSH, LH, and occasionally thyroid function (when hypothyroidism is suspected). These differentiate between the commoner primary hypogonadism and the ***rare secondary hypogonadism***. Secondary hypogonadism is characterized by low or low-normal levels of gonadotrophins and testosterone and may result from hypothalamic or pituitary dysfunction. Although rare, this diagnosis indicates the value of administration of gonadotrophins.
3. Semen or ***prostatic fluid culture*** to confirm prostatitis.
4. ***Testicular biopsy*** to demonstrate arrest of spermatogenesis. It is also utilized to obtain sperm or spermatids for use in ICSI.
5. ***Doppler*** examination to confirm presence of varicocele. The value of detection of such subclinical varicocele is most questionable.
6. ***Karyotyping*** to diagnose Klinefelter syndrome, and Y chromosome deletion.
7. ***Vasography*** is rarely indicated to demonstrate obstructive azoospermia. If sloppily performed, vasography can cause destruction or obstruction of the vas. In addition, since the vast majority of obstructions are epididymal in nature, vasography is of little value in making the diagnosis of obstructive azoospermia.

3. Investigation of Tubal / Peritoneal factor

This integral part of infertility workup *should not be delayed*; usually it should precede repeated attempts at ovulation induction. This is unless the patient is having evidence of an ovarian factor e.g. menstrual irregularity, while having no reason to suspect having tubal factor. However, *tuboperitoneal factor can be present without any antecedent indication* e.g chlamydial or tuberculous salpingitis.

Tubal insufflation (Rubin's test) to demonstrate tubal potency is now rarely done. It has been largely replaced by ***hysterosalpingography (HSG)***, which *document the site of any obstruction*, and can diagnose the type *of tubal pathology, detect any uterine pathology*, and suggest presence of *peritoneal peritubal pathology*. Generally, one should not begin with laparoscopy for evaluation of the tuboperitoneal factor. Laparoscopy is done if 1) there is indication that abnormalities in tubal or peritoneal factor diagnosed or suspected by HSG; 2) if there is strong evidence from the beginning of presence of a peritoneal factor e.g. endometriosis; 3) if there contraindication for HSG, e.g. expected allergy to the dye or suspected tuberculosis; 4) if there is associated symptoms e.g. pain; and 5) in unexplained infertility. Laparoscopy is more costly procedure and carries greater discomfort and risks relative to HSG. In addition, laparoscopy will not detect intraluminal pathology in the uterus and tube. 6) Laparoscopy, however, should always precede reconstructive surgery and medical treatment for suspected endometriosis. In such cases, it is a good policy to be able and permitted (by patients consent) to proceed to operative laparoscopy if needed.

Sonographic hystrosalpingogry (SHSG) utilizing special sonographically detectable fluid (occasionally saline solution) has been introduced and is gaining more ground. It is free of radiological hazards, an office procedure, and can better delineate uterine pathology. However, it is less valuable in delineating tubal and peritoneal pathology than HSG.

Hysteroscopy can be combined to laparoscopy if there is a strong reason to suspect an endometrial factor. Hysteroscopy will not significantly increase the risk and time of laparoscopy, and there is a growing trend to routinely utilize the combination of laparoscopy/hysteroscopy in diagnosis of infertility. Hysteroscopy in itself cannot surely indicate tubal patency or block.

Transuterine ***falloposcopy*** or transabdominal ***salpingoscopy*** are used for very special indications.

▪ *Hysterosalpingography*

Indications and value of HSG:

A. Infertility evaluation

HSG can detect:

- Tubal factors: obstruction and its site, chronic or healed salpingitis, type of tubal abnormality, tuberculous salpingitis, salpingitis isthmica nodosa.
- Peritoneal adhesion: inadequate smearing of the dye.
- Uterine factors: polyp, submucous myoma, congenital mullerian fusion defect, and endometrial adhesion.

B. Postoperative evaluation of previous tubal or uterine surgery:

- Tuboplasty.
- Determination of proximal tubal length before reanastomosis for reversal of sterilization.
- Confirmation of tubal sterilization (if in doubt).
- Myomectomy to detect any consequent abnormality in the uterus, tubes or peritoneum.

C. Evaluation of menstrual abnormalities: (not during an episode of bleeding)

- Menometrorrhagia or menorrhagia (may reveal previously unsuspected submucous fibroid, polyp, adenomyosis).
- Hypomenorrhea or amenorrhea (Asherman's syndrome, endometrial tuberculosis).

D. Evaluation of recurrent abortion

- Congenital uterine anomaly.
- Incompetent cervix.

E. Confirmation of known or suspected uterine anomaly

- Müllerian duct fusion anomaly
- Diethelystilbestrol (DES) syndrome

F. Localization of a missing intrauterine device.

Technique of HSG

Time:

- HSG should be only done during the 5 days following the end of menstruation. This will avoid the risk of disturbing a fertilized ovum and diminishes the chance of intravasation of the dye and embolism. The latter is commoner if the procedure is done in the presence

of uterine bleeding, when blood vessels are open; or during luteal phase when the vessels are congested.

- HSG can have a therapeutic effect in infertility, particularly when an oily dye has been used. The dye may displace a mucus plug, straighten the tube thus breaking flimsy adhesion, or the iodine in the dye may have a bacteriostatic effect or stimulate ciliary function of tubal mucosa.

Dye:

- About 2 to 20 ml of a radio opaque dye is injected depending on the size of the uterus. Oily dyes like lipiodol (a solution of iodine in poppy-seed oil) have been traditionally used for HSG. However, it is progressively replaced by aqueous dyes. These permit completion of the procedure in the same session, has less risk than oil if embolization occurred, and do not produce oil granuloma. Water-soluble dyes give better delineation of mucosal folds of the ampulla of the tube. However, lipiodol better indicates peritoneal adhesions in the second film, which is usually taken 24 hours later.

Canulas:

- Generally, *a canula with an olive or cone, which is fixed to the cervix* is used. *A volsellum* is commonly used to pull down the cervix to make the junction watertight. There are a number of sizes of interchangeable cones which suite the size and configuration of the external os. The cone is movable up and down the canula in order to allow the tip of the canula to just project into the uterine cavity. Whenever there is need to evaluate the cervix and isthmus i.e. isthmography, the cone should be moved to near the tip of the canula. There is an adjustable hook to which the handle of the volsellum is fixed in order to ensure water tightness of coupling to the cervix. Some of the canulas are provided with a manometer to avoid raising the pressure to high levels that may result in embolization.
- Vacuum canula fixed to the portiovaginal of the cervix.
- Balloon catheters (disposable) are now available. The balloon is inflated in the cervical canal, which usually ensure its retention without the need to use a volsellum. If the catheter is expelled from the cervix or there is much leakage of the contrast medium around the balloon and into the vagina, then it will be necessary to advance the catheter through the internal os positioning the inflated balloon in the lower endometrial cavity.
- In case of difficulty in introduction of the canula, a uterine sound is passed into the uterus prior to canualization; the angle of flexion may need to be obliterated by pulling on the cervix by a volsellum.

Procedure:

- Careful history taking should precede the procedure to ensure proper timing and absence of contraindications.
- The procedure is generally done without anesthesia. Apprehensive women may need an oral or an injection of ibuprofen or similar drugs; these also diminish the probability of spasm of the tube that interfere with their visualization. In some women, general anesthesia is needed. This should be given by a specialist under proper precautions to avoid and deal to with any anesthetic accidents.
- Bimanual pelvic examination should precede the procedure. This evaluates presence of vaginal or cervical infections, the size and width of the cervix, the direction of the uterus and its size, and the presence of pelvic tenderness and adnexal masses. It is advantageous if the procedure is done by the gynecologist.
- A bivalve speculum hinged on only one side (Single hinged speculum) will allow its removal after fixing the canula; presence of the speculum can mask important findings.
- Careful aseptic technique should be observed. The external os is wiped repeatedly by a water-based antiseptic like Betadein. The tip of the canula should not touch the vagina.
- It is advantageous to perform HSG *under fluroscopy* with control by a closed television circuit; a picture or two are taken for documentation at the proper time. This will allow injecting the proper volume of the dye; which ensure the filling and proper visualization of the uterine cavity and the tubes. Excess of the dye can mask important features. Fluoroscopy will also detected the presence of air bubbles, which may be mistaken for a filling defect resulting from a polyp. The two conditions can be differentiated by movement of the air bubble with time, while in case of a polyp, the site is stationary. The patient may need to be moved to a lateral or prone position to displace a suspected air bubbles. The two fallopian tubes usually fill simultaneously. However, one may not be visualized at all. Instead of continuing the injection, the patient is better moved to a lateral position with the unfilled tube down. If one tube readily fill with the dye while the other does not fill, this should not be taken as an evidence that the latter is blocked. On the contrary, it is most probably normal, but had a spasm in its proximal part at the time of the injection.
- Intravasation of the dye into a vein or lymphatics can occur and may momentarily mask the tube; particularly when there is tubal block o stenosis. Venous intravasation is rapidly washed away while lymphatic intravasation persists for sometime particularly when oily dye is used. The injection should be discontinued before significant intravasation is made to avoid embolism. In interpreting HSG, intravasation should be differentiated from

peritoneal spill. Venous intravasation follows the course of veins, while lymphatic intravasation form a network of small linear appearance around the uterus and the tubes.

- ***A second film*** is usually taken sometime after removal of the canula to document the adequacy of the spill and adequacy of dispersion of the dye in the pelvic cavity. This is done within 20 to 30 minutes after injection of an aqueous dye, and after 24 hours when an oily dye is used.
- ***Prophylactic antibiotics***, usually in the from of doxycycline 100 mg twice daily, is given if 1) dilated fallopian tubes with or without obstruction are detected. 2) in patients with a history of pelvic inflammatory disease or ectopic pregnancy. This is started 2 days, before the procedure and continued for 10 days.

Complications of HSG

1. ***Immediate pain, with rarely, collapse*** in some unanesthetized women. It is rarely dangerous but the possibility of the occurrence makes it necessary to keep the patient under observation for at least one hour after the procedure. Necessary medications should be always ready.
2. ***Allergic or anaphylactic reaction*** to iodine in the dye.
3. ***Intravasation, Embolism*** can occur in 1% of HSG. Oily preparations are more dangerous, but the consequences are rarely serious and are very rare. This is an added reason to do HSG under fluroscopy; intravasation can be detected early and the injection is stopped.

   The occurrence of intravasation is commoner if the tubes are blocked. It is particularly likely in genital tuberculosis.
4. ***Peritoneal reaction and injection***

   Pelvic peritonitis and salpingitis follow HSG may occur in 0.5% to 1.0% of cases, particularly when aseptic precautions are not perfect. However, the infection is not usually introduced at the time of the procedure, but may represent an exacerbation of a previously dormant PID.

5. ***Abortion***

   Unless care is taken, and especially when the patients has an irregular menstruation.

Contraindications

1. During any bleeding episode.
2. Late in the menstrual cycle.
3. When pregnancy is possible.

4. Acute cervicitis until treated. Vaginitis and vaginosis should not contraindicate the procedure.
5. History suggestive of pelvic tuberculosis. This can be flared up by HSG.
6. Generalized marked allergic tendency, or known allergy to iodine preparations.

Interpretation of HSG

Normal hysterosalpingogram

1. The cervical canal is usually a smooth line with variable length and width. It is occasionally serrated due to cervical arbors. The internal os is narrower and may look empty. It may not show altogether.
2. The endometrial cavity is usually triangular but occasionally T-shaped. The outline of the dye is usually smooth but rarely slightly irregular, particularly if the procedure is done late in the menstrual cycle. The cavity is sometimes seen end-on when the uterus is acutely flexed, when it will look transversely oblong. It can be straightened by pulling on the cervix.
3. The fallopian tube ranges in length between 8 and 14 cm. Its medial third or half is narrow and represents both the interstitial and isthmic portions. The lateral part, the ampulla is wider and its lateral end may show longitudinal folds (if aqueous dye is used) corresponding to the endosalpingeal plicae. This is a good indication of normality of the tube.
4. The peritoneal spill can be seen (and documented) during the injection of the dye. [A curious observation in some normal hysterogram is a fine cone shaped appearance at the site of the interstitial portion of the tube. This appearance is not rare, but the author has not found any explanation for it]. The spill is considered as adequate if it readily flows out of both tubes. In the second film, the adequate dispersion of the dye is indicated by an even distribution of thin upwardly directed arcs (corresponding to the dye around loops of intestines) in the whole of the pelvis, without any tendency to collection or loculation in certain part(s) of pelvis. This is generally better evaluated when oily dye is used.

Abnormalities in hysterosalpingogram

A. Uterus

- Dilatation or *funneling of the cervical canal* may be seen in cervical incompetence. However, this appearance can be associated with normal cervical competence i.e. it is a suggestive but not a diagnostic finding of cervical incompetence.

- *Outpouching* of the upper cervix may be seen after a poorly healed cesarean section. This is better seen in a lateral view.
- Distortion and filling defect in the cervical region can be seen in cases with cervical nabothian follicle or cervical myoma.
- *Adenomyosis* may cause specules of contrast medium varying in length from 1 mm to 1 cm, extending perpendicularly from the endometrial cavity. They may also appear as branching channels or large sacculation projecting out. The uterine cavity can be enlarged as a whole. These pictures suggest the need for USG assessment. The latter, by itself, may not allow differentiation of adenomyosis from fibroid unless these HSG pictures are considered. However, adenomyosis is not always associated with any hysterosalpingographic finding (when the glandular elements are cut off from the endometrial cavity by surrounding fibrosis; which is usually the case).
- *Small endometrial polyp or fibromyomatous polyp* produce smooth, round and sometimes pedunculated filling defects in the shadow of the endometrial cavity. These needs to be differentiated from air bubbles or blood clots. Large fibroids enlarge and distort the uterine cavity; it can accommodate a big volume of the dye e.g. 30 ml before the tubes fill. The cavity can be distorted in shape, but can be only enlarged and normally triangular.
- *Uterine synechiae* produce linear or irregular filling defects. A small synechia may be missed if the dye is not injected gradually under fluroscopy. Moderate to large adhesions compromise the uterine cavity resulting in Asherman's syndrome. Nonvisualization of the endometrial cavity can occur as a result of Asherman's syndrome due to obliteration of the lower part, or the whole of the uterine cavity. Obliteration of the isthmus uteri may result from suturing the edge of a L.S. cesarean section wound to the posterior wall. The few cases the author has seen of this grave complication were not associated with cryptomenorrhea and hematometra. Advanced endometrial tuberculosis will deform or obliterate the uterine cavity, simulating Asherman's syndrome.
- *Displacement of the uterine shadow* can result from full bladder or laden pelvic colon, but it can be caused by displacement of the cavity by a uterine or adnexal tumor.
- *Blood clots or retained products* of conception produce tubular or serpiginous filling defects in the uterine shadow. An early pregnancy causes a round filling defect indistinguishable from the appearance of submucous myoma.
- Mullerian duct deformities and fusion abnormalities can be diagnosed by HSG. *Hypoplasia* results in a small uterine cavity. A *unicornuate uterus* results in an oblong or fusiform endometrial cavity, which is deviated to one side and leads to a single fallopian tube. Axial

rotation of a normal uterus can result in a similar appearance of the uterine cavity, but there are two tubes. The *uterus didelphys* requires canualation of the two cervical canals. One of the two uteri can be larger than the other. *Uterus bicornis, bicorpis unicallis* demonstrates two uterine cavities. *Septate uterus* shows the division of the uterine cavity. Sometimes the congenital septum looks like uterine adhesion. The septum can be so thick and markedly separating the two halves to the extent that a uterus bicorpis is suspected. (see under Development of the female genital system). The two conditions can be difficult to differentiate from one another by HSG, a concomitant pelvic USG or hysteroscopy subsequent laparoscopy is needed to differentiate them. HSG is frequently utilized to assess the result of resection of the uterine septum with hysteroscopic surgery. Occasionally, even with careful surgery a partial unification is apparent on HSG the upper part i.e. the base of the septum still shows. However, the functional improvement is usually achieved, i.e. pregnancy can be successfully carried to term.

- The exposure to *diethylstilbosterol (DES)* during fetal life result in a special syndrome, which is associated with infertility, uterine hypoplasia, with regular or irregular deformity of the uterine cavity, which looks like bifoleate leave with a narrow stem.

B. Tubal and peritoneal abnormalities

- Hydrosalpinx can be of varying size with lateral clubbing or irregular contour. They can be convoluted with hausterations.
- Occasionally the dilation of the lateral part of the tube with loss of pliceal folds is associated with some spilling of the dye but which is usually inadequate.
- Cornual block results in nonfilling of the tube. This needs to be differentiated from inadequate dye injection or its downward leakage around the canula. Persistent spasm of the interstitial part of the tube can result in a similar appearance, which can be negated by a subsequent laparoscopy under general anesthesia; the latter results in relaxation of the tubal spasm. Occasionally persistent nonfilling of the tubes can be successfully canulated during falloposcopy, or under fluroscopy.
- The radiologic features suggestive of tubal tuberculosis include the following: 1) a hydrosalpinx indistinguishable from nontuberculous salpingitis, but the dilation may be limited to the lateral extremity; 2) tubal obstruction in distal, isthmic or proximal ambullary sites; 3) multiple tubal strictures resulting in ragged tubal contour; 4) straight pipe-stem appearance of the tube (better seen in fluroscopy); 5) narrowing of the ampulla with destruction of the mucosal folds; 6) calcified lymph nodes or granuloma in the

pelvis; 7) deformation and partial obliteration of the uterine cavity; 8) the appearance of salpingitis isthmica nodosa.

- Peritubal adhesions can be diagnosed or suspected from 1) inadequate spillage, 2) Inadequate smearing and loculation of the dye, which persist in the delayed film, is highly suggestive. However, collection of the dye in the paracolic gutter can give a similar appearance, which can be negated in subsequent laparoscopy. 3) If the distal end of the tube is displaced or stretched towards the middle line, or upwards in the peritoneal this can suggested tubal retraction by adhesions. These pelvic adhesions can be caused by previous pelvic inflammatory disease, endometriosis or past pelvic surgery.
- ***Salpingitis isthmica nodosa (SIN)***: This appearance can be found in about 3% of hysterosalpingograms. Its etiology is disputed; it may be related to salpingitis or may be analogous to adenomyosis. SIN is associated with infertility and increased incidence of tubal pregnancy. The medial portion of the isthmic portion of the tube grossly appears thickened and/or nodular. Its radiologic features on HSG is the presence of diverticular out-pouching or small channels of contrast medium projecting from the thin, proximal portion of the fallopian tube, that is, the interstitial segment and the isthmus. The tubal involvement varies in extent but is usually bilateral.

▪ *Laparoscopy in evaluation of infertility*

Indications:

1. When HSG has demonstrated or suggested abnormalities in tubal or peritoneal factors, such as tubal block, stenosis or distortion, inadequate spillage, or inadequate dispersion of the dye; loculation of the dye in the part of pelvic peritoneum. Subsequent laparoscopy can diagnose *false positive* HSG findings, e.g., 1) cornual spasm can relax under anesthesia, 2) the incomplete visualization of the tube or inadequate spill that have been due to inadequate volume of the dye injected, or 3) loculation of the dye has been due to collection of the dye in a normal paracolic gutter.

   The special value of laparoscopy in cases with abnormal hystero-salpingographic finding is the detection of the site, extent, type, and the cause of such abnormalities. This can assess the feasibility of operative interference, and whether this can be achieved laparoscopically or will need open microsurgery. The tuberculous nature of the lesion can be known from the appearance of the tubes, and presence of multiple tubercles or patches of tubercles. Peritoneal biopsies can be taken and/or aspirates of the peritoneal fluid can be cultured to demonstrate the organism. Bilharzial lesions in the tubes and pelvic peritoneum

may produce a picture similar to that of tuberculosis, but in the former condition, the lesions are not very marked. The differentiation needs peritoneal biopsy. The *endometriotic* nature of the lesion can be detected by presence of deep brown spots or chocolate cysts on the pelvic peritoneum or the ovaries. Occasionally atypical endometriotic lesions can seen. Biopsies may be required.

Laparoscopy can assess the extent of adhesions in the pelvic peritoneum and the extent of availability of ovarian surfaces. It gives a visual evaluation of ovario-tubal relationship and extent of damage of fimbria. Flimsy bands of adhesion can be seen, intervening between the tubal ostium and the ovary or fumbrial agglutination or phimosis may be defected. These might have not been suspected in HSG, i.e. false negative HSG.

Laparoscopic correction can be attempted in the same sitting.

2. ***Evaluation of the result of a prior tubal surgery.***

   A second-look laparoscopy (SLL) was traditionally done after the lapse of some months, but an early SLL 2–4 weeks after the first surgery is preferable. This allows timely breakage of neoformed or recurring flimsy adhesions before they have become fibrosed or vascularized. However, controlled trials did not confirm a higher pregnancy rate when an early SLL was used.

3. Cases of ***unexplained infertility*** need to be subjected to laparoscopy. Negative HSG findings may prove at laparoscopy to have missed minimal, but significant, adhesion bands, pelvic endometriosis or mild chronic pelvic inflammatory lesion.

4. ***Primary resort to laparoscopic evaluation***: HSG is much less costly, less invasive and safer tool of investigation of tubal and peritoneal factor. It can occasionally has a therapeutic effect. Therefore, HSG should be generally used first. Primary resort to laparoscopic evaluation is indicated in the following situations:

   a. Prior pelvic surgery like appendectomy, ovarian surgery, or treatment of ectopic pregnancy when peritoneal factor is likely.
   b. When there are reasons to suspect endometriosis, like presence of menstruation-related pain or tender pelvic mass.
   c. When there is a possibility of tuberculous nature, e.g. history of tuberculosis elsewhere. Tuberculosis may flare up after HSG.
   d. In elderly patients approaching menopause; a definitive diagnosis is required as early as possible.

e. When there is an abnormality requiring laparoscopic evaluation besides the evaluation of tubal, factor e.g. amenorrhea, oligomenorrhea, pelvic pain, undiagnosed adnexal mass, or uterine tumor.
f. When there is a contraindication for HSG e.g. allergy to the dye.
g. If the patient refuses HSG, or refuses to have it without anesthesia. If anesthesia will be anyway given, it is better to do laparoscopy that will yield more information.

Contraindications:

A. Absolute contraindications

- Severe cardiorespiratory disease.
- Suspected (present) peritonitis.
- Diaphragmatic hernia.
- Suspected severe intraperitoneal adhesions.

B. Relative contraindications i.e. Laparoscopy if necessary requires special care, particularly during indication of pneumoperitoneum:

- Extreme obesity.
- Previous laparotomy, even for minor surgery, necessitates exercise of great care particularly during indication of pneumoperitoneum.
- Large abdominal mass.
- Suspected intrauterine pregnancy.

Technique:

1. It is usually of the interest of the patient to secure her *consent to proceed to operative interference,* particularly utilizing operative laparoscopy, if need is found during diagnostic laparoscopy. Some of the lesions that may be discovered can be effectively managed with little additional effort or risk e.g. breaking of thin adhesion band or cauterization of endometriotic rests. Ideally, the consent of laparoscopy contains permission for possible surgical laparoscopy, if circumstances make this necessary.
2. A *double-puncture laparoscopy* is generally needed for proper diagnostic visualization. It is frequently difficult to assess the lateral ends of the tubes with a single puncture. Occasionally a third puncture is needed.
3. ***Anesthesia:*** Diagnostic laparoscopy may be done under local anesthesia backed up by strong sedation. However, general anesthesia is usually used, it allows the time and manipulations needed to make the complete evaluation. Local anesthesia occasionally compromises the value of the operation.

Several physiological changes should be considered in administration of general anesthesia for laparoscopy. Absorption of carbon dioxide from the peritoneum can result in hypercapnia if large volume of CO_2 is injected or the operation is prolonged as in operative laparoscopy. Use of trendelenberg position and elevation of the diaphragm result in decreased space in the thoracic cavity and difficulty in achieving adequate ventilation. Increased abdominal pressure can lead to decreased venous return and increased peripheral vascular resistance. These effects can result in reduction of cardiac output. These considerations usually necessitate the use of general anesthesia with endotracheal *intubation* in most laparoscopic procedures.

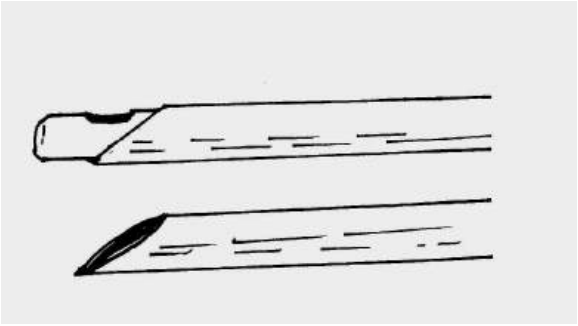
4. The patient is put in lithotomy position with *the buttocks of the patient brought to the edge of the table*. The arm on the side where the surgeon will stand is kept to the patient's side. The patient should be asked to void urine just before the procedure; this obviates the need for catheterization.
5. A pelvic examination should be done with the patient under anesthesia.
6. Pneumoperitoneum is usually induced by inserting a Verres meddle through a small skin incision in the inferior rim of the umbilicus or in one of the umbilical creases. Verres needle has a spring–laden blunt shaft which protrudes beyond the sharp edge of the beveled needle tip once the resistance of the abdominal wall has been traversed. The blunt shaft serves to displace viscera from the sharp end of the needle (Figure 4). The abdominal wall should be lifted by the surgeon and his assistant during pushing the needle. The direction of pushing is determined by the size of the belly. In lean patients the Verres needle (and the trocar) should be inserted almost parallel to abdominal wall in the direction of the promontory of the sacrum because the distance between the anterior abdominal wall and the aorta can be quite small. In obese patient, the direction can be backward. It needs to be remembered that bifurcation of the aorta is at the level of disc between lumbar 4 and lumbar 5, which corresponds to the level of the iliac crests.

   The site of the inserting the Verres needle and the trocar can be supraumbilical if there is an immediately subumbilical laparotomy scar. If the presence of significant intraperitoneal adhesions is suspected, an alternative technique like open-laparoscopy (see under sterilization). The Verres needle may rarely be inserted through the posterior fornix if the abdominal wall has bad laparotomy scars.

   The Verres needle should be connected at the time of insertion to the insufflator; the gas flow will be momentarily stopped during traversing the abdominal wall, but after that the recorded interperitoneal pressure should not exceed 10 mm Hg (0 if automatic insufflator is

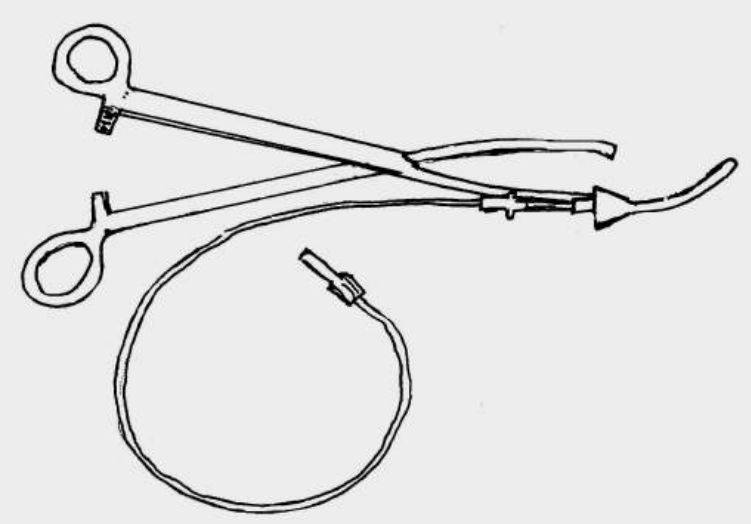
used). Appropriate position of the needle can be verified by placing a drop of water on the opening and observing its suction into the peritoneum occurring when the abdominal wall is lifted. The syringe test can be done in case of doubt. Approximately 5 ml of saline is injected through the needle and aspirated. If the needle is correctly intraperitoneal, the saline cannot be retrieved; only gas bubbles can be withdrawn. If the fluid returns, the surgeon should suspect that he has entered a closed space, like peritoneal space, omentum or intestines. In this case the needle is withdrawn an inserted again, and may be at an alternative site. Thereafter, the surgeon should observe that the insufflation of CO_2 results in progressive, even distension of the abdomen. Loss of liver dullness occurs after passage of one liter of CO_2 into the abdominal cavity, which is also reassuring. Generally, 2 to 3 L CO_2 ensure adequate pneumoperitoneum.

All the above details need to be always observed.



Infertility: Figure 4: Verres Needle.

7. A canula e.g. HSG canula or a uterine manipulation canula (Figure 5) needs to be attached to the cervix. This allows manipulating the uterus and the injection of a dye like a diluted solution of methylene blue, which will demonstrate tubal patency, or the site of any obstruction.



Infertility: Figure 5: Cannulated uterine manipulator

8. The appropriate trocar is then inserted. The abdominal wall is lifted, the trocar is directed for few millimeters under the skin before it directed downward and backward toward the pelvis. This ensures that peritoneal puncture is not directly under the skin incision, something that can result in herniation of the omentum or intestines in the track of the trocar.
9. The plunger of the trocar is then replaced with the scope which is introduced with the light source connected, the scope is introduced under visual inspection. The surgeon should begin with a systematic inspection of the upper and lower abdomen, before the patient is put in trendelenburg position to facilitate visualization of the pelvis.
10. A second puncture is usually needed to allow manipulating pelvic structures and displacing overriding omentum and intestinal loops. Usually this puncture is made above the pubic hairline. The insertion of the second trocar is monitored by looking from the inside, to avoid puncturing a full bladder or blood vessel. Usually a blunt probe or atraumatic grasping laparoscopic forceps is inserted through the second puncture to allow visualizing the lateral end of the tube and lateral side of the ovary.
11. Systematic inspection of the anterior and posterior surfaces of the uterus, the adjoining peritoneal pouches; the broad ligaments, the tube ovarian on both sides. Force should not be used to break adhesion. The fimbriae should be inspected, and any adhesion should be noted. Care should be exercised not to injure a vascular corpus luteum that can result in significant bleeding. If infection is suspected aspiration of peritoneal fluid should be done for culture.
12. Chromopertubation is done by dilute solution of methylene blue through the uterine canula. Lack of tubal filling may be due to obstruction, spasm, or leakage from the cervix.

13. In patients who have undergone prior surgical produces, visualization of pelvic structures may be obscured by a curtain of omental adhesion. These can be moved to one side or an avascular thin area may be passed through by the tip of the laparoscope. Occasionally the omentum may need to be sharply or bluntly dissected to make a window through which the laparoscope is passed.
14. After completion of the producer, the pneumoperitoneum should be completely emptied.

Complication of diagnostic laparoscopy

1. Anesthetic complications (see above).
2. Puncture of a big blood vessel. Punctured a small vessel in the abdominal wall will stop bleeding in few minutes.
3. Injury of intestines and the omentum.
4. The latter two complications are preventable if meticulous care is made in the technique of induction of pneumoperitoneum and in inserting the trocars. They usually need exploration and open management.
5. Extraperitoneal gas insufflation is possible occurrence. If excess gas is insufflated the extraperitoneal emphysema may spread to the mediastinum, an occurrence which may result in respiratory embracement.
6. Herniation of the omentum or a loop of intestines in the track of the canula. This may be immediately recognized but it can be detected some days later.

New technology:

The technology of laparoscopy is rapidly advancing. Newer plastic needles, which are disposable. Camera can now be attached to the Verres needles and trocars. These should reduce the chance of perforating intestines. An abdominal wall elevator has been introduced to obviate the need for pneumoperitoneum.

▪ *Salpingoscopy and Falloposcopy*

These are two approaches to visualize the tube from the inside, utilizing fine fiberoptical scopes introduced into the tubal lumen. In salpingoscopy or fimbrioscopy the probe is introduced through the laparoscope into the abdominal ostium. It can visualize the endosalpinx of the ampullary portion of the tube, but cannot be advance into the narrow isthmic and interstitial portions. It is used for GIFT and ZIET procedure (see under assisted reproduction).

In falloposcopy the fine visualizing probe is introduced transcervically through the uterine cavity into the uterine ostium and advanced along the whole length of the tube. The probe

insertion can be done blindly (feeling-your-way), or guided by fluroscopy or sonography. Falloposcopy builds upon the experience gained in coronary angioplasty. The uterine ostium can be cannulated through hysteroscopy. The isthmointerstitial part of the tube can be distended by fine balloon. Successive canulation of the uterine orifice has been achieved in a good number (30%) of cases of cornual block. This latter technique is being rapidly developed and may be used in the future as an office procedure. Falloposcopy requires training-gained experience. However, falloposcopy has already indicated that the uterine ostium can undergo spasm, and intraluminal debris or albuminous plug can be present and cause tubal obstruction. Balloon tuboplasty has been successful in the same way as it is used in coronary angioplasty for blocked or stenosed small or medium sized arteries.

4. Diagnosis of ovarian factor infertility

A. Diagnosis of anovulation and severe oligoovulation

1. Symptoms

- Menstrual irregularity in the form of oligomenorrhea or amenorrhea, and sometime dysfunctional uterine bleeding is frequently associated with anovulation.
- Women who have menstrual periods at monthly intervals marked by premenstrual symptoms and dysmenorrhea are usually ovulatory, but not always; 5% of regularly menstruating women presenting for infertility are having anovulation or oligoovulation. The diagnosis of anovulation depends upon the following investigation, which are complementary to each other.

2. Basal body temperature (BBT) chart

The methodology is described under Periodic Abstinence for contraception. BBT chart is a useful preliminary method for screening for ovulation and is kept for 3 to 6 successive cycles. A special chart may be provided. Days when intercourse has taken place should be marked on the chart, and this may give the physician an indication that coital frequency is inadequate, or might have been untimely.

The BBT chart indicates that ovulation has occurred and a corpus luteum has been formed, the slight rise of temperature during the second half of the cycle is due to the thermogenic effect of progesterone. BBT chart cannot pinpoint the day of ovulation. There is a relationship between the midcycle nadir (a slight drop preceding the rise in the temperature) and ovulation. The nadir coincide with the LH surge, but this is not consistant. The nadir is not always conspicuous. The physiological basis of this nadir is not clear.

Utilizing the BBT chart to avoid or increase the chance of conception depends upon information about the duration of viability of the gametes. This information is not very certain. It is estimated that the sperm retain their ability to fertilize for 24 to 48 hours and that human egg is fertilizable for 12 to 24 hours. However, individual variability has been recorded.

The shortcomings of BBT chart monitoring are:

1. It cannot always be correctly observed by all women.
2. A small percentage of ovulatory women show a monophasic chart.
3. There is a normal variability within 4 days of the cycle length from month to month.
4. Pressing the husband to have coitus in certain dates can result in periodic impotence in these particular days.

However, it is reasonable to advise the couple to have intercourse every 36 to 48 hours during a period encompassing 3 to 4 days prior and 2 days after the expected day of the ovulation.

Two other measures have been used to assist the diagnostic and therapeutic timing of ovulation:

1. Home (do-it-yourself) testing of urine for detection of the LH surge.
2. Repeated sonographyic assessment around midcycle. When the dominant follicle reaches a diameter of 18 to 20 mm ovulation should be imminent.

BBT chart over 3–6 successive months helps in choosing the day of performing the postcoital test and intrauterine insemination (IUI).

Value of BBT chart

1. Diagnosis of ovulation.
2. Suggests luteal phase deficiency (short-lived or irregular rise of temperature).
3. A method for guiding periodic abstinance, as a method for contraception.
4. Help in identifying the fertile days for couples with infertility.
5. Choice of the day for performing postcoital test.
6. Choice of the day for doing IUI.
7. Persistence of the luteal phase rise suggests the occurrence of pregnancy in a woman missing her period.

3. Premenstrual endometrial biopsy

Endometrial biopsy taken 2 to 3 days prior to the expected day of the period is frequently used to detect the secretary changes which are indicative of prior ovulation. Some advise having a midluteal biopsy. The extent of the various secretary changes in the different component of the endometrium: mitosis in the glandular epithelium and stromal fibroblasts, stromal edema, pseudodecidulization, stromal collapse, blood lakes, exudation, tissue necrosis can be used to date the endometrium and assess the adequacy of luteal phase according to Noyes, Hertig and Rock

criteria. For this to be meaningful the date of biopsy should be judged retrospectively from the beginning of subsequent menstruation or assessed prospectively relative to day of ovulation if this could be known by repeated transvaginal sonography or testing the urine for the LH surge.

The fear of interrupting an early pregnancy has led to the practice of taking the biopsy on the first day of menses. This however may produce an inadequate specimen, which is difficult to assess.

The biopsy is usually taken by a Novak curette. The curette is easy to use, requires no cervical dilation (the curette has a 3 mm diameter), and is usually painless. The danger of interrupting an early pregnancy by such procedure should be very small or even theoretical.

4. Progesterone measurement

Serum progesterone of less than 10 nmol/L (3 ng/ml) is consistent with follicular phase level. To confirm ovulation, values at midluteal phase (approximately 6 to 7 days before the subsequent menstrual period) should be at least 21 nmol/L (6.5 NG/mL) and preferably 32 nmol/L (10 ng/mL) or more. Single midluteal phase measurement is frequently insufficient evidence of adequate luteal phase (unless it is $\geq$32 nmol/L); repeated measurements are usually needed.

5. Serial ultrasonographic assessments

Utilizing the vaginal probe ultrasonography the growth of the dominant follicle can be monitored. This needs to done daily or every other days starting from the time of emergence of a dominant follicle. This follicle can grow in a spontaneous, unstimulated cycle to diameter of 18 mm to 24 mm (maximally 30 mm) in diameter before it ovulates. This latter happening is usually indicated by sudden disappearance, or marked diminution of the size of the dominant follicle. The subsequent formation of the corpus luteum can be indicated by formation in its site of a body, which can have a festooned corrugated lining, or by irregular ingrowths in the follicle cavity of tissue from the wall. The corpus luteum grows in size to about 20-25 mm in diameter, and occasionally larger. It can undergo a cystic formation and, project above the general surface of the ovary. However, the corpus luteum is occasionally indistinguishable from the ovarian stroma on ultrasonographic examination.

This approach is costly and it is too inconvenient for the patient to be routinely used for diagnosis of anovulation. However, it is commonly used for monitoring assisted conception techniques, or for choosing the time for IUI.

B. Testing of ovarian follicular reserve in middle-aged women

In the last 10-15 years before menopause, there is an acceleration of follicular loss. This occurs when the total number of follicles remaining in the ovaries reaches 25,000. Consequently, the level of inhibin production is reduced. This is associated with markedly compromised fertility and poor success in any induction of ovulation and IVF. This is also augmented by aging of ova. In order to assess the chances of response to ovulation induction in women above the age of 35 (or 30), the following criteria are utilized:

1. High serum FSH level on day 3 of the menstrual cycle. The cut-off level is 20 mIU/ml. However, between-laboratory variations are possible.
2. High serum estradiol on day 3 of the cycle above 80 pg/ml. This is reflects a hurried recruitment of ovarian follicles in response to high FSH and to make good the low inhibin levels.
3. Clomiphene challenge test: Clomiphene is given in a dose of 100 mg daily on days 5 to 9 of the cycle. An exaggerated rise of FSH on day 10 compared to day 3 baseline carries a poor prognosis for achieving pregnancy.

C. Diagnosis of luteal phase defect (LPD)

The diagnosis of the condition is usually not definite, and its contribution to infertility is not certain. The laboratory features of LPP can be present in 30% of isolated cycles in normal fertile women and in 2 successive cycles in 5%. There is evidence that repeated LPP is the cause of infertility in 1% of cases of infertility; but this has been doubted in recent literature. The diagnosis of LPD in infertile couple can have the following indicators:

1. The diagnosis should be considered in women with otherwise unexplained infertility, or patient with recurrent early pregnancy abortions.
2. It can be suspected from a short luteal phase rise of temperature in BBT charts. However, such charts cannot be relied upon alone in making the diagnosis of LPD.
3. LPD is to be expected when GnRH analogues are used to produce controlled hyperstimulation of the ovaries in assisted reproduction techniques.
4. Repeated progesterone assays around the midluteal time. The time can be chosen by BBT chart; by repeated vaginal sonography; or by home monitoring for LH surge in urine specimens in order to define the time of ovulation. To detect the LH surge, the patient should do the test daily beginning 3 days before the expected day of the ovulation. If these parameters have not been used, the midluteal phase is dated retrograde from the

beginning of next menstruation. Progesterone assay should be done 7 days after the LH surge (ovulation) and repeated at least once, and better twice at 2-day intervals. For making the diagnosis of LPD, the level of progesterone should not exceed 32 nmol/L (10 ng/mL) in any of these days.

5. Dating of a mid-luteal (diagnosed as above mentioned) endometrial biopsy. Dating the endometrium depends upon changes in the various components of the endometrium utilizing the Noyes et al criteria. There should be a lag of more than two days in the endometrial dating to diagnosis LPP. However there can be variability in the pathologists' assessment of endometrial date. This variability is possible both between pathologists and with the same pathologist repeating the assessment of the same specimen several times.

D. Diagnosis of luteinized unruptured follicle (LUF)

This is a very rare phenomenon in which the mature follicle is luteinized without releasing the ovum. The condition is suspected when repeated VUSG is done in conjunction of repeated measurement of progesterone level; during the luteal phase. For LUF to be considered as a cause for infertility, the condition should be repetitive in subsequent cycles.

C. Diagnosis of specific syndromes associated with anovulation

Two specific syndromes need special consideration; the polycystic ovary syndrome (PCOS) and hyperprolactinemia. These are associated with amenorrhea or oligomenorrhea and their diagnosis will be dealt with under Amenorrhea.

5. Diagnosis of Cervical Factor abnormalities

In the preovulatory period the cervical mucus filters abnormal sperm, nourishes sperm, protect sperm from vaginal acidity, acts as a sperm reservoir, and allows capcitation of sperm. Cervical factor abnormality as diagnosed by postcoital test is present in 5% 10% of infertile marriages. However, the abnormality may not be always dependant on production of abnormal mucus by the endocervical epithelium i.e. a uterine cervix abnormality. The abnormal sperm-mucus interaction can be caused by deficient hormonal stimulation of the mucus, presence of infection or presence of sperm antibodies in the mucus or by defect in the sperm themselves.

A. Postcoital test: Sims' – Huhner's test

The postcoital test provides information regarding both the *receptivity* of cervical mucus and the ability of sperm to *reach and survive* in the mucus. Cervical mucus is a storehouse for sperm; some sperm can remain stored in the cervical mucus for many hours or some days, accounting for the relatively long interval that may transpire between a single coitus and ovulation in cycles leading to conception. *Postcoital test is not a substitute for semen analysis,* (see above).

Timing of postcoital test

The postcoital test is performed around the time of the preovulatory estrogen surge. Timing is made by 1) the length of the prior cycle, 2) previous BBT chart kept for some months, 3) LH monitoring by home testes done on urine in a previous cycle, or by 4) ultrasonography (when a leading follicle of ≥17 mm diameter is detected).

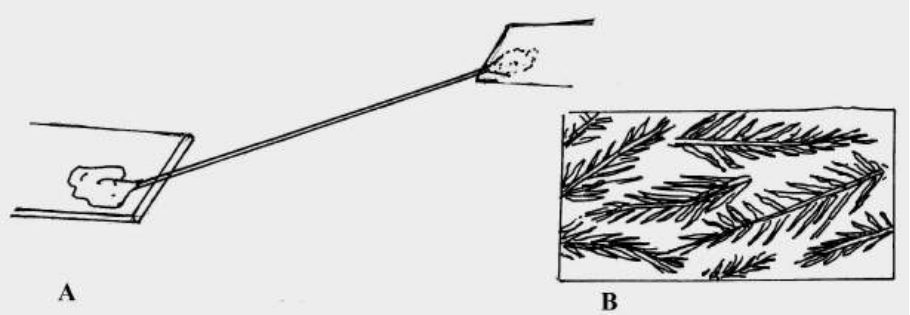
The test is done 2 to 8 hours after intercourse. If done earlier no information will be obtained on the ability of the sperm to survive in the cervical mucus. On the other hand, the number of motile sperm may drop after longer time intervals. The women should not use vaginal douche after intercourse.

Technique

- The characters of cervical mucous cascade are noted.
- The external os is swabbed by normal saline, and mucus is removed from the endocervix by a nasal polyp forceps, tuberculine syringe, or a polyethylene tubing (size 12 F) to which an aspirating syringe is attached. Attempts to refine the postcoital test by studying individual fractions from different levels in the cervical canal, with emphasis on the sample from the internal os have not produced convincing merits. Another drop of posterior vaginal fornix discharge is simultaneously examined for presence of sperm.
- The mucus is placed on a clean microscopic slide and is covered by cover slip and examined under high power magnification of x 400.

  The following features characterize the normal cervical mucus. 1) It is abundant; 2) watery thin; 3) clear; 4) acellular; 5) and shows adequate stretchability (= spinnbarkeit, in German) of 8–10 cm or more. This latter characteristic can be assessed as the mucus is pulled from the cervix, or alternatively, by lifting the cover slip from the specimen on the slide. 6) When dried on the slide, the normal preovulatory mucus produce distinct fern pattern (like a palm-leaf appearance) (Figure 6). Drying of the mucus without a cover slip may show a distorted fern. The above features indicate that the mucus is under the effect

of the preovulatory estrogen surge. Such mucus is the type in which testing of sperm-mucus interaction can be reliably assessed.



Infertility: Figure 6: Preovulatory cervical mucus; *A. Spinnbarkeit; b. Ferning.*

If the mucus is thick, opaque, the possibility that the timing of the test is not properly preovulatory should be considered. This can be judged retrograde by the onset of subsequent menstruation and the time of postovulatory rise of temperature if BBT is being charted during this cycle. If poor mucus quality is related to inaccurate timing, the test should be repeated in a subsequent cycle with scheduling based on repeated sonographic assessment of folliculogenesis. If such poor quality mucus repeats itself in spite of correct timing, it can be safely assumed that it will decrease sperm penetration, and requires treatment.

The criteria for assessment of sperm-mucus interaction are not consistent between centers. Some require the presence of 5, other require 20 motile sperm per high power field (X 400). The WHO guidelines require the latter cutoff figure. The type of motility should be noted; whether it is forward and progressive or sideward, or in the form of head jerking. The presence of the latter phenomenon suggests the presence of antisperm antibodies on the sperm, and tests for such antibodies should be done (see above)

In some infertile patients, no spermatozoa are seen in the cervical mucus. A faulty coital technique must be suspected if the vaginal pool material contains no sperm. Careful asking about the coital technique is needed, one may discover that there has been no penetration, vaginismus or severe dyspareunia.

B. In vitro tests of sperm – mucus interaction

These may be used if the in vivo test has shown abnormal sperm-mucus interaction, and before proceeding to treatment with IUI. These in vitro tests utilize either donor mucus or bovine mucus, to its immediate proximity the husbands or donors sperm are placed, and the degree of penetration of the sperm in the mucus is assessed.

6. Diagnosis of endometrial / uterine factor

Endometrial and structural uterine abnormality may rarely contribute to infertility. However, the role of such factor in infertility is difficult to evaluate because of frequent association with other abnormalities like amenorrhea, and tubal pathology. Uterine abnormalities are more commonly associated with recurrent abortion, rather than failure of conception.

The diagnosis of endometrial and structural abnormalities may be suspected from the history of hypomenorrhea, previous D & C for postabortive bleeding, but is frequently made by hystrosalpingography and hysteroscopy

a. Hysterosalpingography

The diagnosis of uterine cavity abnormality is frequently suspected during hysterosalpinography. The abnormality will be more readily diagnosed if HSG is done under fluroscopy and with gradual injection of the dye; overfilling of the uterine or excessive peritoneal spill may conceal a flimsy adhesion. Documentation of the pathology by taking film may need pulling on the cervix by a volsellum in order to avoid taking end-on pictures of acutely flexed uterus.

The hystrosalpingographic findings of endometrial and structural abnormalities have been described before.

b. Diagnostic Hysteroscopy

Transcervical endoscopy is a frequently used technique with many applications to reproductive problems. It is advantageous if diagnostic hysteroscopy is combined with operative intervention through the same route, if needs arises.

Indications:

A. Suspected intrauterine pathology

Hysteroscopy is used to establish definitively the presence of the following intrauterine conditions:

1. ***Uterine synechiae*** can be definitively diagnosed and their extent evaluated. Synechiae can be lysed or cut under vision. The success of treatment can be evaluated by repeat hysteroscopy or HSG. Fibrosis in the endometrium does not always bridge the uterine cavity forming synachiae, but may be seen as areas in which there is replacement of the lush endometrium by fibrous tissue.

   Intrauterine adhesions (IUAs) are classified according to their extent of involvement of uterine cavity, their thickness and their site and nearness to the tubal ostia.

   Table 3: Classification of IUAs by hysteroscopic findings.

Class	Findings
Severe	More than three fourth of the uterine cavity involved; agglutination of walls or thick bands; and/or osteal areas and upper cavity involved.
Moderate	One-fourth to three fourths of uterine cavity involved; no agglutination of walls, adhesions only; and or osteal areas and upper fundus only partially occluded.
Minimal	Less than one fourth of the uterine cavity involved; thin or filmy adhesions; and upper fundus minimally involved or clear.

   The American Fertility Society classification of IUAs added other data of prognostic significance as menstrual history (amenorrhea, hypomenorrhea and normal menstruation). These classifications help to assess the prognosis and compare results of different reports on treatment.

2. Canulation of tubal ostia may be done under vision if HSG has suggested ***cornual block***. False positive rate of HSG detection of cornual block can be as high as 20%. Cornual block seen on HSG may prove to be just caused by inadequate degree of distension of uterine cavity by the dye (usually resulting from cervical leakage); or to spasm, which will relax under anesthesia. Follopscopy or canulation of uterine osteum should be attempted.
3. ***Endometrial polyps*** can be differentiated from submucous myoma, which is not always possible, by HSG. The polyps should be excised under direct vision.
4. ***Submucous myomas*** can be diagnosed and the extent of their encroachment on the uterine cavity. They can be sampled for biopsy, but are frequently hysteroscopyically removable, particularly if they project in the uterine cavity by more than half of the

circumference, or if polypoidal i.e. transcervical hysteroscopy resection of myoma (THRM).

5. ***Fusion defect of the two mullerian halves of the uterus:*** the extent of congenital fusion anomalies of the uterus can be accurately defined, treatment planned and subsequent results are assessed after operative hysteroscopic intervention. The septate uterus is nowadays unified by hysteroscopic surgery; transabdominal metroplasty is no more done.
6. Embedded IUDs can be visualized and removed by hysteroscopy.
7. Evaluation of patient with abnormal uterine bleeding. In patients with abnormal uterine bleeding, the organic cause can be evaluated or ruled out, so that appropriate medical or surgical management is advocated:

   Endometrial malignancies may occasionally be missed by curettage, a hysteroscopically directed biopsy avoids this possibly and can assess the downward spread of endometrial carcinoma to the cervix.

   Endometrial ablation can be done hysteroscopically after exclusion of organic lesion requiring hysterectomy.

B. Unexplained infertility and recurrent abortion

It is advisable to submit these cases to hysteroscopic evaluation. Previously unsuspected abnormalities like thin IUA, endometrial or myomatous polyp or thin septum are occasionally diagnosed. The extent of this occurrence depends on the care exercised in previous HSG.

Contraindications

1. Acute pelvic infection.
2. Acute bleeding.
3. Suspected pregnancy.
4. Recent perforation.
5. Pelvic endometriosis.

Technique of Hysteroscopy

A. Instrumentation:

1. Telescope

Diagnostic hysteroscopy can be usually achieved by a scope with an outside diameter of 4 mm to 5 mm, which usually does not need cervical dilatation. It can be done in the office utilizing carbon dioxide distension. For operative hysteroscopy a bigger sheath of 7 to 8 mm outside diameter, this needs prior cervical dilatation. The sheath incorporates besides the scope two

separate channels for the inflow and outflow of the distending medium and one or two channels for operating instruments.

2. Distension media

Because the anterior and posterior walls of the uterine cavity are in apposition; the cavity must be distended by one of three different type of media to ensure proper visualization:

a. ***Low–viscosity solution:*** Saline or glucose can be used but the most commonly used is 1.5% glycine or 4% sorbitol solutions which are instilled from 3–litter infusion bags. Infusion pressure is controlled by gravity or by a blood pressure cuff. Constant high pressure is applied to instill the solution. The main problem with this medium is that it easily mixes with blood, which obscure the field. Therefore, a continuous irrigation of the uterine cavity by inflow and outflow of the medium is necessary to remove blood and debris. A continuous watch should be kept on the volume of the outflow. Loss of the fluid inside the body can cause serious hypernatremia.

b. ***Carbon dioxide:*** This is suitable for office hysteroscopy. If needs a special insufflator (different from that used in laparoscopy) which allow the flow in a rate of 25 to 100 ml/min, at a maximum pressure of 200 mm Hg. A patulous cervix limits the ability to maintain uterine distension.

c. ***Dextran:*** Hyskon (32% dextran 70 in dextrose) is highly viscid solution that is optically clear. The medium will not readily mix with blood. With good cervical water-tight fit uterine distension can be maintained for a good time that allow clear vision needed for operative hysteroscopy. It can be delivered by a 50 ml syringe. It was the medium choice for operative hysteroscopy. The disadvantages of Hyskon are its messiness, making it not suitable for office work. It can harden and clog the instruments if they are not carefully and repeatedly rinsed by warm water. Very rarely, it cause what is called Hyskon reaction which result when the macromolecules gain entry into the circulation initiating a consumptive coagulopathy producing hypofibrinogenemia and bleeding diathesis. A total amount of the instilled Hyskon should not exceed 250 ml. Presently; most hysteroprocedures are done with continuous inflow-outflow system of sorbitol or glycine.

3. Timing

Except during menses, hysteroscopy can be performed any time during the menstrual cycle. However, visualization is best within 2 to 3 days after the cessation of menstrual flow. The endometrium is thin early in the cycle; in later procedure, the tubal ostia can become obscured by

endometrial growth. If hysteroscopy is performed during the later part of the cycle, It is necessary for the patient to have used reliable contraceptive.

4. Technique of Diagnostic Hysteroscopy:

For Operative Hysteroscopy see under Management of uterine factor:

- Diagnostic hysteroscopy can be done under local paracervical anesthesia; but for apprehensive patient general anesthesia is need.
- The suitable hysteroscope is selected and tested before use to check clarity of vision and flow of distending medium: Air is displaced out of the system.
- A single-hinged speculum or Sim's speculum is inserted and the anterior lip of the cervix held by a single-toothed vosellum.
- Dilatation of the cervix should better be avoided.
- While the telescope is ascending in the cervical canal; the longitudinal folds, papillae and clefts in the endocervix are noted. The internal os appears as a narrow constriction at the top of the cervical canal. The isthmus is a cylinderical extension above the internal os. The corpus is a capacious cavity above the isthmus. The site of mullerian duct fusion is frequently noted as a faint anteroposterior ridge in the fundus; the cornua are on either side of this ridge. The tubal ostea are visible at the upper lateral extremities of the fundal cornua and show great variation in their appearance and the angle of entry in the uterine cavity.

The proliferative endometrium is thinner and pink–white in color. The secretory endometrium is thick (indentable when stroked by the scope) and velvety pink. It is usually protrude in the cavity irregularly can be mistaken for polyps. The cornual ostia may be obscured during the secretory phase.

7. Unexplained Infertility

The diagnostic infertility evaluation determines the possible cause of infertility in approximately 80% to 90% of couples. The term "unexplained infertility" denotes that the basic evaluation detailed above has failed to disclose any specific etiological factor. Unexplained infertility is a diagnosis of exclusion, and depends upon the type of diagnostic workout utilized. The prevalence of such diagnosis is in the region of 10% to 15% of infertile couples. It needs to be remembered that if more time is allowed for these couple, conception can occur in a good percentage of them. Estimates of this percentage vary depending on the thoroughness of the diagnostic workout and the duration of infertility. Cumulative pregnancy rate at the end of 2 to 7

years without any treatment can range from 40% to 60%. Therefore, to determine that any method of treatment of infertility is superior to no treatment, careful statistical analysis utilizing life-table probability approach is required. This analysis will determine whether the treatment improves the monthly probability of conception (fecundability). Keeping observation of a comparable control group, receiving no treatment is not usually possible, and one may depend on historical control group.

Continuation of the investigation of cases of unexplained infertility (or repeating certain investigations) may disclose an unsuspected explanation like one of the following factors: The importance of some of these factors in treatment of infertility has not been validated by evidence-based evaluation.

1. ***Female partner's age*** (see above)

   Fecundability decrease with increasing age. This has been shown in natural cycles, induction of ovulation, donor insemination, IVF, and ICSI. The IVF programs generally report a rate of delivery per retrieval of ova of about 20% for women under the age of 40, and of about 8% for women 40 and above. This has been generally ascribed to poor response to ovulation induction, and aging of ova in the ovary with advancing age. Other factors like endometrial receptivity may be involved.
2. ***Subtle male factor*** undetected by standard semen analysis. Functional tests of sperm may disclose inability of sperm to fertilize ova, e.g. by in vitro sperm penetration tests (SPT), OR Hamster zona penetration (HZP) tests.
3. ***Cervical factor*** and abnormal postcoital test.
4. ***Luteal phase defects***.
5. ***Luteinized unruptured follicle (LUF***).
6. ***Subtle endometrial factors*** like fibrosis and IUA, can be disclosed with hysteroscopy. Some gynecologists consider the infertility diagnostic workout incomplete if it has not comprised hysteroscopy. However, this has not been confirmed by evidence – based approach.
7. ***Subtle subclinical female genital tract infection*** may be present in cases of infertility. Two organisms have be suspected Myoplasma (Ureaplasma urealytieum) or chlamydia Trachomatus. However, many tests for diagnosis such infections lack specificity or accuracy.
8. ***Immunological factors:*** These are mainly diagnosed by the presence of antisperm antibodies on the surface of spermatozoa (see above).
9. ***Premature menopause*** or resistant ovary syndrome with persistently high FSH levels. These can be the underlying cause of unexplained infertility.
10. ***Subtle hyperprolactinemia*** (see under Amenorrhea).

III. Treatment Modalities in Infertility

1. Induction of Ovulation

Attempts at induction of ovulation should be preceded by diagnostic workup that indicate the need for such therapy, and the exact or probable cause of anovulation. Anovulation is frequently associated with amenorrhea or oligomenorrhea; the cause of which usually falls in one of the following etiological groups:

1. Hypothalamic dysfunctions including: stress related, drug induced or exercise related amenorrhea, anorexia nervosa and its variants, or Kalmann's syndrome.
2. Hyperprolactinemic amenorrhea.
3. Pituitary abnormalities including tumors and necrosis.
4. Polycystic ovary syndrome.
5. Ovarian failure, including premature menopause and resistant ovary syndrome.

Fortunately, we are now having a number of treatment modalities with definitive effects including:

1. Clomiphene citrate and similar drugs.
2. Dopaminomimitic drugs like bromocreptine and similar drugs.
3. Gonadotrophin treatment including human menopausal gonadotrophins (HMG), purified FSH, and recombinant FSH.
4. Gonadrotrophin Releasing Hormone,(Gn RH).
5. Gn RH agonists and antagonist, which are used as an adjuvant treatment with Gonadotrophin therapy.
6. Laparoscopic treatment of polycystic ovary.
7. Controlled ovarian hyperstimulation used with various Assisted Reproduction Techniques (ARTs) including mainly, intrauterine insemination IUI, In Vitro Fertilization (IVF) and Intracystoplasmic Sperm Injection (ICSI). These should be last resort.

I. Clomiphene Citrate (CC)

Clomiphene citrate (clomid) is an orally active nonsteroidal agents distantly related to diethylstilboestrol. It belongs to a group of drugs called triphenylethylenes which include besides clomiphene citrate, tamoxifen (Nolvadex) and Cyclophenyl (Ondogyne) which are generally classified as antiestrogens or selective estrogen receptor modulators (SERMs). Clomiphene is

available in 50 mg tablets. It has been shown to induce ovulation in anovulatory women particularly those with polycystic ovary syndrome (PCOS). The use of clomiphene citrate has mostly obviated the need and the risk of ovarian wedge resection of PCO. The use of tamoxifen or cyclophenyl has not been proven to have any merit over the more widely tested clomiphene.

Mechanism of action is not fully clear:

Clomiphene citrate is a selective estrogen receptor modulator, which has a weak estrogenic effect, but acts mainly as antiestrogen through competing with endogenous estrogens for estrogen binding sites in the hypothalamus. Therefore, it blocks the negative feedback of endogenous estrogens. In patients with persistent anovulation and particularly those with PCOS, there is an exaggeration of this negative feedback effect. As a result, Gn RH pulse, as determined by measuring LH pulses, is lower in frequency and amplitude than in the normal follicular phase; they are infrequent, or even absent. During administration of clomiphene early in the follicular phase, the frequency of Gn RH pulse increases. This stimulates FSH and LH release with resultant stimulation of both recruitment of ova and oocyte maturation, with an associated increase in estradiol (E_2) production. Preovulatory peaking of E_2 then induces the LH peak through a positive feedback that triggers ovulation. Clomiphene may also act directly on the pituitary, perhaps by enhancing its sensitivity to Gn RH. This is mostly an estrogen effect.

At the same time, clomiphene exerts some peripheral antiestrogen effect on the cervical mucus, endometrium and the vaginal epithelium. This may be one of the possible explanations of the discrepancy between a high ovulation induction rate and a moderate conception rate. Human chorionic gonadotrophin may be given in midcycle after folliculogenesis has proceeded to a dominant follicle of a diameter of $\geq$18 mm. This may augment the endogenous LH peak and help to trigger ovulation, and may also help correct the antiestrogenic effect of clomiphene on the cervical mucus and the endometrium. However, the value of this HCG dose has not been proven by controlled trials.

patient Selection:

The following are the feature in the patients that ensure good response to clomiphene:

1. Absent or infrequent ovulations is the only cause of infertility.
2. Response to progesterone withdrawal by occurrence of menstruation. This indicates that the patient is not suffering from estrogen deficiency like those with primary or secondary hypogonadism. Patients with hypoestrogenemia rarely respond to clomid.
3. No evidence of thyroid or adrenal dysfunction.

4. No hyperprolactinemia.
5. Patients with PCOS are typically treated with clomiphene. Ovulation can be achieved in the majority of them. PCOS is diagnosed by a number of clinical and laboratory parameters, but finally the ovarian pathology is diagnosed by demonstrating in vaginal sonography the necklace appearance resulting from a multitude of subsurface small follicles.

Dose of clomiphene

Clomiphene citrate is usually administered in a five-day course early in the follicular phase, usually starting from the second or third day in the menstrual cycle. In amenorrheic patients, a progesterone withdrawal menstrual bleeding is usually induced before beginning the treatment. The effective daily dose is usually either 50 or 100 mg. It is usually advisable to start with the lower does, and if after the first cycle, there is no response, shift to higher dose. If this result in an ovulation, the treatment is repeated for 3 to 4 successive months. If this succeeds in three cycles in inducing ovulation and conception does not occur, the diagnostic workup needs to be revised. Resistant cases may need the does to be increased to 150 to 200 mg daily. This may be required in obese women with some evidence of virilization. However, it is always advisable to begin with the lowest dose of 50 mg daily in all cases.

Ovulation is expected 5 to 10 days after the end of the treatment. The patient is advised to have intercourse every other day during this time. The injection of 10,000 IU of HCG about 7 days after end of clomiphene treatment has been commonly prescribed. This is in attempt to trigger ovulation at that time. However, there is no convincing evidence that this practice increases the chances of success in induction of ovulation. Moreover, an early injection of HCG during folliculogenesis may interfere with the final stages of graafian follicle maturation, and result in poor oocyte quality i.e. defeat its cause.

The long half-life of clomiphene citrate and a cumulative effect may result in spontaneous ovulation in one or two cycles after discontinuation of3 cycles treatment. Repetition of another three cycles of clomiphene treatment after an intermission of some months may be tried in some cases, particularly if the husband is subfertile, or if there has been infrequent intercourse during previous cycles of treatment.

Documentation of ovulation during clomiphene treatment: This can be achieved through one of the following means:

1. BBT charting showing a biphasic temperature chart.
2. Rise in serum progesterone: This is better measured on more than one occasion starting from 7 days after the end of clomiphene treatment and repeated every 3 days. If only one measurement is affordable, the sample should be taken two weeks after ingestion of the

last tablet, i.e. coinciding with the time of the expected mid luteal progesterone peak. A level of 15 ng/mL is expected at that time. In general, the level of progesterone in clomiphene cycle may be higher than in spontaneous ovulatory cycle, because of the higher frequency of multiple ovulation as a result of the treatment.

3. Repeated sonographic examination: Using the vaginal probe, the process of folliculogenesis is followed up on daily basis starting from the fifth day after the last tablet of clomiphene. This can follow up a dominant follicle(s) until it disappears at ovulation or is replaced by a corpus luteum some two or three days later. This practice may be proving inconvenient or too costly for the patient. Moreover, the corpus luteum may not be always conspicuous; the simple disappearance of the dominant follicle does not always indicate ovulation.
4. Do it-yourself tests to detect the LH peak: these tests performed at home by women have become available. These tests use monocolomal antibody for LH. They are all-or-none tests designed to detect a high level of LH in urine, as the concentration, which occurs during the midcycle LH peak. Ovulation is expected within 24 hours after detection of the peak. However, there are two shortcomings of these tests: The occurrence of a rise of LH is not always followed by ovulation. Second, while clomiphene is being ingested, large amounts of LH are released; thus, urinary LH testing during or immediately after stopping clomiphene could yield false-positive results. Therefore, at least 2 days should elapse between the last tablet and the initiation of testing.

Results of clomiphene treatment

1. In properly selected patients, 80% can be expected to ovulate, and approximately 40% become pregnant. The difference is contributed to by a number of factors including a) failure to have intercourse at the proper time; b) failure of fertilization or implantation; c) unfavorable cervical mucus resulting from prolongation of the antiestrogenic effect of clomiphene on the mucus; d) presence of other factors contributing to infertility i.e. improper choice of case. In patients with no other causes of infertility, the cumulative 6-month conception rate approach normal rate of 60–75%.
2. Multiple pregnancy rate is approximately 5%, almost entirely twines. Higher order multifetal pregnancy is most exceptional. Twining rate should be diminished by gradual stepping up of the daily dose.
3. The abortion rate is higher than normal in patient with PCOS.

4. The incidence of congenital malformation is not increased, and infant survival and performance are not different from normal.

Complications of clomiphene

1. Vasomator flushes in 10% of cases during clomiphene administration.
2. Blurred vision may occur, but is usually slight.
3. Abdominal distention, bloating and pelvic pain in 5%.
4. Nausea and vomiting are rare.
5. Headache.
6. Breast discomfort.
7. Hypomenorrhea i.e. diminished amount of menstrual flow is frequently noted by the patients.
8. Significant enlargement of the ovarian may be noted if sonography is done. This is noticed 5 to 7 days after discontinuation of clomiphene and is a response to increased gonadotrophin secretion. It is more common when high doses of clomiphene are used. This ovarian enlargement is usually modest and disappears within days. Rarely the subsequent treatment needs to be delayed to avoid cumulative effect.
9. Twin pregnancy is increased.
10. There slight increase of ectopic pregnancy rate.

Management of clomiphene failures

It is expected that, at least 20% of properly chosen may fail to conceive after 6 courses of clomiphene treatment. In these cases, the diagnostic workup will need revision. A previously unsuspected hyperprolactinemia, premature ovarian failure, or a subtle male factor may be detected. After exclusion of these possibilities one of the following options can be tried; not necessarily in the following order:

1) *Addition of corticosteroids to clomiphene:*

Some cases of persistent anovulation and POCS are having excess of androgens. These androgens may be produced in the ovarian stroma because of the relative excess of LH (see under PCOS). They can also be produced as a result of an associated adrenal dysfunction resulting in excessive production of dehdroepiandrosterone sulphate (DHEA-S). The excess androgen can interfere with follicular ripening or ovulation. Women with excess adrenal adrogens i.e. levels of dehdroepiandrosterone sulphate DHAS higher than the upper limit of normal can benefit from the addition of dexamethosone 0.5 mg daily to clomiphene

treatment. This dose is given at bedtime to blunt the nighttime peak of ACTH. Dexamethasone is started monthly with clomiphene course and continued beyond it, and until the subsequent period begins, or until pregnancy is suspected. It is advisable to return to beginning, with the lower dose of 50 mg daily dose of clomiphene. Corticosteroids should not be used routinely, only when there is excess in adrenal androgens. Corticosteroids may augment the insulin resistance associated with some cases of PCOS. This may augment formation of ovarian androgens.

2) *Addition of dopamine agonists (like promocreptine) to clomiphene:*

This combination is evidently needed if hyperprolactinemia is present. Elevated prolactin levels interfere with menstrual cycle by suppressing the pulsatile secretion of Gn RH. This is manifested in anovualtion, oligomenorrhea, amenorrhea, or subtle luteal phase deficiency. Hyperprolactinemia is usually associated with galactorrhea, but not necessarily so. Moreover, mild galactorrhea can be present in absence of hyperprolactinea. This latter occurrence suggests the possibility of enhanced sensitivity of target cells in the breast to the normal levels of prolactin. The possibility of existence of a similar enhanced sensitivity of the hypothalamo-pituitary axis to prolactin has been the basis of addition of bromocreptine to clomiphene treatment in euprolactinemic cases with anovulation. Therefore, this combination is particularly advisable if galactorrhea is present. A subtle hyperprolactinemia can be documented in these doubtful cases by repeating prolactin assay during nighttime or in the midluteal phase when normally relatively higher prolactin secretion is expected. A third method is the demonstration of increased response to a bolus injection of thyrotropin releasing hormone (TRH). However, these tests are not always economically justifiable before trial of this combination therapy. In women with persistent anovulation and PCOS, LH secretion can be decreased by bromocreptine treatment, thus providing a rationale for why it might enhance the ovulatory response in these case.

For the dose and implication of dopamine agonist treatment (see under section with this title).

3) *Stepping up clomiphene dose (see above):*

This is only resorted to after documenting failure of ovulation with the smaller doses.

4) *Extended clomiphene treatment:*

This has been tried, but there is no documented evidence that prolongation of clomiphene treatment beyond the usual 5-day course increases the ovulation induction rate. Clinical experience indicates that this prolongation, when monitored by repeated sonographic examination, rarely improve the results.

5) *Addition of HMG (or FSH) to clomiphene:*

Human menopausal gonadotrophin administration may be added to clomiphene to augment the FSH rise necessary for folliculogenesis, and can be used in cases with clomiphene failures. HMG is started after the end of clomiphene 5-day-course. The administration of this preparation should be always monitored by daily assessment of follicular growth by sonography and by measurement of estradiol daily in order to avoid hyperstimulation of the ovary. HMG contains a small fraction of LH, which may augment the already existing high level of LH in patients of PCOS. This may interfere with the final stages of follicular maturation, and may precipitate hyperstimulation syndrome. Therefore, pure FSH, or recombinant FSH may be better suited for the purpose of treatment of PCOS.

6) *Resort to carefully monitored HMG or FSH stimulation:*

This may be resorted to in cases of clomiphene failures but may be used, without beginning with clomiphene. This therapy needs to be carefully monitored and the dose titrated against the ovarian response as detailed later. Patient with PCOS are more likely to develop hyperstimulation syndrome.

7) *Downregulation of ovarian activity*

The anovulation state is a dysfunctional condition associated with relative excess of LH and excessive formation of estrone (E_1) and of ovarian androgen mainly androstenedione. It is reasonable to expect that suppression of these disorderly-produced endogenous hormones may pave the way for orderly response to clomiphene and FSH preparations. Women with elevated endogenous LH and androgens may, not only have trouble to conceive but are also predisposed to spontaneous early abortion.

Two approaches have been utilized to downregulate the disorderly ovarian function. First, a period of suppression of ovarian function through the use COCs for 6 months was through to be followed by a better response to clomiphene. However, such approach has not been based on controlled trials. The second, and validated approach is the use of Gn RH agonists to downregulate the ovarian function prior to use of clomiphene or HMG. The latter treatment is initiated after estradiol has dropped to levels below 25 pg/mL, and the agonist is continued up to the time of obtaining evidence of ovulation. This type of downregulation will be discussed later in the chapter on assisted reproduction technique (ART).

8) *Administration of low dose of estrogen for few days after clomiphene:*

This has been used to counteract the antiestrogen effect upon cervical mucus. However, this additional estrogen treatment has never been validated by clinical trials. Moreover, the administration of estrogen in the late follicular phase may interfere with the

sequence of events leading to ovulation. *This practice is therefore, better avoided*. It is however a possible modality of treatment when unfavorable cervical mucus is repeatedly demonstrated. The lowest possible dose of natural estrogens e.g. primarine 0.625 mg should be used.

9) *Timely intrauterine insemination (IUI)*

This can be used in women who show inadequate cervical mucus or inadequate mucus-sperm interaction after clomiphene treatment. This is probably resulting from the antiestrogenic effect of clomiphene on the cervical mucus. The IUI is timed to coincide with the time of ovulation.

10) *Surgical treatment of PCOS*

Stein and Leventhal who first described the PCOS advocated its treatment by bilateral ovarian wedge resection (BOWR). This was empirically based upon two assumptions. First, the thick ovarian capsule prevents ovulation. Second, that associated ovarian stromal hyperplasia produce excess androgens, which through a local paracrine and autocrine effects, interfere with the follicular dominance and maturation of one follicle, and enhance follicular atresia. In fact, BOWR is followed by reduction of circulating testosterone and inhibin levels. These result in significant rise of FSH, emergence of a dominant follicle and ovulation.

Many BOWRs were done before clomiphene treatment has been established in the practice. However, the operation has fallen into disrepute after it has been established that 1) the various medical means described above are highly effective, and 2) that BOWR frequently results in pelvic adhesions that may mechanically compromise the chance of conception.

However, after the advent of laparoscopic surgery, interest in surgical management of resistant case of PCOS has been revived. This depends upon the assumption that adhesion formation would be less likely to result from endoscopic surgery. Laparoscopic surgery consists of making diathermy or laser drills (5–10 per ovary). Some surgeon advocate incising the antimesenteric border of the ovary by the diathermy hook scissor or laser beam. There are reports of a reasonable success rate after laparoscopic surgery. However, in many instance the beneficial effect is short-lived; the syndrome recurs after some months. Surgical management may improve the responsiveness to clomiphene treatment. There is no available evidence based on randomized controlled trials that this modern time laparoscopic treatment is superior to the various methods of medical treatment including FSH treatment with or without downregulation of aberrant ovarian functions. Moreover, the risk of postoperative

adhesion after laparoscopic surgery, though less than in BOWR is not completely absent. Excessive destruction of ovarian tissue may result in premature ovarian failure. Therefore, laparoscopic surgical management is reserved for women that fail to ovulate after 6 courses of clomiphene, and who are not willing to go in further trials with elaborate and frequently expensive medical treatment with FSH and Gn RH agonists and antagonist.

It has been recently advised that the laparoscopic drilling should be limited to 5 drills in each ovary, each lasting for no more than 5 seconds.

11) *Pulsatile administration of Gn RH. (See later)*

12) *Weight reduction*

There evidence that persistent anovulation and PCOS is a multifaceted syndrome frequently showing metabolic components like obesity, dyslipidemia and increased insulin resistance. Significant weight reduction may improve the lipid and carbohydrate metabolism and may result in resumption of regular ovulation. Weight reduction can help PCOS cases having obesity, hyperinsulinemia, diabetes and virilization. The use of insulin-sensitizing agent, e.g., metformin to improve endocrine profile, reduce weight and restore fertility is subject to recent research.

II. Dopaminomimitic drugs (dopamine agonists)

The neurotransmitter dopamine is the strongest inhibitor of prolactin secretion at the anterior pituitary. Hyperprolactinemia results from deficient dopamine effect and is commonly associated with inhibition of Gn RH release by the hypothalamus. This results in suppression of gonadotrophin secretion and folliculogenesis. This is usually attended with amenorrhea, oligomenorrhea, anovulatory menstruation, or luteal phase deficiency. These conditions are described in more details in the chapter on Amenorrhea. The use of dopaminomimitic drugs correct hyperprolactinemia and result in resumption of ovulatory menstruation. There are now available a number of highly effective drugs including the ergot preparations bromoergocreptine (Porladel, Novartis), and Lisuride hydrogen maleate (Dopergine, Schering), Cabergoline (Dostinx, Pharmacia & Upjohn); and the synthetic nonergot preparation guinagolide (Norprolac, Novartis).

- **Bromocreptine** has been the mostly widely used, strong long acting dopaminommitic drug used for induction of ovulation in hyperprolactinimic patients. It is usually administered orally in 2.5 mg tablets, but is occasionally used in form of depo-monthly injection (Porladel-L.A). Bromocreptine directly stimulate the dopamine D_2-receptors in

the pituitary (also in hypothalamus and ovaries). This results in inhibition of prolactin secretion and restoration of the hypothalamuo-pituitary gonadotrophin functions. It may also increase ovarian responsiveness to gonadotrophins. Consequently, there is rapid restoration of normal ovulatory menstruation. The success rate of treatment of anovulation associated with hyperprolactinemia is very high (80% to 90%), and rapid; the patient may get pregnant early in the treatment before having her first menstruation during the therapy. The therapy corrects the commonly associated galactorrhea. Treatment with bromocreptine results in gastrointestinal, cardiovascular and central nervous system actions. The side effects are mainly nausea, diarrhea, dizziness, headache, fatigue, mood disturbance, and rarely postural hypotension. These side effects of bromocreptine are mainly caused by concomitant effects on D_1 receptors, and α 1 adrenergic and serotinine receptors.

- **Lisuride** (Dopergine) is an ergot derivative. It is an effective dopamine agonist, but it has not demonstrated any advantage over bromocreptine in controlled trials (or vice versa), neither from the point of view of effectiveness or side effect severity.
- **Cabergoline** is a strong, long lasting dopaminergic ergolin, which is usually used in the dose of 0.5 mg (one tablet) twice weekly. It can have a better side-effect profile.
- The newer **Ouinagolide** (Norprolac) possesses a selective binding to D_2-receptors of the prolactin secreting cells. It should, therefore have a stronger inhibitory effects on prolactin secretion, and milder side effects.

Indications for use of Dopaminomimitic drugs.

1. ***Amenorrhea, oligomenorrhea, dysfunctional uterine bleeding, anovulation or, corpus luteum deficiency associated with increased prolactin level (>20 ng/mL)***. There are many causes for hyperprolactinemia (detailed under Amenorrhea), including mainly mental distress, psychological disturbances, pituitary adenomas and use of certain neurotropic drugs. Some cases have functional disturbance not explainable by any cause. Amenorrhea associated with hyperprolactinemia is characterized by 1) presence of galactorrhea, 2) nonresponsiveness to progesterone withdrawal, and, occasionally associated with small uterus, and atrophic vaginal smear and appearance.
2. ***Galactorrhea.*** This is inappropriate milk secretion from the nipple, which is commonly associated with hyperprolactinemic amenorrhea. Galactorrhea varies in severity from expression of a milky drop on breast squeezing, to milky spurts on pressure, to spontaneous milk discharge and /or breast engorgement. Minimal galactorrhea may be present without any

associated increased prolactin; and may indicate increased sensitivity of breast alveoli to normal prolactin level. Galactorrhea in itself is occasionally a cause for seeking medical advise apart from amenorrhea or infertility.

3. ***Pituitary prolactinoma***

Prolactin secreting adenomas are the most common pituitary tumor. In autopsy series, they have been found in 10–27% of cadavers. However, they are frequently symptomless and usually do not disturb menstruation or cause infertility. The adenoma is benign and may enlarge very slowly or may not enlarge at all. They may not be associated with hyperprolactinemia. This may be due to either inherent inactivity of the cells of the tumors, or heterogeneity of the glycoprotein hormone. Prolactin circulates in various forms with structural differences resulting from polymerization, and variation in the extent of glycosylation and phosphorylation. The various forms are associated with varying bioactivity (manifested by amenorrhea or galactorrhea) and immunoreactivity (recognition by immunoassays). The predominant form of prolactin is little prolactin, which has more biological activity as compared to large sized variants, big prolactin or big-big prolactin. This heterogeneity of circulating prolactin may account for discrepancy between immunologically detected hormone level and the extent of associated disruption of reproductive function.

Women with accidentally discovered small adenoma (by coned lateral X ray view or CT scan) without having symptoms need observation at yearly intervals for symptoms resulting from pressure on optic chiasma and by repeating simple X ray examination. However, cases with endocrine effects like amenorrhea or galactorrhea or those suffering from pressure symptoms of a large adenoma are to be treated with bromocreptine and similar drugs. This latter treatment has largely replaced surgical treatment for both micro and macroadenomas (diameter $\geq$10 mm). Bromocreptine treatment results in rapid shrinkage of the size of the tumor and amelioration of hyperprolactinemia and disappearance of its consequences. The amenorrhea disappears and infertile women can conceive. In the latter event, the size of the tumor may increase under the effect of high estrogen secretion from the placenta. There has been a concern about the consequence of this enlargement on the optic chiasma. However, this enlargement is usually benign, and in the rare instances of occurrence of pressure on the chiasma the enlargement can be checked and ameliorated by reinstitution of bromocreptine treatment during pregnancy. Patients with symptomatic prolactinoma will need to use dopamine agonists indefinitely, because discontinuation results in recurrence of manifestations.

4. ***Benign breast disease like fibrocystic disease***

   Fibrocystic disease is effectively improved by bromocreptine treatment.

5. ***Ablactation and treatment of lactational breast engorgement.***

   Whenever there is a need to stop milk secretion in women who would like to wean their child or diminish it in case milk engorgement, a short course of a dopamine agonist is usually helpful. This treatment has largely replaced estrogen treatment, which carried the risk of predisposing to thrombotic complications.

6. ***Impotence*** associated with hyperprolactinemia is effectively improved by bromocreptine treatment.

7. ***Parkinsonism*** and related neurological disease can be effectively treated with dopamine agonists. Here, high doses of the drug are usually required.

8. ***Dopamine agonists in normoprolactinemic women:*** there have been a number of reports of successful bromocreptine treatment of cases of anovulation that have normal prolactin levels. The success rate is however less marked than in hyperprolactinemic women. The rationale of such beneficial effect in normoprolactinemic patient is the variable sensitivity of target tissue to prolactinemic. The decrease of prolactin may enhance the ovarian responsiveness to gonadotrophin. The heterogeneity of circulating prolactin, referred to above, may be the basis for difference between the immunological properties of the hormone (which is the basis of immune assays) and biological effect. The selection of normoprolactinemic patient who may benefit from bromocreptine treatment can be based upon: 1) clomiphene failure; 2) presence of galactorrhea; 3) negative progesterone withdrawal test; 4) presence of luteal phase deficiency; 5) demonstration of slightly increased level of nighttime or mid-luteal prolactin, 6) enhanced prolactin release after administration of TRH.

Dosage of bromocreptine

Gradual stepping up of the dose will build up tolerance to the drug and help to diminish the incidence of side effects. The starting dose is 1.25 mg (half a tablet) at bedtime, and after 3 to 6 day the dose is increased gradually until the dose of two tablets daily is reached, and this is persisted upon until the desired effect is reached. The dose rarely needs to be increased to 3 or 4 tablets daily, rarely to more than this. Women not tolerant to bromocreptine orally can be shifted to vaginal administration of the drug (using the same oral tablets). This results in effective absorption of bromocreptine. The newer costly drugs are specific D_2-receptor dopamine agonists as cabergoline or quinagolide may produce less severe side-effects. However, this does not always occur.

For women treated for infertility the therapy is continued for 6 months, after which the diagnostic workup needs to be reevaluated. Women with adenoma can use the drug indefinitely. However, the treatment can be discontinued after one year, and reinstituted when symptoms recur.

Results of Bromocreptine treatment

- In properly chosen hyperprolactinemic women presenting for infertility, the pregnancy rate is high (80% to 90% in most series). The success is usually achieved early in the treatment; there is usually no need to prolong the therapy for more than 6 months. Resistance to dopamine agonists is rare but is occasionally encountered. A shift to the newer D_2-receptors specific agonist may be occasionally successful in these cases.
- Abortion rate and preterm delivery are not increased in the resulting pregnancies.
- There has been no increase in multifetal pregnancy or in the congenital anomaly rate in bromocreptine pregnancies. There is the possibility of continuing bromocreptine or lisuride treatment in women who persist to have amenorrhea because of getting pregnant. This inadvertent use of these dopamine agonists in early pregnancy does not increase any congenital anomaly rate.
- The enlargement of the pituitary and the contained adenoma because of increased estrogen production during pregnancy, very exceptionally result in a dangerous mechanical effect. The patient should, however, be kept under observation for development of pressure symptoms on the optic chiasma.
- Hyperprolactinemic women can be successfully allowed to breastfeed their babies.
- There is generally no danger in allowing these hyperprolactinemic women to use low-dose COCs (containing estrogens).

Management of Bromocreptine failure

Rarely bromocreptine fails to correct hyperprolactinemia and the associated syndrome. This can result from inability to tolerate the required dose. These latter cases can be shifted to vaginal administration of the drug; the use of long-acting depot monthly injectable parlodel (parlodel LA) or to D_2-receptor specific dopamine agonists like Cabergoline or Quinagolide. Patients resistant to dopaminomimetic drugs can be managed by one of the following approaches:

1. Increasing the dose. There is rarely a need to increase the dose to 12 tablets (30 mg) daily.
2. Shifting to more potent D_2 receptor specific dopamine agonist.

3. Resort to surgery in cases of macro-adenoma threatening the optic nerve. A transsphenoidal approach is utilized. The use of the operating microscope has allowed the distinction of tumor tissue from the health pituitary component. Preoperative bromocreptine treatment may make the operation easier. However, surgery may fail to achieve complete cure (in about 50%), and recurrence may follow a period of improvement. Surgery may result in panhypopituitarism.
4. When infertility is the problem and conception fails to occur after reasonable correction of hyperprolactinemia, clomiphene or HMG stimulation can be superadded to bromocreptine treatment. These women can be also treated by pulsatile administration of Gn RH.

III. Human Menopausal Gonadotrophins (HMG)

Human menopausal gonadotrophins consist of a purified preparation extracted from the urine of postmenopausal women which is rich in FSH and LH. The commercial preparations available, Humegon, Menogen and Pergonal, contain 75 units of FSH and 75 units of LH per ampoule and which are given intramuscularly. This should not be taken as meaning that HMG preparations are containing equal amounts of FHS and LH, since the international unit of LH is much smaller than the IU of FSH. i.e HMG is predominantly an FSH preparation. These preparations have been widely used for induction of ovulation. However, there are two problems with this treatment: first, the high cost; and secondary the needs to monitor the ovarian response to therapy. There is a great deal of individual variability, and between cycle variability, in the same women, in response to HMG treatment. Overdosage can result in multifetal pregnancy and ovarian hyperstimulation syndrome (OHSS). Although a small amount of LH activity is required besides FSH for folliculogenesis, an excess of LH has been shown to occasionally interfere with follicular maturation and increase the chance of ovarian hyperstimulation syndrome. This can be due to the LH induced increase of local production of ovarian androgens. These have undesired paracrine effect on ovarian tissue. Purified HMG has now been produced (Metrodine) with minimal LH component, and is progressively replacing the original preparations, but with increasing the cost of therapy. Recombinant FSH (e.g. Purigone) has been recently produced through modern biochemical (recombinant) technology and is expected to be used particularly in assisted reproduction techniques (ARTs).

HMG is used to produce 1) ***controlled stimulation*** in treatment of cases of anovulation, or to result in ***controlled hyperstimulation*** required for IVF and similar techniques used for assisted reproduction (ART). The latter enhanced stimulation is required to allow procurement of multiple ova (usually 6–8) needed for in vitro fertilization, and the uterine transfer of about 3 embryos in order to achieve a optimal conception rate.

Selection of patients for HMG induction of ovulation

1. The best case should be the *hypogonadotrophin anovulation* i.e. hypothalamic amenorrhea. These cases are having potentially responsive ovaries with a rich endowment of ova. Patients with high FSH levels (hypergonadotrophic patients) are cases of primary ovarian failure and possess few ova, and have little chance of responding to HMG (see above, under Diagnosis).
2. Rare but suitable candidates are the unfortunate women with Sheehan's syndrome. This is there only hope to get pregnancy. Their other endocrine deficits must be cared for.
3. Due to expense and risk of HMG treatment, all other causes for infertility, mechanical or otherwise should be excluded before trial of use of HMG for induction of ovulation.
4. Cases of persistent anovulation who have failed to be *treated by clomiphene* can be successfully treated with HMG. These are cases with normal gonadotrophin levels but persistent anovulation. Because of the implications of HMG treatment, clomiphene treatment should be attempt first. However, cases with evidence of PCOS require increased care in monitoring of HMG treatment, because of their increased liability to hyperstimulation. These patients are having relative excess of endogenous LH and androgens, which also increase the abortion rate should pregnancy occur. Such cases may require prior or concomitant downregulation of ovarian function (as discussed under ART).
5. HMG stimulation and IUI for unexplained infertility

   Controlled HMG stimulation combined with timed intrauterine inseminations by husband sperm (IUIH) can improve fecundity rate in case of unexplained infertility. The rational is the correction of occult defects in either the female or male. Two IUIs, one after $\pm$18 hours and 42 hours after HCG injection are usually done.

   However, it is uncertain whether IUI is superior to timed natural course in these cases of unexplained infertility. However, the need for IUI is clear when there is abnormal cervical mucus factor or with a subfertile male. Controlled ovarian stimulation plus IUI is reasonably tried before resort to the more demanding ARTs.
6. HMG can be used for treatment of infertile women with hyperprolactinemia who are not tolerant to dopamine agonists.

HMG treatment schedule and its monitoring

The graded increasing dosage of HMG (step-up regimen) has replaced the fixed dosage regimen. Generally, one ampoule is given daily starting from the first day of a natural or induced period. The ampoule of dried HMG is dissolved in 1 ml of the diluent. The treatment is monitored daily (or every other day) after receiving the 5th injection, *better by both measurement of serum estradiol and by ultrasound* (better with the vaginal probe) measurement of the growing follicles. If the response is suboptimal by the 5th day, the does of HMG is increased to two ampoule (in 2 ml of diluent). After receiving the 7th dose if the response is still suboptimal the dose can be increased to three or four ampoules daily. The course usually takes 10–15 days; courses less than 10 day long have high abortion rate. The final goal is to reach a level of serum estradiol between 1000 and 1500 pg/ml and a diameter of the leading follicle between 20 and 24 mm. *Aiming at achieving the estradiol levels seen in the normal cycle (500 pg/ml) gives less conception rate*. There can be a number of subordinate follicles less than 17 ml, and in 5 to 10% of cycles there can be two leading follicles. During the five days preceding ovulation, the dominant follicle(s) exhibits a linear growth pattern of approximately 2 to 3 mm per day, followed by rapid exponential growth during the last 24 hours before ovulation.

The *endometrial thickness* as measured by the vaginal sonography indicates its responsiveness. The chance of pregnancy is greatest if an endometrial thickness between 6–9 mm or more is observed at the time of ovulation.

When estradiol and ultrasound monitoring indicate that the adequate response has been achieved, 10,000 unit of HCG (dissolved in one ml of the diluent) is injected 24 to 36 hours after the last does of HMG. The LH effect of HCG triggers ovulation. The couple is advised to have intercourse on the day of HCG injection, 24, and 42 hours later. Because of the fragility of hyperstimulated ovaries, further intercourse as well as strenuous physical exercise should be avoided, thereafter. Scheduled intercourse may be problematic for some husbands. Repeating ultrasound examination $\pm$48 hours after HCG will indicate the occurrence of ovulation. This is indicated by the disappearance of the leading follicle or its sudden regression in its size. A corrugated-wall corpus luteum may appear in its place; but this is not always visible.

In general, no supportive treatment is needed for the corpus luteum, except if Gn RH downregulation has been given (see later). In this case 2000 units of HCG can be given every other day for 3 doses, in addition to progesterone support in the form of two tablets of micronized progesterone (100 mg each) daily until the time of expected period. These can be used vaginally (probably with advantage). By that time, i.e. 14 to 20 days after HCG bolus, a sensitive

pregnancy test or serum HCG indicates the occurrence of pregnancy. This occurrence can be also suggested by the persistence the luteal phase rise of BBT, if this is traced.

With the utilization of this double monitoring of by estradiol assays and vaginal sonography, the occurrence of multiple gestation and ovarian hyperstimulation cannot be completely avoided *but can be effectively reduced*. The chance of this occurrence is higher if the above levels of estradiol are exceeded or if multiple maturing follicles are produce. It has to be remembered that hyperstimulation syndrome is precipitated by HCG injection. This injection should be withheld, and the cycle is better consequently wasted if the level of estradiol exceeds 2500 pg/mL or there are many ($\geq$5) large follicles ($\geq$17 mm) in the two ovaries.

It should be reemphasized again that patients with PCOS are more likely to develop ovarian hyperstimualtion, and should receive careful monitoring during HMG treatment.

Recently, cases with PCOS are treated by chronic low-dose HMG therapy. In this regimen, the starting dose is 37.5 to 75 IU/day and this dose is maintained for 14 days. If necessary, incremental increase in the daily dose is 37.5 IU (half ampoule). The increase is given after 7 day intervals, and if the ovary shows no significant response. This regimen reduces the number of leading follicles on the day of HCG administration, improves the pregnancy rate in patients with PCOS, and reduces the incidence of OHSS. The use of "pure" FSH or recombinant FSH is particularly indicted for patients with PCOS. Down-regulation of endogenous LH production by Gn RH agonists (or antagonists) is also beneficial for cases of PCO, but this may increase the chance of OHSS (see later, under ARTs).

Result of HMG treatment for ovulation induction

1. ***Pregnancy***

   If the cases are properly chosen, and are hypogonadotrophic and have no other cause for infertility the cumulative success rate should be high 90% after six treatment cycles. Normogonadotrophic women with anovulation achieve a lower rate of 40%.
2. ***Abortion*** rate is higher than normal; 25%. It is particularly high ($\pm$30%) in patients with PCOS.
3. The risk of ***ectopic pregnancy*** is increased with all methods of ovulation induction (except dopamine agonists), a consequence of multiple ovulation and high hormonal levels during the luteal phase (see under Ectopic Pregnancy).

4. Multifetal pregnancy: Prior to careful monitoring of HMG the multiple pregnancy rate was 30%. This has been brought down by experienced care to 10%, which is still much higher than the normal rate of 1%. High order of multifetal pregnancy is particularly high after HMG treatment, with the consequent risk of serious complications including abortion, preterm labour, toxemia and hemorrhage. The multiple pregnancies are usually secondary to multiple ovulations, i.e. frequency of monozygotic twinning also increases, but to much lower extent.

   In high order multifetal pregnancy 3 or more, reduction of the number embryos can be done (embryocide). The moral and ethical aspects of this fetal reduction are grave, but in view of the potential problems associated with high order plural pregnancy, it is usually done. Under ultrasonic guidance; the most accessible gestational sac is aspirated and a cardiotoxic drug (potassium chloride) is injected in or near the heart of the embryo. The procedure can be accomplished either transvaginally between the 8^{th} or 9^{th} week of gestation or transabdominally between 11 and 12 week. The dead embryo will be either absorbed or gets dried down and flattened on one aspect of the growing sac. The procedure needs experience and carries a risk of losing the whole pregnancy; however this should be lower than if all the embryos are allowed to grow. The risk and benefit have to be discussed with the patient and grave consideration should be given to ethical and personal factor.

5. ***Ovarian hyperstimulation syndrome (OHSS):*** It results from recruiting and stimulating a big number of ovarian follicles to grow and overgrow, and to produce a multitude of corpora luteal after ovulation. The spectrum of manifestations OHSS is big ranging from mild to moderate enlargement of the ovaries to huge enlargement, massive ascites, hydrothorax, hemoconcentration, hypovolemia, oligurea, electrolyte imbalance, nitrogen retention, hypotension and thrombotic complications. Adult respiratory distress syndrome may rarely develop and the condition may prove fetal. The OHSS is frequently classified into mild, moderate or severe according to the degree of ovarian enlargement, development of ascites and changes in the haemostatic system. The incidence of severe forms can be in the region of 1 to 2%. Because of the enlargement, torsion of the adnexa can occur. The syndrome is a temporary one resolving in about 4 weeks. However, if pregnancy begins the manifestation of ovarian stimulation can be perpetuated by placental HCG for up to 6 to 8 weeks.

   Pathogenesis of OHSS:

   The basic disturbance in severe forms OHSS is a shift of body fluid to a third space in the peritoneal cavity with the development of massive ascites. The genesis of ascites is unclear. It can be caused by very high estrogen level enhancing capillary

permeability and leakage of fluid from the capillaries on the ovarian surface to the general peritoneum and in the pleura. Local autocrine and paracrine effects of excessive histamine and prostaglandins produced in the hyperstimulated ovary can cause enhanced capillary permeability.

The shift of body fluid to the third space causes hypovolemia, and hemoconcentration. This in turn results in low blood pressure decreased central venous pressure and decreased renal perfusion. The latter results in a rise of the blood urea nitrogen, oliguria and low urinary sodium secretion. With less sodium reaching the distal conovoluted tubules of the kidney, there is a decrease in exchange of hydrogen and potassium for sodium, resulting in hyperkalemic acidosis. The latter is the cause of the adult RDS. The major clinical complication is increased coagulability of blood.

Management of OHSS

A. Prevention:

1. Careful monitoring of stimulation protocols (see above).
2. Cases of PCOS need special care. The chronic low dose therapy for these patients can lower the incidence of OHSS. At least this was hoped, but the hope was not always realized.
3. Administration of Gn RH analogues; (see later). Actually, this may increase the incidence of OHSS.
4. Withholding HCG administration if there is a threat of developing the syndrome (see above).
5. Avoidance of luteal phase administration of boaster HCG injection, unless Gn RH down-regulation has been used.
6. Administration of albumin at the time of HCG injection has been tried with some success. The albumin can help in keeping fluid in the intravascular compartment.

Therapeutic:

1. Mild cases need observation only.
2. Admission of severe cases to hospital, monitoring clinical condition, blood chemistries and hemostatic parameter. Abdominal and vaginal examinations should be avoided because of extreme fragility of the ballooned ovaries.
3. Intravenous fluid should be administered to correct the hypovolemia, hemoconcentration and reduced renal perfusion. About 4 liters are given daily in the form of lactated Ringers and 5% glucose. No saline, and no diuretics should

be given. Central venous pressure should be monitored and will indicate the volume of fluid to be infused, together with the urine output monitoring.

4. Anticoagulant should be considered in cases with severe hemoconcentration.
5. Aspiration of ascitic fluid can relieve severe respiratory difficulty. This is done under ultrasound guidance to avoid injury of the ovaries. Replacement of last albumin should be done by 10–20 g of human albumin (after exclusion of risk of transfer of HIV).

Hyperstimulation is an alarming but the condition is a temporary syndrome.

Management of HMG Failures

1. ***Repeated courses***, generally six courses need to be given before giving up. There is nothing bad on repeating the course on consecutive cycles, other than the intense disappointment of the couple with the failures.
2. ***Revise the diagnostic workup:*** Two points need be considered, the presence of additional cause for infertility and the raised FSH level.
3. Use of pure FSH or recombinant FSH (see above).
4. ***Gn RH Agonists*** (and antagonists):

Recognizing that women with increased endogenous LH and ovarian androgens do not respond to ovulation induction, attention was given to a method that could turn off the woman's endogenous reproductive hormone production. Thereafter, the ovaries are stimulated by carefully monitored administration of exogenous gonadotrophins. Gn RH agonist have been commonly used to downregulate the pituitary ovarian axis. They are long acting analogues of the natural Gn RH. The prolonged effect drain the pituitary cells from their gonadotrophin content and prevents fresh formation, which requires the pulsatite stimulation of Gn RH. Therefore, after the occurrence of an initial stimulation by this agonist, called "flare" effect there is suppression of gonadotrophin function. The normogonadotrophic anovulators are thus shifted to a hypogonadotrophic hypogonad state by the process of pituitary Gn RH receptor down-regulation and desensitization. Premature LH effects on the ovarian follicles, and the deleterious effect of excess local androgen can be diminished; and an improved therapeutic response to gonadotrophin stimulation is thus achieved.

A number of Gn RH agonists are available as a nasal spray (e.g. Buserelin) or subcutaneous injections (e.g. decapetyl or lupron). In a menstruating woman the Gn RH agonist is usual started during the mid-luteal phase; (beginning during follicular phase may

produced more pronounced initial "flare" which can cause breast tenderness or some bleeding). The administration is usually continued for 15 days. During the later part of these days, serum estradiol is measured daily or every other day. Suppression of gonadotrophin secretion is confirmed by an E_2 concentration of less than 25 pg/mL. The patient may miss the expected period and may complain of menopausal-like hot flushed. When the required suppression is achieved gonadotrophin is started as described above. The administration of the Gn RH agonist needs to be continued up to the day of HCG injection. A subnormal hormone production is expected from the formed corpus luteum due to depression of endogenous LH. Therefore the luteal phase of this cycle require support by administration of HCG (2,000 IU) twice, 3 days, and 6 days after ovulation, or progesterone supplementation beginning 3 days after ovulation (4 days after the ovulatory dose of HCG). It is usually given as intravaginal progesterone pessaries, which is continued for two weeks. The pregnancy rates with either treatment are the same but the use of HCG luteal support increases the risk of OHSS.

The Gn RH agonist down–regulation is widely used in vitro fertilization programme and for patients with PCOS who fail to respond to induction of ovulation by HMG stimulation.

The use of the agonists can have the following effects compared with HMG treatment alone:

1. Improves the per cycle fecundity.
2. Increase the number of HMG ampoules required.
3. May lower the abortion rate (has not been confirmed in RCT).
4. May diminish the number of cycles cancelled in IVF programme as a result occurrence of a premature LH surge and shedding of ova before being picked up, which if the patient has been treated by HMG alone.
5. It was hoped that the combined therapy can reduce the incidence of OHSS. However this was not fulfilled, and the opposite occurred, particularly when a luteal support by HCG is given which increases the chance of OHSS.

In recent years the *Gn RH antagonistic analogues* have become available. They work by competitive inhibition of Gn RH receptors. Antagonists avoid the initial flare, and can achieve the ovarian suppression in a shorter time. However, the experience with these Gn RH antagonists is still limited. They may produce allergic and occasionally anaphylactic reactions. It seems that these side effects have been overcome, and the antagonists have entered practice. They are used concomitantly with gonadotrophin induction of ovulation to prevent premature LH surge.

5. Addition of Growth Hormone to HMG treatment

Insulin-like growth factor-I (IGF-I) plays a critical paracrine and autocrine effect in folluclogenesis. Since the administration of growth hormone increases IGG-I production, the addition of growth hormone or growth hormone releasing hormone to HMG stimulation has been tried. Such combination may improve per cycle fecundity and reduce the number of HMG ampoules needed. However, Growth hormone is costly. Administration of recombinant growth hormone (Genotropin, Pharmacia & Upjohn) in a dose of 24 IU given intramuscularly every other day may facilitate ovulation induction in poor responders. However, it is quite expensive.

IV. Pulsatile Gonadotrophin Releasing Hormone administration Gn RH

Gonadotrophin-releasing hormone is a simple molecule (decapeptide) that has been synthesized long time ago. It can be used for induction of ovulation by a pulsatile administration from a continuously carried minipump. Attempt is made to imitate nature by administration of a bolus of Gn RH every 90 minutes throughout the treatment. Gn RH is administered constantly in a pulsatile fashion by a programmable portable minipump. Either subcutaneous or intravenous administration is possible. There is a special merit of the latter because it ensures the required spikes; the base of the blood level peak can be broad with subcutaneous administration. Consequently, the success rate is higher with the intravenous administration. The dose for subcutaneous administration is 20 μg per bolus; for intravenous administration, 5 μg per bolus. If the patient fails to respond (as assessed by weekly E_2 assay or vaginal sonography), the dose is increased by 5 μg increments.

The ovulation can be detected by one of the methods used for the purpose, like BBT chart or home done tests for identification of LH peak or daily vaginal sonography in mid-cycle. Usually ovulation occurs on day 14 of the cycle but this can vary between 10 days and 21 days. During this period, the couple are advised to have intercourse every other day. If this is difficult, the day of ovulation needs to be pinpointed either by the LH surge test or by sonographic monitoring; and intercourse is advised for 2–3 days after the event.

After ovulation, the corpus luteum is usually maintained either by continuation of pulsatile administration at the same rate during luteal phase or by administration of HCG in the dose of 2000 IU at the time of rise of BBT and then every 3 days for 3 doses.

Choice of patients: The patients who can use Gn RH pulsatile therapy are the same who can use gonadotrophin therapy (see above). The best results are obtained in cases with

hypogonadotrophic amenorrhea. The results are comparable with the two therapies as regard per cycle fecundity and abortion rate. For women with PCO the chances of success are lower, again comparable to HMG treatment. They are liable to hyperstimulation and Gn RH therapy should begin with lower doses. Such patients may require ovarian down regulation by Gn RH agonist simultaneous with the pulsatile Gn RH administration Gn RH agonist simultaneous with the pulsatile Gn RH administration.

Advantage of Pulsatile Gn RH:

1. Overall, less costly than HMG treatment.
2. Does not require extensive and expensive follicular monitoring. Gn RH pulsatile administration duplicate natural events.
3. Safer than HMG–OHSS and multiple gestation are much less frequent than with HMG therapy. Severe hyperstimulation is not seen and high order plural pregnancy is exceptional. ***It is unfortunate that this modality is not commonly utilized.***

Disadvantages of Pulsatile Gn RH:

1. The need to carry the pump day and night and care in observing its function may require a cooperative patient.
2. Thormbophlebitis may develop around the IV canula. This requires heparinizing the patient during the therapy by adding to the Gn RH solution heparin in the concentration of 1000 units/ml. This requires monitoring clotting time in the early days of therapy. The canula needs to be changed if a local reaction develops around it.

2. Management of luteal phase deficiency

- For definition and causes see under ***definition and causes of infertility***.
- For diagnosis see under Investigation of Infertile Couple.

Management

We are now in the era of evidence-based medicine. It needs to be mentioned at the beginning that there are reports that are challenging the methods of making the diagnosis of luteal phase defects and that denied that the efficacy of the various treatment modalities has been proven. The existence of the luteal phase defect itself as an independent cause of infertility or habitual abortion is being doubted. To date, there have been few studies in which women with documented luteal phase defects were assigned randomly to receiving drug therapy or a placebo.

Nevertheless, five types of treatment have been proposed for patients with inadequate luteal phase:

1. Clomiphene citrate.
2. Gonadotrophins.
3. Bromocreptine.
4. Progesterone.
5. HCG.

The ideal choice depends upon suspecting a particular cause for luteal phase defect.

1. ***Clomiphene citrate***

   Clomiphene citrate is the treatment of choice for patients with short luteal phase. These patients can have reduced levels of FSH in the early follicular phase that can be corrected by clomiphene administration on days 2 to 6 of the cycle.

   On the other hand there are the conflicting report of clomiphene itself causing inadequate luteal phase; the explanation offered is the antiestrogen effect of the drug on the endometrium.

2. ***HMG***

   Small doses of gonadotrophins can correct luteal phase defect. The mechanism is presumably the induction of better follicular recruitment and early development. Treatment should start on day 2 of the cycle, and with small dose like one ampoule daily and the dose is increased according to the response of the ovary (as discussed in the section on HMG).

3. ***Bromocreptine***

   Some patients with luteal phase defects have mild to moderate hyperprolactinemia (and may be galactorrhea). For these bromocreptine can improve the situation.

4. ***HCG***

   A dose of 2000 IU is given intramuscularly every other day, beginning on the day after the rise in BBT and continuing until menses begins, or if conception has occurred, until the 10^{th} week. On no account, the therapy is initiated before ovulation. HCG support of luteal phase has been widely used in IVF programmes both when HMG is given along or with down-regulation of pituitary function by Gn RH analogue. It is presumed that inadequate amounts of LH will be produced to support the corpus luteum of menstruation and of early pregnancy until the placenta takes over the function of progesterone production. This treatment carried two disadvantages: One is that it increased the occurrence of OHSS, and second, qualitative pregnancy tests cannot be used to diagnoses the occurrence of conception.

Only a rise in the concentration of serum HCG can diagnose the pregnancy. This is why this approach has been mostly replaced by progesterone administration.

5. ***Progesterone***

Progesterone treatment enhances secretory transformation of the endometrium and maintains the decidua until the placenta takes over the function of progesterone production. Accurate timing of ovulation is essential because the therapy is started at this day. This can be detected if daily sonographic assessment is made or when one of the tests used to identify the LH becomes positive. Progesterone should not be initiated before ovulation, because then it may block the ovulation or inhibit cervical mucus production. The therapy should be continued until the 10th week of pregnancy. Natural progesterone should be used; synthetic progestogen may not produce normal secretary endometrium, and may be luteolytic. One 200 mg pill of micronized progesterone is placed in the vagina or 12.5 mg of oily progesterone injected intramuscularly for the whole period. The only disadvantage of this treatment is that in absence of conception the menses may be delayed and BBT can remain elevated raising hopes that pregnancy has occurred. A sensitive serum pregnancy test can suggest pregnancy by 14th day after ovulation; a rising titer of HCG will confirm it.

3. Management of infertility due to tubal / peritoneal factors

Three main approaches are now available for management of infertility due to abnormalities in the tubes and/or pelvic peritoneum: a) correction by operative laparoscopy, or b) by microsurgery through laparotomy, or c) IVF / ET and other assisted reproduction techniques, thus bypassing the tubes. Generally, the choice between these three modalities depends on the severity of the pathology in the order given. However, bypassing earlier modality is sometimes determined by the expertise available, or the presence of another factor contributing to infertility. The choice is decided by a diagnostic, double puncture diagnostic laparoscopy. The availability and improved results of IVF/ET has diminished the resort to operative correction of tubal factor infertility, particularly the need for difficult tuboplastic operations. On the other side, most of the easy, minimal pathology cases are now treated by laparoscopic approach. Moreover, some cases of proximal tubal blocks can be tackled by a fourth option: transcervical cannulation of the cornual end of the tube with-may be balloon distension. This has been tried either through hysteroscopy or blindly fluoroscopic guide.

The age of the patient is an important factor in deciding the extent of resort to IVF/ET. If the patient is above 35 years, no time should be lost in trying first the operative correction.

a) Laparoscopic management:

This approach is usually resorted to for management of less advanced pathology including 1) pelvic adhesion, 2) endometriosis, 3) distal tubal block. For proximal or mid-segment tubal block or extensive peritoneal adhesions, the benefits of laparotomy and application of microsurgical approaches are usually utilized. However, advocates of laparoscopic surgery extend its application to severer cases. Comparison between the two approaches is most difficult to achieve through controlled studies. On one hand, some of the principles of microsurgical technique such as delicate tissue handling, and careful placement of fine sutures at strategic points cannot be fully accomplished in laparoscopic surgery. The larger instruments and large amount of tissue damage or necrosis in operative laparoscopy might increase the incidence of postoperative adhesions. On the other hand, there is *little chance of tissue dryness and less exposure* to environmental contaminants in laparoscopic approach. The *magnification* afforded by the laparoscope permits *pinpoint application of energy source* (diathermy, laser or ultrasound knife), and allows access to some areas with less trauma than is possible with laparotomy. In addition, the laparoscopic surgery has the advantages of minimal hospital stay, less pain and rapid recovery.

Laparoscopic procedures:

1. ***Adhesiolysis:*** Effective ovario-salpingolysis restores normal anatomy and enhance the chance of ovum pickup and its conduction to its distension in the uterus: The following principles should be applied:
    a) Proper identification of anatomical landmarks is the first requirement. Each structure should be undoubtedly identified before it is cut.
    b) Attempt should be made to reach to normal peritoneal planes, in order not to leave behind fresh raw surfaces.
    c) Proper utilization of traction and counter traction utilizing the uterine manipulator in addition to one or more grasping forceps. Excessive traction can however, result in avulsion or laceration and should be avoided.
    d) Adhesiolysis is achieved through a fine layer-by-layer approach using the hook scissors, blunt probe dissection, laser or ultrasound knife (Figure 7). Hydrodissection can be useful particularly avoiding vascular or ureteric injury.
    e) The adhesions are cut on a perpendicular plane. The bands should be removed rather than cut only.

f) Avoid use of unipolar cautary because of inherent risk of undesired conduction of energy and subsequent occult injury to abdominal structures such as the ureter, bladder or bowel.

g) Meticulous hemostasis should be achieved.

h) Frequent irrigation by Ringer's lactate removes blood and debris.

i) Tubal potency should be demonstrated by dye hydropertubation.

j) For denuded peritoneal surface, patches of methylcellulose. (Interceed; Johnson & Johnson) are placed in strategic locations.

k) Terminal irrigation with heparinized Ringer's lactate (5000 U/L).

l) Antibiotics during and after surgery.

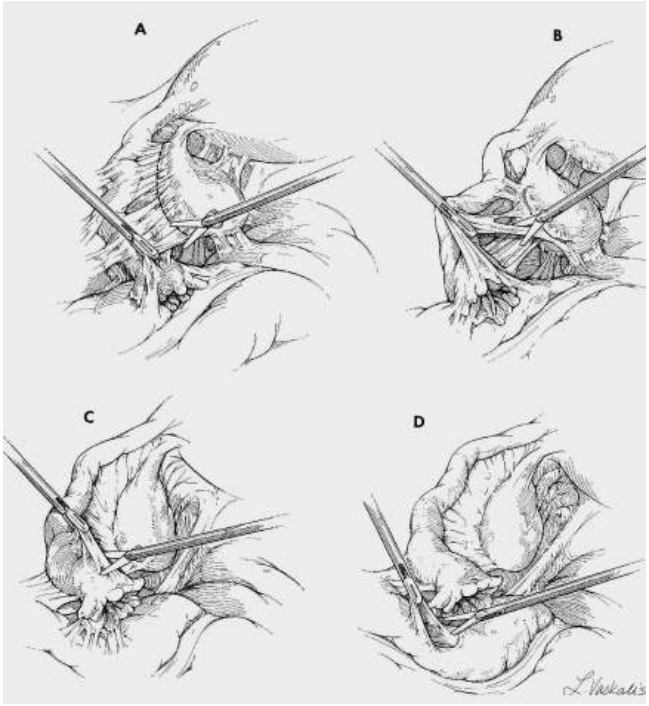
m) Systemic corticosteroids: short course for two week after laparoscopic surgery.

Ovarioadhesiolysis can be most beneficial in correcting peritoneal abnormalities, without the risk of adding new adhesion.

2. ***Fimbrioplasy***

- This procedure refers to reconstruction of *existent* fimbria, while the term salpingoneostomy is used to describe the surgical creation of new tubal ostium in a totally occluded fallopian tube. Fimbrioplasty corrects phimosis, agglutination or clubbing of the fimbriated end.
- After ovarioadhesiolysis has been achieved, hydrodistention of the fallopian tube is done by means of transvaginal insufflation through a canulated uterine manipulator with diluted methylene blue dye.
- The distal tube is stabilized by an atraumatic grasper and the ***tubal dimple is identified***. This is the point of convergent of cicatricial lines of occlusion and is frequently identifiable. It should be carefully searched on the upper anterior aspect of the clubbed fimbrial end, i.e. on the antimesosalpingeal end. Its identification minimizes the trauma entailed in releasing fimbrial agglutination, this may require cutting (by laser, needle diathermy or endocoaculation) of a crossing band of adhesion (Figure 8).
- The tubal dimple is dilated using tongs (probes) or a fine alligator-type forceps. The closed forceps is advanced into the dimple with use of little force. Once the tubal lumen is entered the jaws are opened and slowly withdrawn. This will break down line of agglutination. The procedure may need to be repeated in a perpendicular plane. The dye come out and the fimbria *flower out*. Perifimbrial band should be transected.
- The eversion of fimbria may be achieved, if not spontaneously restored by fine touches of a ball electrode using *low voltage diathermy* to result in heat dissecation of the serosa around

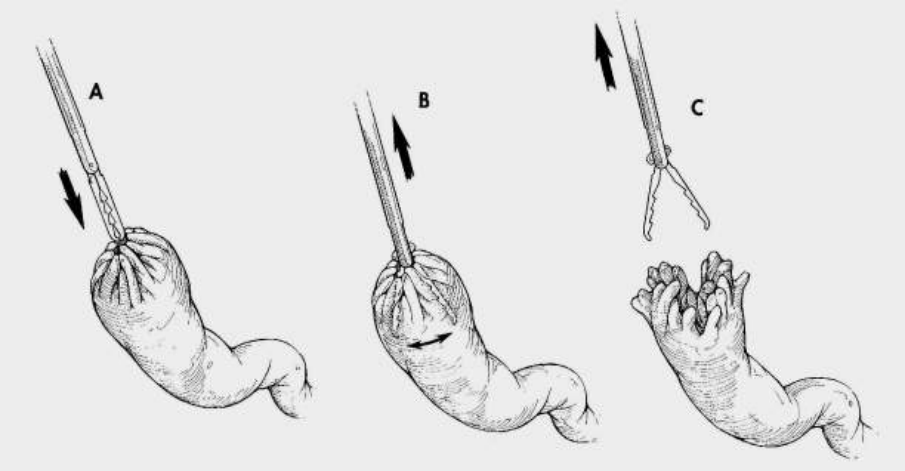
the fimbrial end. The subsequent fibrosis ensures better eversion of the fimbria. If more eversion is needed, this can be achieved by one or two sutures, using extracorporial or intracorporial knotting approach.



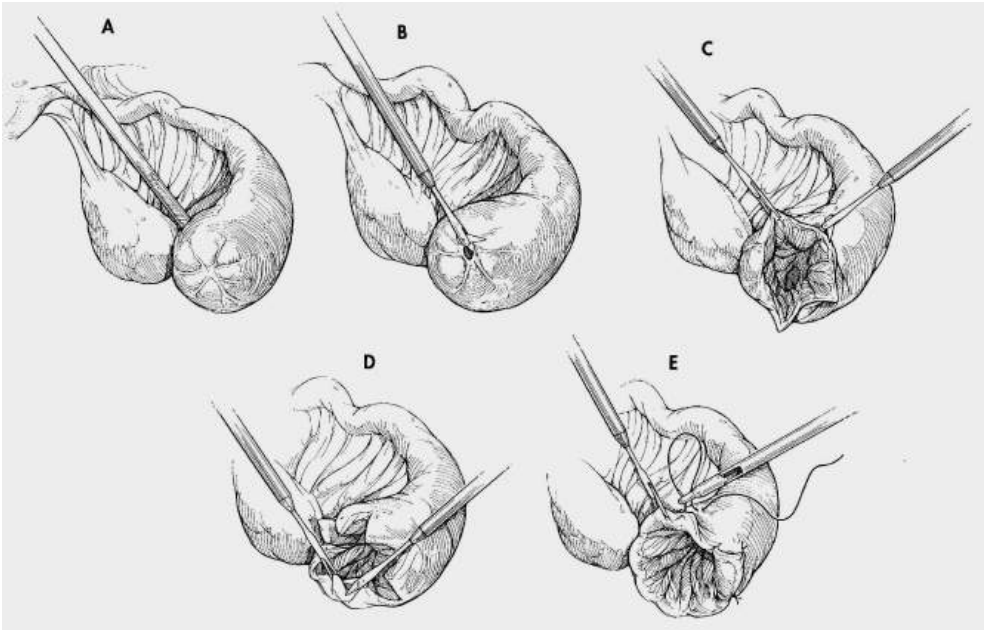
Infertility: Figure 7: Salpingo-ovariolysis; A, *Division of adhesions in a well-exposed area.* ***B,*** *Adhesions are stretched and divided one layer at time parallel to the organ of interest.* ***C,*** *Broad adhesion are freed at all points and removed from the peritoneal cavity.* ***D,*** *Salpingo-ovariolysis being completed (After V. Gomel and P.I. Taylor: Diagnostic and Operative Laparoscopy, Mosby 1995)*

3. ***Salpingoneostomy***

In the experience of the author (so far), a better neostoma can be achieved by open surgery. However, the proponents of laparoscopic approach claim success in creating satisfactory stomas. The steps are essentially the same up to distension of the tube. The scarred tissue beyond the distension needs to excised. A variety of instruments may be used to incise the obstructed end including scissors, micropoint cautary or high power density laser beam. The avascular lines of agglutination are carefully incised (Figure 9). Hemostasis is achieved. Eversion of edges should be achieved by fine stitches.



Infertility: Figure 8: Fimbrioplasty: Disagglutination of the fimbria*; **A,** The 3 mm alligator jawed forceps is introduced through the stenosed opening. **B**, The jaws of the forceps are opened within the tube. **C,** The forceps are gently withdrawn while keeping the jaws open.(After V. Gomel and P.I. Taylor: Diagnostic and Operative Laparoscopy, Mosby 1995).*



***Infertility: Figure 9; Salpingoneostomy; A,** The occluded distal end of the tube usually has a centrally placed avascular area from which avascular scarred lines extended in a cartwheel manner. **B,** The first incision is made along an avascular line towards the ovary. **C,** Avascular line is incised viewing from within the tube along the circumference of the initial opening. **D,** Cutting along the avascular lines is continued until a satisfactory stoma is fashioned. **E,** The flaps may be reverted by placement of two-or three 6-0 absorbable synthetic sutures. (After V. Gomel and P.I. Taylor: Diagnostic and Operative Laparoscopy, Mosby 1995)*

4. ***Tubal reanastomasis***

Tubal reanastomosis for reversal of sterilization is better done through laparotomy utilizing a minilaparotomy approach. The fine manipulations and the number of fine sutures required are difficult to achieve via the laparoscope.

The *results* of laparoscopic surgery for distal tubal obstruction and peritoneal factor infertility are approaching those of microsurgery after laparotomy. The results are better when the operative procedure is minimal, the success varying from conception rate of 70% to 30%. Each patient should be evaluated individually, and the expertise of the surgeon is the decisive factor in the choice of laparoscopy versus laparotomy .

b. Transcervical Tubal Cannulation

Proximal fallopian tube obstruction is present in about 10–20% of hystrosalpingographies in which the tubes fail to be visualized. Even after exclusion of the possibility of inadequate filling of the uterus, this finding can be due to physiological spasm in the interstitial segment of the tubes in as many as one third of the instances. Pharmacological agents like isoxsuprine or terbutiline do not always succeed in eliminating the spasm. Laparoscopy under general anesthesia is the most effective method to rule out physiologic spasm and evaluate other pelvic and fallopian tube pathology. The next step should be an attempt at transcervical tubal cannulation, and this should precede (wherever expertise is available) the resort to microsurgical correction of proximal tubal block and IVF/ET. This attitude has been implied by: 1) histopathological assessment of excised proximal tubal segment with microsurgical approach which did not always show organic block but clogging by proteinaceous material, mucous plugs or debris, and 2) the poor result of microsurgical correction for this type of blook. Two approaches have been utilizing for transcervical cannulation:

1. ***Fluroscopic*** approach, which is favored by interventional radiologists. The approach utilizes angiographic techniques; under fluroscopic, guidance. Tubal cannulation can succeed using coaxial catheter. Some used a catheter fitted with a distal balloon that permits distention of the interstitial and isthmic region. Cannulation by a coaxial catheter is frequently enough to ensure tubal patency.
2. ***Hysteroscopic*** approach permits directing the catheter into the uterotubal junction under vision. It is the approach favored by gynecological endoscopists. Furthermore, the concomitant use of laparoscopy helps to demonstrate tubal patency, and provides information about the rest of the tube, and about the uterine cavity.

There are reports about establishment of tubal patency by transcervical cannulation in about *one third of cases* with demonstrated proximal block. Where expertise is available, the procedure should be tried before resort to IVF/ET or to the difficult uterotubal implantation.

c. Microsurgical correction of peritoneal and tubal factors contributing to infertility

The microsurgical approach to pelvic reconstructive surgery has nearly doubled the pregnancy rate of conventional macrosurgical techniques. The expertise in microsurgery is now generalized to all surgical procedures dealing with pelvic and intraperitoneal structures, particularly in young patient and those interested in further childbearing: Microsurgical approach depends upon: 1) ***conservation of structures and tissues,*** 2) ***restoration of the anatomy*** to its normal appearance, 3) and taking certain measures to ***prevent recurrence or de novo formation of adhesions***.

- ***Principles of Microsurgery:***

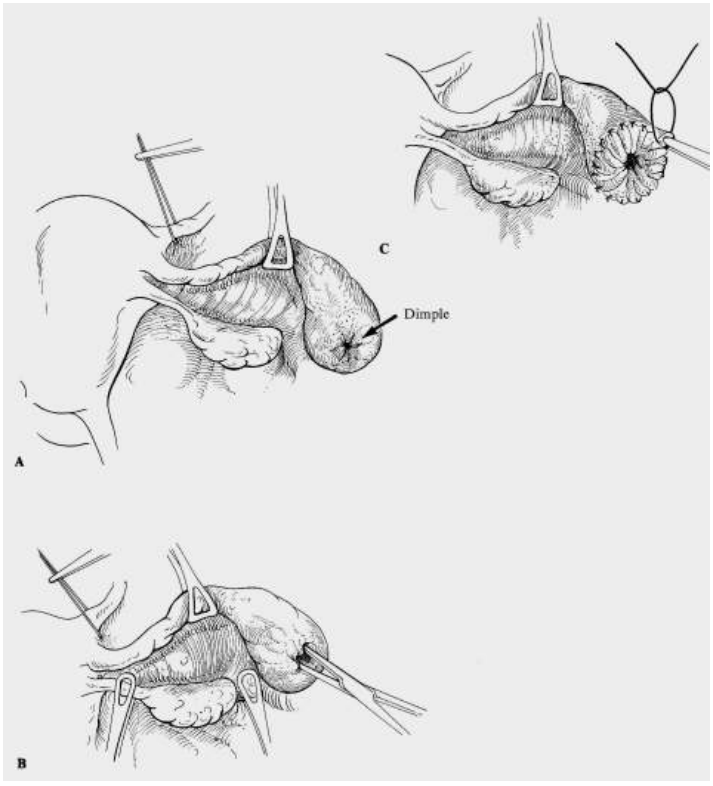
1. **Proper choice of cases:** This depends upon adequate preoperative investigations. This includes both hysterosalpingographyic and laparoscopic assessment. These should be viewed as complementary methods; the first provide an assessment from within and the later an assessment from the outside. The feasibility and the prospect of correction of the anatomy should be assessed before laparotomy-microsurgery. At present time, minimal-pathology cases should go to laparoscopic surgery and marked- pathology cases should go to IVF. These have diminished the resort to tuboplasty with laparotomy.
2. ***Adequate exposure:*** The patient is put in a combined dorsal and lithotomy position with fixation of a foley's catheter in the bladder. Exposure is usually achieved through a pfannenstiel's incision and four-way self retaining retractor. Thorough hemostasis of wound sides is necessary. The incision needs to be adequate to avoid excessive manipulation of pelvic structures. A uterine manipulator provided with cannulation is used to allow for repeated introperative pertubation with a diluted dye solution or normal saline. The intestines are packed away by *plastic cover abdominal packs.* Otherwise, *gauze mobbing should be avoided* since it can result in injury of peritoneal surfaces. Removal of effused blood should depends upon a continuous irrigation with heparinized Ringer's solution combined with frequent suctions.
3. Constant attention should be made to ***avoid serosal insult, which can be the starting point of formation of fibrinous clots***. Such insults can result from: 1) tissue trauma, 2) hemorrhage, 3) ischemia, 4) infection, 5) dryness, 6) foreign body reactions (suture materials, talk power on gloves and shreds of gauze material), and 7) leaving raw surfaces.

Pathogenesis of peritoneal adhesions:

a. A cascade of events leading to fibrin clot formation occurs following a serosal injury. This phenomenon involves release of prostaglandines, lymphokines, bradykinine, histamine chemotactic factors as a result of serosal injury. This inflammatory reaction enhances serofibrinous exudates. The fimbrial clot formation is decided by the balance of coagulation enhancing and inhibiting system and the fibrinolytic system. The fibrinolytic system is inhibited by serosal traumatization and ischemia, which result in, decreased levels of local plasminogen activator (PA), a fibrin-lysing enzyme. This reduction in PA activity contributes to increase in fibrin deposition.
b. The above insults can result in effusion of serosangunous material from the peritoneal surface. This forms a fibrin clots or bands between peritoneal surfaces. The fibrin clots are later invaded by leucocytes, macrophages, and later fibroblasts forming bands of granulation tissue. The bands are later transformed to fibrous bands.

4. ***Measures to avoid adhesion formation*** include the following:
   a. Avoidance of tissue dissection resulting from exposure to the heat of operation theatre lamps. This can be prevented by continuous irrigation with heparanized Ringers (5000 Unit of heparin to one liter of the solution).
   b. *Magnification* using an operating microscope has been used for tubal microsurgery. Magnification allows micromanipulation. However, most cases do not require the use of the microscope, except for isthmic tubal anastmosis. A loupe that gives a magnification of x 6 times is usually enough, and frequently no magnification is required at all.
   c. *Entering in proper planes: This is the most important point for avoidance of recurrences of adhesion and formation of neoadhessions*. The surgeon should strive to reach and open cleavage lines. This gives the best healing, without the need for peritonization.
   d. Minimal handling of the tube. Teflon or glass rods are used to manipulate structures.
   e. Hemostasis is meticulously maintained using bipolar cautary, which restricts the burn area and reduce tissue trauma.
   f. When needed sutures are made with fine (6–0 or finer) synthetic absorbable material like polyglycolic acid (Dexon), polyglactin (Vicryl), or monofilament polydioxanone (PDS II). These suture material minimize foreign-body reactions and are preferred over more strongly antigenic material such as chromic catgut.

g. Reperitonization is accomplished using strategically placed sutures. However, tension across suture lines should be avoided because it stimulates rather than prevents adhesion formation (Figure 10). Occasionally raw surfaces are better left behind instead of apply sutures under tension. If there has been no damage of the underlying tissue small bare areas can get peritonized without adhesion formation. Omental grafts are better avoided.



Infertility: Figure 10: Microsurgical Fimbrioplasty*.(After R.W. Kistner, G.W. Patton, and E.S. Tagrin: Atlas of Infertility, Little, Brown and Comp. 1975)*

h. Large raw surfaces can be covered by oxidized regenerated cellulose (Interceed or Corelex) barriers. Experience with these absorbable fabrics has been shown to lower adhesion formation after microsurgery.

i. Leaving behind in the peritoneum of either a *crystalloid solution* like Ringer's lactate or normal saline containing heparin and corticosteroids, or a viscid solution of *Dextran 70*. Dextran is antithrombotic and coats raw areas within the abdomen. It draws fluid into the peritoneal cavity reducing the clot adherence and preventing surface approximation. Clinical experience has indicated its effect as adjunct to microsurgery in preventing adhesion formation. However, this point has been doubted however, in controlled trials using an early second-look laparoscopy.

j. Preoperative administration of prophylactic antibiotics. These should be broad-spectrum combination, and if there is a possibility of subclinical chlamydeal infection, these should comprise doxycycline.

- ***Operative procedures***

a) For distal tubal surgery

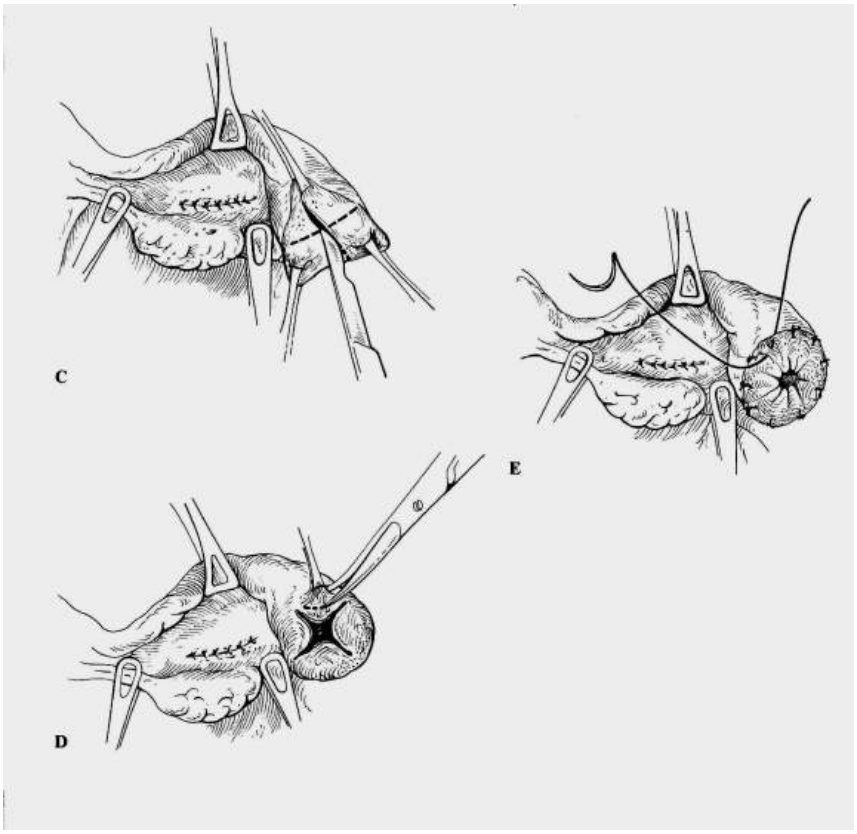
After careful and meticulous salpingo-ovariolysis, either a fimbrioplasty or neosalpingostomy is done as described under operative laparoscopy. The petals of the neosalpingostomy can be everted by 2 to 4 strategically placed fine sutures (Figure 11). Tubal patency is demonstrated at the end of surgery by hydropertubation.

Laparotomy allows better utilization of microsurgical principles relative to what is possible in laparoscopic surgery, e.g. ensuring entering in the right planes, less manipulation of structures, and better placement of sutures in strategic points. However, it remains to be seen whether the advantages gained in laparoscopic surgery outweigh the above merits of laparotomy-microsurgery. Controlled, randomized trials are lacking, and difficult to achieve.

Overall, term pregnancy rates after neosalpingostomy are variable, but are generally below 30%. Unfortunately, ectopic pregnancy occurs in about 10% of conceptions. These rates depend upon the degree of the tubal damage at the time of surgery and the type of operation needed. The best term-pregnancy rates are achieved after salpingolysis (70%), followed by fimbrioplasty (60%), and salpingostomy (30%). The results are also strongly influenced by the expertise in microsurgery. The outcome can improve by prolongation of the follow-up.

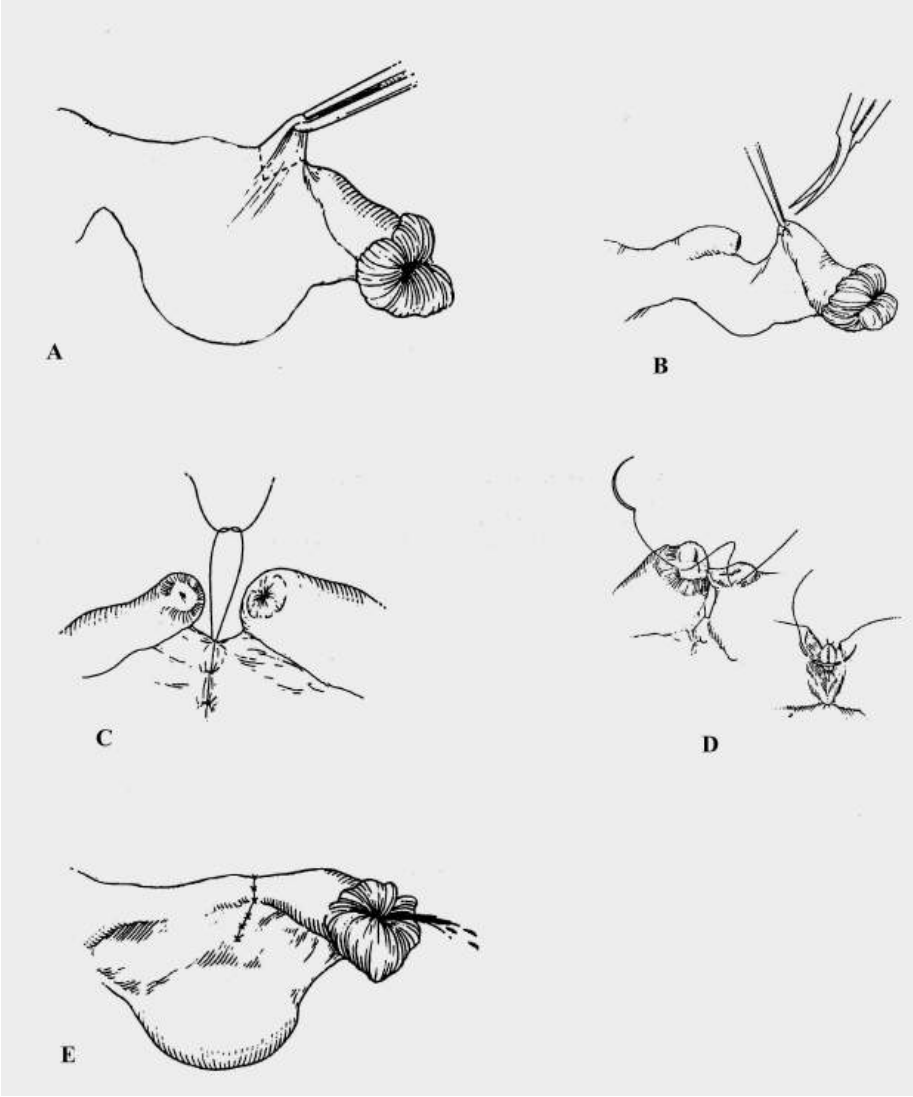
The use of carbon dioxide laser has become increasingly used in infertility surgery. It is expected that the laser beam produce less tissue injury. However, there is no reliable data indicating its superiority over standard microsurgical practice in randomized trials.

The results of microsurgery will need to be compared with the results of IFV/ET. Pregnancy rate rates after these ART approaches have dramatically improved, and are improving. A clinical pregnancy rate of about 25% per retrieval cycle resulting in about 20% live birth rate are generally reported. It is thus apparent that with respect to distal tubal disease, that only surgical procedures in which the likelihood of success equals or surpass this rate should be attempted. When the tubes and ovaries are relatively free of adhesions, and the tubes are not thickened or dilated, salpingoplasty remains a usable alternative to IVF/ET. It leaves behind an apparatus that can be used repeatedly to achieve pregnancy. The age of the patient is a decisive factor for extent of resort to IVF. The patient should not be left to approach 40 years before this is used.



Infertility: Figure 11: Microsurgical Salpingo-ostomy*.(After R.W. Kistner, G.W. Patton, and E.S. Tagrin: Atlas of Infertility, Little, Brown and Comp. 1975)*

b) Mid tubal obstruction



Infertility: Figure 12: Microsurgical tubal reanastomosis.

This comprises resection of the occluded part and end-to-end anastomosis. This need mainly arises for reversal of sterilization; the use in other types of mid-segment block e.g. postinflammatory block, is much less used; and yields least promising results. Microsurgical reversal of sterilization yield good results ranging from 50 to 90% depending on the length of the segment destroyed by the sterilization technique and the microsurgical expertise.

Steps (Figure 12): 1) the old scared segment is excised. 2) Tubal patency is demonstrated in both segments of the tube. 3) The mesosalpinx is over sewn using 6-0 synthetic absorbable sutures to closely approximate the divided segments. 4) Anastomosis is

performed with four-quadrant sutures (at 6, 3, 9, and 12 Oclock) of 8-0 synthetic absorbable sutures involving the inner parts of the myosalpinx 5) These are oversewn by four other similar sutures which involve the serosa. The help of a loupe is usually enough for the required magnification. b) Patency is demonstrated by transcervical hydropertubation. Generally, a stint is not required.

Pregnancy rate correlates with the final length of the tube. The highest rate is achieved when this is >4 cm. This shows the merit of achieving tubal sterilization with techniques entailing damage for the shortest segment of the tube.

c) Proximal tubal block

Transcervical tubal cannulation should be attempted before the resort to microsurgery (see above). If this fails, microsurgical correction can be tried if the rest of the tube is healthy. This can be usually achieved by isthmic-cornual anastmosis. Magnification is usually required. The tube is transversely incised at the point of the proximal tubal obstruction. The isthmus is shaved back stepwise until a patent segment is demonstrated by the transcervical hydropertubation. Usually the obstruction does not involve the whole interstitial portion of the tube. With a stint passed down the two tubal segment and left curling in the uterine cavity, the two patent segments are approximated by four-quadrant suture involving the muscularis and utilizing 8–0 absorbable synthetic sutures. The serosa is reapproximated with interrupted 6–0 sutures. Patency is demonstrated at the end of surgery. The stint is transcervically hooked out 10 days after the surgery.

Isthmo-cornual anasmosis has mostly replaced uterotubal implantation. The latter is still needed if the interstitial portion of the tube is not identifiable. The tube is incised at the point of proximal occlusion. The isthmus is shaved back in layers until the interstitium is reached. If patency is not reestablished, a hole is bored using diathermy or a *reaming device* (reamer) at the cornua. The distal tubal segment is split longitudinally into two halves for a short distance. A 4–0 synthetic absorbable suture is passed in each segment and the two ends of the thread are left long. The long threads are passed through the hole in the cornua and through the upper and lateral wall of the myometrium. This draws in the split ends of the tube into the uterine cavity. An additional 4–0 sutures are placed in the serosa to close peritoneal detects and take pressure off the anastomosis. *Alternatively, an open technique* is used. The uterus is entered by a transverse incision in the posterior aspect of the fundus until the endometrium is entered. The prepared distal segment is sutured directly to the endometrium

with 4 – 0 suture material. The uterine incision is then closed in two layers, the latter of which involves the serosa of the tube.

Disadvantages of tubal implantation include; shortening of the tube inherent in the pull-through procedures. Postoperative chronic pelvic pain and menorrhagia are common. There is a real threat after tubal implantation of the occurrence cornual rupture during pregnancy that can necessitate hysterectomy. *This together with modest pregnancy rate of generally less than 20% makes IVF/ET a better alternative to tubouterine implantation.*

d) IVF-ET

This technology has largely replaced difficult reconstructive surgery for tuboperitoneal-factor infertility (see later under ARTs). It has been recently demonstrated that the results of IVF/ET can be improved by prior removal of hydrosalpinx. The latter pathology may result in flushing out the transferred embryos by tubal fluid in the hydrosalpinx.

4. Treatment for Cervical Factors Abnormalities

The treatment of poor cervical mucus include giving estrogen like 0.625 mg of conjugated estrogen daily for the 8 or 9 days preceding the expected time of ovulation. If there is evidence of chronic cervicitis with thick yellow mucus, culture for chlamydia is done and course of doxycycline is given if positive. Cervical cautary may be done but care should be exercised not to destroy the whole cervical mucus.

If the cervical mucus is having a pH below 7, precoital vaginal douches with 1 tablespoon of sodium bicarbonate in half a liter of water is tried .

The recommended treatment for a couple with persistently abnormal postcoital test (PCT) is *intrauterine insemination* (IUI). This is to be tried, first without ovarian stimulation, if there are evidences that the female is regularly ovulating. If these trials fail on 2–3 occasions, the IUI is to be tried after controlled HMG ovarian stimulation. If these fail and in couple with subfertile semen quality, ICSI will be needed.

IUI should not be done by whole semen sample; this will always fail due to lack of capicitation of sperm and the presence of certain constituents of seminal plasma that interfere with sperm. The sperm should be prepared by washing the sperm in order to 1) dilute decapicitation factors, 2) remove reactive oxygen species; 3) result in a high recovery of spermatozoa 4) separate sperm of better quality.

Indications of IUI:

1. Persistently inadequate postcoital test in absence of any other contributing factor.
2. Infertility associated with failure of deposition of sperm in the vagina due to failure of maintenance of erection, or retrograde ejaculation (IUI is done by utilizing washed postcoital urine).
3. Infertility associated with subfertile semen quality i.e. male with semen showing marginal grade. Cases with poor abnormal semen grades are better treated by ICSI.
4. Unexplained infertility. It is advantageous to perform controlled ovarian hyperstimulation by gonadotrophins, followed by IUI.

Technique of IUI:

A semen specimen is collected by masturbation and ejaculated into a sterile container. The specimen is transferred to a sterile, tapered centrifuge tube, and washed by one of the following techniques:

1. Simple wash

This washing separates sperm from the harmful constituents present in seminal plasma. It is the standard minimal treatment of semen used for IUI, and IVF. Commercially available sperm wash medium (e.g. human tubal fluid medium, HTF) is stored at 4°C and warmed before use in an incubator to 37 °C. A 1:5 dilution is achieved by adding 4 ml of warmed sperm wash medium to every 1 ml of semen sample. The specimen is then centrifuged for 10 minutes at 300 g. The supernatant is discarded using a transfer pipette. The sperm pellet is resuspended in 4 ml of warmed sperm wash medium and centrifuged again for 10 minutes. Again, the supernatant is discarded with a transfer pipette. The sperm pellet is resuspended in 0.3 ml (total volume) of warmed sperm wash medium, and this suspension is used for IUI.

One of the commercially available polyethylene insemination catheter, or a 5F or 8F feeding tube is used for IUI. Usually no dilation of the cervix or sounding is required. The cervix is cleaned with a dry swab and the specimen is gradually deposited high in the fundus of the uterus. A preparatory “dummy” cannulation of the cervix is needed, if cervical stenosis is suspected in order to avoid sounding the uterus at the time of IUI. This sounding, if done at the time of IUI, may stimulate uterine spasm (due to release of prostaglandins) which can reduce the chance of success.

2. Percoll technique (discontinuous density gradient) for sperm selection

This technique separates motile sperm from immobilized and defective sperm, and gets rid of white cells and seminal plasma debris. Percoll (silicone particles coated with polyvinyl pyrrolidone) provides a viscous medium for active sperm to penetrate in. Sperm are layered on top of a percoll column of gradients of differing density. After centrifugation, the sperm in the densest fraction are retrieved by further washing and centrifugation, and the final pellet is suspended in 0.4 ml, which is used for insemination.

Steps of discontinuous density gradient sperm selection:

Step 1: Prepare an isotonic solution of 9 ml of Percoll and 1 ml of regular human tubal fluid (HTF) medium.

Step 2: Prepare 80% solution by adding 3.2 ml of isotonic solution to 0.8 ml of regular HTF medium = 4.0 ml.

Step 3: Prepare 55% solution by adding 2.2 ml of isotonic solution to 1.8 ml of regular HTF medium = 4 ml.

Step 4: Column preparation:

1. Place 2 ml of the 80% solution on the bottom of the tapered centrifuge tube.
2. Slowly add 2 ml of the 55% solution without disturbing the interface.
3. Slowly add up to 2 ml of whole semen.
4. Centrifuge at 300 g for 20 minutes: during this, the sperm will more readily move down the Percoll gradient; the best motile sperm will move down to the lowermost part of the column.

Step 5: Discard everything down to 0.5 ml above the pellet by an aspirating pipette. Add 3 ml of regular HTF medium and centrifuge for 5 minutes at 300 g.

Step 6: Discard supernatant. Add 0.4 ml of HTF medium and perform the intrauterine insemination as above.

This method generally results in a sperm concentration below 50% of the total sperm in the ejaculate, but since it separates out most of the immotile sperm, it recovers almost same number of motile sperm as originally present in the semen sample. This technique also removes most of the harmful contaminants. *Percoll separation is needed when there is high percentage of immotile or poorly motile sperm in the semen*.

3. Swim-up technique:

This rather easily performed technique is also used for separating motile sperm from immobilized sperm, pus cells, and debris in seminal plasma. The sperm are washed as above (method no.1). Then, an aliquot of 0.5 ml of washed sperm is layered beneath 2 ml of Ham's F–10 solution in a 12 x 75–mm culture tube. After 60 minutes incubation at 37°C, the upper 1ml layer is aspirated carefully with a Pasteur pipette and discarded; this removes most of the debris. After an additional hour, the upper interface is aspirated and washed twice in serum-supplemented wash medium. The separated spermatozoa are then used to perform IUI.

This type of sperm wash increases the percentage of motile sperm. These methods should not be used for oligospermia or in specimens of sperm with very poor motility. Only 10 to 20% of sperm are recovered with procedure. *If less than one million total motile sperm are recovered the chance of fertilization are poor.*

Swim-up technique is recommended for sperm contaminated with bacteria. Treatment of infections with suitable antibiotic should precede IUI. If pus cells persist the swim-up technique can then be tried with the addition of antibiotics (penicillin and streptomycin) to the washing solution. This has been shown to result in negative culture of the treated washed sperm.

Timing of IUI:

Using IUI is done twice in each cycle; the first on the day of presumed ovulation (as described before), and the second 36 to 48 hours later.

Conception rate after IUI:

In couples with defective PCT a conception rate of about 40% is expected. The pregnancy rate is lower in presence of subnormal seminal quality. In idiopathic infertility, the conception rate is definitely improved with IUI following controlled ovarian hyperstimulation.

5. Treatment of Uterine Factor-related Infertility

A. Treatment of intrauterine adhesions (IUA)

Hysteroscopic lysis under direct vision has become the standard treatment of IUAs. It has replaced blind curettage or breaking adhesions after hysterotomy. The 8–9 mm operating hysteroscope is used with a low-viscosity media (e.g. glycine solution or normal saline) in a continuous flow system. The use of these media has largely replaced the use of the viscous, messy hyscone. To avoid loss of low viscosity medium by intravasation into the general

circulation and the risk of circulatory overload, a continuous attention is given to the volume of the inflow and outflow. A special system is now available for continuous monitoring of the deficit in the washing fluid.

The adhesion are cut in their center using flexible or semirigid scissors, or a loop resectoscope. Diathermy or laser energy is used. NO attempt is made to excise adhesion.

The adhesiolysis is begun inferiorly and carried upward until the uterine architecture has been normalized. Complete lysis of adhesions can be achieved even in cases with extensive scarring. For the latter cases, simultaneous laparoscopy should be used to monitor the hysteroscopic activities, in order to reduce the risk of uterine perforation.

Following hysteroscopic adhesiolysis an inert IUD (better Lippes' loop) is placed in the uterine cavity to prevent reformation of adhesion, and left for 3 months. To stimulate the growth of endometrium, three 21-day courses of conjugated estrogen are given during the 3 months following the surgery. During the last 5 days of each monthly course, MPA is added to produce secretory transformation and withdrawal bleeding. The adequacy of hysteroscopic surgery is assessed after three months by either HSG or hysteroscopy.

The overall pregnancy rate following hysteroscopic treatment of IUAs is approximately 60 to 75. However, there can be higher than normal abortion rate and increased chance of placenta accrete.

Hysterotomy may be necessary in patients with extensive adhesions involving the endocervix and isthmus uteri in which access to the upper fundus is unsuccessful with the hysteroscope.

B. Treatment of congenital anomalies in mullerian fusion

HSG and hysteroscopy delineate the uterine defect and indicate the needed treatment. Septate and subseptate uterine cavity is corrected by hysteroscopic surgery. Hysteroscopic resection of a uterine septum has now replaced hysterotomy approach. This is hysteroscopic surgery is usually done with laparoscopic control to avoid perforating the uterus.

Scissors (or resctoscope) are passed through the operating hysteroscope with an inflow-outflow system. The central part of the septum is divided starting from its lower edge and proceeding upward until the uterine cavity is normalized. The fibromuscular band of tissue retracts immediately and does not usually bleed. The postoperative management is the same as with IUAs.

Hysteroscopic resection of uterine septum has been shown to be highly effective in reducing the occurrence of abortion. However, recent RCTs of hysteroscopic resection of

septate and subseptate uterus versus no treatment has given equal results as regard completion of pregnancy.

When the two cavities are widely separated hysteroscopic correction is not possible. A concurrent cervical incompetence can be associated and some of these patients may be helped by cervical cerclage early during subsequent pregnancy in order to carry pregnancy to near term. If this repeatedly fails, metroplasty may be performed. This approach is resorted to in cases with history of recurrent abortions. This metroplasty operation carry a definite risk of rupture uterus during subsequent pregnancy, and are to be treated by elective cesarean section after reasonable viability of the fetus has been achieved.

C. Treatment of Myoma associated with infertility

Myomas are very common tumors of the uterus, found in more than 30% of women above the age of 30 and are usually multiple. Myoma is a highly benign tumor, malignant transformation occurs in less than 0.01% of myomas. The pathogenesis of myoma remains unclear.

Most myomas are asymptomatic and when they symptomatize they result in menorrhagia. Infertility, abortion, premature labor and abnormal presentation may be associated with myomas. It needs to be remembered that in the management, *that myomas are part of a syndrome including, besides the presence of the tumors, infertility, frequent anovulation, endometrial hyperplasia, cystic ovaries, dysfunctional uterine bleeding, endometriosis, peritubal adhesion and increased incidence of endometrial cancer.* Though commonly associated with infertility, myomas rarely contribute to infertility by their simple mechanical presence. The submucous and intramural myomas have greater impact on reproductive capacity than subserous myomas. Submucous myomas can hinder endometrial nutrition and offer a poor implantation site resulting in abortion and infertility. Large intramural myomas can cause enlargement of the uterine cavity, possibly resulting in poor sperm transport or occlude the intramural part of the tube. They can interfere with uterine enlargement during pregnancy, and cause abortion or premature labor, by inciting frequent abnormal uterine contractions.

Myomectomy in women presenting for infertility should be preceded by complete diagnostic workup of infertility to exclude other contributing factors. *Before resort to myomectomy, correction of other factors contributing to infertility is to be tried, particularly when the myomas are not distorting the uterine cavity or resulting in abnormal bleeding.*

Myomectomy can be achieved by *hysteroscopic, laparoscopic* or *open* surgery. The choice between the three modalities depends upon the number of the myomas and their location in the uterine wall. Any of these approaches can be preceded by 3–6 months treatment by Gn RH agonists (for details see under Tumors of the Corpus Uteri) that can serve to 1) reduce the size of myomas, 2) diminish their vascularity, 3) and gives time for improvement of associated anemia. However, Gn RH treatment may occasionally result in less definition of the pseudo-capsule around the myomas and render their subsequent enucleation more difficult.

a. Hysteroscopic myomectomy

This approach is best suited for polypoidal submucous myomas, or small interstitial one (<8 cm) projecting into the cavity by more than half of their circumference (as demonstrated by USG and hysteroscopic assessment).

A continuous-flow operating hysteroscope is used with scissors or resectoscope. The pedicle of a myomatous polyp is cut. If it is wide, it needs to be coagulated. If the myomas are small less than 2 cm, it can be pulled out through external os. Large myomas require morcellation. The sessile myoma can be progressively shaved by the resctoscope using unipolar diathermy. Occasionally a two-stage procedure can be done. In the first session, the myoma is shaved down to the endometrial surface. Some weeks later (under further Gn RH treatment) the remaining part will be found extruded into the uterine cavity and become easier to resect. Hysteroscopic myomectomy can be lengthy and should be monitored by laparoscopy. The outflow of the distending solution should be observed to prevent the development circulatory overload and hyponatremia.

b. Laparoscopic myomectomy

In the opinion of the author, it is better to be reserved, for women not interested in future fertility. The imperfect hemostasis and uterine wound coaptation affordable by operative laparoscopy may increase the chance of postoperative adhesions. Certainly, the technique needs experience and should be only used with a single or few subserous myomas of a small size. Morcellation (with automatic morcellator) will be needed to get rid of the enuculated myoma and the uterine wall is closed by laparoscopic suturing.

C. Conventional Myomectomy

Laparotomy is still the usual approach for removing myomas, particularly when infertility is a problem. The use of microsurgical approach is highly needed to diminish the chance of formation of adhesions. ***The following principles should be observed in myomectomy operations:***

1. Performing the operation through the *smallest possible laparotomy*. The uterus can be delivered in the wound after removal of accessible myomas through a small laparotomy incision. This can allow subsequent exteriorization of the uterus through the small laparotomy wound.
2. *Avoidance of use tourniquet or clamping* of the isthmus, which was traditionally used in attempt to diminish intraoperative bleeding. Recognizing bleeding vessels and controlling them by diathermy coagulation or underrunning sutures is done stepwise, and will ensure less bleeding from the final bed. Moreover, the tourniquet can result in devitalization and ischemic injury of serosa, which can start formation of adhesion.
3. Utilize the *smallest possible uterine incision* in the middle-line(least vascular) of the anterior wall and by utilizing side tunneling to remove most of the myomas. Myomas on the side of the uterine incision can be mobilized and pushed towards the incision.
4. *Avoidance of posterior wall incision* as far as possible.
5. *Avoidance of opening the uterine cavity* unless the preoperative ultrasonographic examination has revealed the presence of a polyp. This is to avoid the chance of IUA formation.
6. *Bonney's hood operation* for removal of a posterior wall myoma can compromise the patency of the proximal segment of the tubes. This is better avoided in patients interested in future fertility. A carefully sutured posterior wall incision is a better compromise. One or more myoma may be left behind, if they are situated in a bad site on the posterior wall. Careful transcavitary resection can be done for posterior-wall myomas abutting on the cavity.
7. *Careful closure of the myoma bed* by two or three tires of sutures. This ensures proper hemostasis and prevents leaving behind hematomas in the uterine wall.
8. The *serosal suturing* should be done by fine atraumatic needles and fine suture material, utilizing synthetic absorbable suture material (Dixon or Vicryl) and interning the serosal edges leaving no suture on the serosal surface (as done in subcuticular closure of the skin wound).
9. *Avoidance of serosal dryness* and leaving behind some heparinized Ringer's solution, (more details are given under tubal microsurgery).

6. Treatment Modalities for Male Factor Infertility

A male factor is involved in 30% to 40% of cases of infertility, either as a sole cause or as a contributing factor. Male factor infertility carries relatively less chances for corrective treatment than female factors. The situation has changed after introduction of ARTs particularly ICSI. This male factor infertility is a heterogeneous disorder with few defined diseased entities. The majority of subfertile men has no definite cause. This is the major obstacle to improvement of pharmacological therapy.

The selection of a treatment regimen for an infertile man depends on the history, the presence of endocrine abnormality, and the results of semen analysis; and testicular biopsy. Based on these data, patients can be placed into major diagnostic categories but overlap between causes and combination of causes can be present. These groups include:

1. Idiopathic oligospermia / asthenospermia.
2. Varicocele–associated oligospermia.
3. Genital tract infections: Pyospermia and prostatitis.
4. Immunologically–determined subfertility.
5. Hypogonadotrophic hypogonadism.
6. Obstructive azoospermia.
7. Non-obstructive azoospermia.
8. Retrograde ejaculation.
9. Impotence.

The following description is not meant as belittling the role of specialized andrologists. Close cooperation is required between the gynecologists and andrologists in many infertility problems.

1. Idiopathic oligo/asthenospermia

Oligoasthenospermia is the commonest abnormality found on male evaluation and is usually idiopathic. It does not comprise one pathological entity. Medications that have been used for idiopathic oligoasthenospermia include 1) androgens; 2) gonadotrophins; 3) antiestrogens; and 4) certain miscellaneous drugs (however, the therapeutic values of these therapies have not been proven by placebo controlled double-blind trials), 5) correction of general medical disease e.g. diabetes, thyroid disorders; 6) Intrauterine insemination; and 7) ICSI. The latter two approaches are now increasingly used for management of these cases of subnormal semen quality. ICSI is preferable to IVF in male factor infertility, and should be the primary treatment in cases with poor

semen quality, whenever a density of less than 1,000,000 sperm can be reached in the final product of washing of semen.

1. Androgen therapy:

There are two forms of androgen therapy: low dose testosterone and high dose testosterone regimens. In the low-dose testosterone regimen, weak androgens are given as oral daily dose of either 50 mg of mesterolone or 10 mg of flusxymesterone (e.g. Proviron, Schering) for at least 3 months. This is in an effort to supplement allegedly inadequate endogenous production of testosterone in the testicle, and thus stimulating spermatogenesis. Generally, this treatment is rarely effective.

Rebound therapy involves the administration of higher doses of testosterone like testosterone enanthate (e.g. Sustanon, Organon), 200 to 500 mg intramuscularly every 2 weeks for four doses. These doses suppress LH and spermatogenesis. Following the cessation of therapy, sperm production usually resumes and in some patients, sperm concentration may rebound to higher levels than at the initiation of therapy. This treatment is also rarely effective in achieving enhanced conception rate.

2. Gonadotrophins

Gonadotrophin therapy has been tried with patients with idiopathic oligospermia in a manner similar to that for patients with hypogandotrophic hypogonadism. The latter is a rare entity in male infertility. However, such therapy does not enhance fertility in patients with idiopathic oligo-asthenospermia. The dosage usually used is 2000 IU twice weekly for 8 weeks.

3. Gn RH therapy

Pulsatile gonadotrophin releasing hormone therapy has been tried with men with idiopathic oligospermia, but with no much success.

4. Antiestrogens

The most popular drugs used to treat oligospermia are antiestrogen like clomiphene citrate or tamoxifen citrate. Clomiphene is usually administered intermittently in the dose of 50 mg daily for 10 days every month for 3 successive months, or as a continuous regimen of 25 mg daily for three months. Tamoxifen is given in a daily dose of 10 mg for three months. These antiestrogens act as competitive inhibitors of estrogen action by occupying estrogen receptors in the hypothalamus. This interferes with the feedback signals of estrogens which are either locally produced by the leydig cells or through peripheral conversion of testosterone. Because of preventing any negative feedback of these estrogen on the hypothalamus, secretion of Gn RH is enhanced. This in turn, stimulates increased

gonadotrophin secretion, which in turn increases testosterone production and induces germ cell maturation. Local effect of the antiestrogens on sperm production has also been suggested.

This antiestrogen therapy has been shown to increase sperm density and motility and to enhance pregnancy rate. However, recent placebo-controlled trials have failed to confirm the relative beneficial effect. Blurring of vision, headache, hot flushes and diminished libido are possible side effects of treatment with antiestrogens.

5. ***Other drugs***: that have been tried in the treatment of idiopathic oligospermia include vitamins: A, C, E, zinc, rutin, other antioxidants and bromocreptine. None of these has proven successful in treatment of idiopathic infertility. The role of stopping or reducing smoking has been frequently suggested for the purpose.
6. ***Avoidance of tight under wears***: have also been suggested in the management of the condition. This can obviate high temperature in the scrotum, which can inhibit spermatogenesis.

2. Varicocele associated infertility

A varicocele is a dilatation of the scrotal portion of the pampiniform plexus-internal spermatic venous system, which drains the testicles. Varicocele is more common on the left side. Since 1950s, varicocele has been implicated as a cause of male infertility. Support for this notion is derived from the reportedly increased incidence of clinically evident varicocele in men evaluated for infertility (30%), as compared to the incidence of 10% in unselected males. Marked varicoceles are associated with small sized or softer testicles. Recently there has been implication of subclinical varicocele, which is clinically not detectable but diagnosed by Doppler ultrasonography in male infertility. This notion is presently at the best, controversial. The pathophysiology of varicocele-induced infertility remains undefined. Proposed mechanisms include higher testicular temperature, hormone imbalance, hypooxia secondary to defective venous drainage, and reflux of adrenal or renal metabolites.

High ligation of spermatic vein is the usual treatment, which is widely used, in subfertile men with varicocele. The clinical studies that demonstrated improved sperm quality and increased pregnancy rate have been mostly uncontrolled. Prospective controlled studies reported no improvement in pregnancy rates with varicocele ligation, particularly when done for subclinical varicoceles. More data are needed before the conclusion can be made that varicocelectomy definitely improves pregnancy rate. Radiological embolization of spermatic

vein has recently been tried for varicocele, but the beneficial effect, again awaits controlled trials.

The present attitude is that most of the cases of varicocele-associated oligospermia are to be treated as the idiopathic group.

3. Treatment of genital infection in infertile men

- The presence of increased pus cells in semen analysis should indicate urological assessment including culture and sensitivity of the semen and/or prostatic secretions.
- Men with proved bacterial prostatitis should be treated for 6 weeks to 3 months by an appropriate antibiotic; which is determined by sensitivity tests.
- Men with nonspecific urethritis should be treated for chlamydia infection with oral doxycycline 100 mg two times per day for 10 days.
- The treatment of idiopathic pyospermia, which resists antimicrobial treatment, is by IUI after sperm washing. ICSI should be a last resort.

4. Treatment of infertile couples with antisperm antibodies

- Corticosteroids have been given in 3-month course to infertile men with antisperm antibodies fixed to sperm, particularly when a defective postcoital tests is repeatedly demonstrated. This treatment can diminish the percentage of antibody-carrying sperm but it has not been proven that this therapy improves conception rate.
- IUI with swim up washing of sperm can increase the conception rate.
- ICSI should be a last resort.

5. Hypogonadotrophic hypogonadism

This is a rare type of hypogonadism in the male. These men will show low levels of FSH, LH and testosterone, and frequently show oligospermia or non-obstructive type of azoospermia (fructose positive). The etiology is either congenital or acquired. The former include Kallmann's syndrome or an idiopathic isolated hypogonadotrophin hypogonadism. Acquired causes include tumors, infections, infiltrative diseases, and autoimmune hypophysitis. Prolactin secreting pituitary tumors are rare in men, are usually large at the time of discovery and therapy must be primarily directed to reduction of the size of the tumor. This can be achieved by bromocreptine; surgery is rarely indicated.

The treatment (in the absence of hyperprolactinemia) is either by exogenous gonadotrophin or Gn RH pulsatile pump. Gonadotrophin therapy is either by HCG 5000 IU twice weekly for 24 weeks. If this fails, HMG or purified FSH is added in a dose of 75 IU daily for 3 months. Pulsatile Gn RH is the specific treatment. This is given by an infusion pump.

6. Treatment of Obstructive Azoospermia

The main causes of obstructive azoospermia include epididymal obstruction secondary to acute and chronic infection, inadvertent ligation of the vasa during herniotomy or pelvic surgery, congenital absence of the vasa, or their ligation for sterilization. Men with obstructive azoospermia have normal hormones and normal sized testes. The size of the testes is a good indicator of spermatogenesis; the seminiferous tubules form about 90% of the size of the testicle. With obstruction of the vasa or epididymides, the semen volume is normal, and it is alkaline and fructose positive (fructose is produced in the seminal vesicles). If the obstruction is at the level of the ejaculatory ducts, the semen volume is small, the pH acidic, and little or no fructose is present. Patients with congenital absence of the vasa are also having fructose negative semen due to the usually associated absence of the seminal vesicles.

A testicular biopsy is performed to differential between obstruction and spermatogenic arrest and defective spermatogenesis. If normal spermatogenesis is found, microsurgical repair of obstruction of obstruction may be attempted. Vasography may be performed at the time of surgery to demonstrate ductal patency proximal to obstruction. Extensive damage to duct of system usually makes the surgery useless. Vasectomy reversal yields the most successful results for this type of surgery. However, restoration of patency does not always result in restoration of fertility: Ideally, sperm can be demonstrated in the ejaculate in about 80% vasectomy reversal, but pregnancy can be achieved in only 50%. There is an inverse correlation of success rate and the duration of ductal obstruction. The deficit is due to formation of antisperm antibodies as a result of the trauma of surgery and prolonged retention of sperm.

ICSI has recently given new hope for these men with obstructive azoospermia, and diminished resort to corrective surgery. The sperm can be obtained by needle aspiration from the seminal vesicles or biopsy from the testicles.

7. Treatment of non obstructive azoospermia

A good percentage (±60%) of cases of azoospermia are non-obstructive. These patients have fructose positive semen. These men either have evidently small or normal sized tests, usually the gonadotrophins (particularly FSH) are elevated and testosterone is low. If the testes are of normal size, the hormonal profile is normal, testicular biopsy usually shows various grades of defective spermatogenesis or arrest. Frequently some sperm can be demonstrated (in reduced density) in the lumen of seminiferous tubules. The subnormal sperm formation results in absence, or scarcity of sperm in the ejaculate. In severe form various grades of spermatogenic arrest no perm is found in the biopsy.

It is increasingly appreciated that non-obstructive azoospermia is commonly associated with some, albeit reduced spermatogenesis. The sperm reach the ejaculate when they are produced above a certain critical population (*the spill-over level*). Moreover, spermatogenic arrest can be focal and not all parts of the testes are showing spermatogenic failure. Sperm that can be used for ICSI can be obtained from multiple testicular samplings. Many techniques are available for testicular sperm retrieval ranging from minimally invasive testicular fine needle aspiration (TEFNA) to multiple open testicular biopsies, which usually can be performed under local anesthesia.

ICSI has opened new chances of treatment of these men with non-obstructive azoospermia. The sperm can be obtained from the pellet of centrifuged semen or from testicular biopsy. Recently, spermatides obtained by testicular biopsy have been used in ICSI, with some successes. It is always advisable to try to get sperm by centrifugation of the ejaculate before resort to testicular biopsy to obtain sperm; the fertilization capacity of the former type of sperm is better than any of those obtained by the latter approach.

Freezing of embryos have allowed keeping them for transfer in subsequent cycles, in case of failure of contraception in the stimulation cycle. The further attempts at transfer of such frozen embryos are usually done without ovarian stimulation. This can reduce the chance of abortion that is observed in stimulation cycle.

It is important to appreciate that the prognosis of ICSI greatly depends upon the age of the wife, and its used should not be delayed much.

8. Retrograde ejaculation

Disruption of the innervation of the bladder neck can result in retrograde ejaculation. Diabetes mellitus complicated by peripheral neuropathy, multiple sclerosis, medical therapies

interfering with sympathetic tone, transuretheral resection of the prostate, bladder neck surgery and extensive pelvic surgery can lead to retrograde ejaculation.

Patients with retrograde ejaculation report absent or near absent ejaculate following orgasm. The diagnosis is confirmed by small volumed ejaculates and identification of large numbers of sperm in a postejaculatory urine. Patients with medical causes for this condition respond to sympathomimetic drugs. If medical therapy is not indicated, the urine is alkalinized and sperm are recovered from postejaculation urine specimen; washed in Ham-F 10 tissue culture medium with superadded albumin, and used for IUI, or failing this for ICSI.

9. Treatment for impotence

The various medical and surgical treatments of impotence are beyond the scope of this text.

7. Unexplained Infertility

Definition and prevalence:

Unexplained infertility is usually defined as the presence of infertility, for at least one year despite of documented ovulation, tubal patency, and normal semen analysis. It needs to be noted that this definition is not universally agreed upon (some require lapse of 2 years). Unexplained infertility is a diagnosis of exclusion, and its prevalence depends on the care exercised in excluding these three basic causes. The published prevalence of unexplained infertility appears to be decreasing, possibly as a result of improved diagnostic technique. Presently, the prevalence is thought to be in the region of 10% to 15%.

Diagnosis (see above):

With presently available diagnostic tools the diagnosis of unexplained infertility is only justified after excluding abnormalities by the following investigation

- Carefully done laparoscopy.
- Semen analysis in two or more reliable labs, who use the WHO recommended criteria.
- Documented evidence of ovulation by either midluteal progesterone value of 10 ng/ml or a midluteal endometrial biopsy showing secretory endometrium.
- The female partner should be regularly menstruating.

Repeating some of the basic assessments is indicated if the infertility specialist doubts the reliability of any component of the aforementioned diagnostic workup.

Postulated causes of unexplained infertility:

1. **Age of the wife**

Fecundability begins to decline after the age of 30 years and the decline becomes marked after 40 years. This has been shown by follow-up of untreated couples, results of IUI with donor insemination, and in IVF-ET series. Cycle fecundability declines to 4% after the age of 40 years.

2. **Male factor** (with normal semen analysis)

Subtle abnormalities in sperm may escape detection by the standard semen analysis (utilizing the WHO criteria of normality). This has been supported by the recent observation in IVF/ET programs that fertilization rate is lower in couples with unexplained infertility relative to couples with tubal factor infertility. However, poorer ovum is an equally possible contribution to this observation. It has been suggested that sperm function tests like the zona-free hamster egg can be used to detect such subtle abnormalities in sperm. However, the value of addition of this test to IVF program did not improve much the prediction of fertilization in IVF.

The fertility of the male though continuing to old age, it definitely declines with age beyond the fifties.

3. **Cervical factor and abnormal postcoital test**

The postcoital test (see under cervical factor) is widely used test. However, it is not universally standardized. Recent evidences have questioned the validity of the test. This does not mean however, that the cervical factor is not important for fertility, but it only means that the postcoital test is not a very useful diagnostic tool.

4. **Immunological factors**

The presence of antisperm antibodies in the blood of the circulation of the female or male partner has been suggested to interfere with sperm motility and oocyte fertilization. However, the detection of serum antisperm antibodies as an isolated factor among couples with unexplained infertility has not been shown to alter the prognosis of infertility.

However, the presence of antisperm antibodies on the surface of the sperm have been shown to be associated with reduced sperm motility, increased agglutination of sperm, unsatisfactory postcoital test, and reduced fertility.

Treatment of the male or female partners with corticosteroids have not resulted in lowering the titer of antibodies in the circulation, increasing the percentage of motile sperm

in the semen, decreasing the percentage of sperm carrying antibodies, improving the postcoital test, or improving conception rate in unexplained infertility.

IUI with washed sperm in stimulated or unstimulated ovarian cycles, is the treatment commonly used when a big percentage of sperm carry antibodies on their surface.

5. **Subtle ovulatory dysfunction**

Subtle ovulatory dysfunctions have also been postulated as an etiology of unexplained infertility. This should be uncommon in women with regular cycle and adequate rise of progesterone during the midluteal days. The latter can be judged either retrospectively from the day of the subsequent period or prospectively from detecting the day of LH peak by certain do-it-yourself assays on urine, or by repeated midcyclic sonographic assessment utilizing the vaginal transducer.

The lutinized unruptured follicle syndrome (LUFS) has been suggested to be a cause of infertility in couple in whom the hormonal evaluation is normal yet conception does not take place. The condition is diagnosed by repeated VUSG assessment after the midcycle showing persistence of the dominant follicle coupled with normal luteal phase levels of progesterone. Although the condition arises sporadically with some frequency, no evidence suggests that it occurs consistently in certain women.

6. **Luteal phase defect**

Luteal phase defect LPD has been suggested as a cause of failure of embryo to implant in the endometrium. Recently the significance of LPD in infertility and even the mere presence of the syndrome have been questioned (see above).

7. **Subtle hyperprolactinemia**

Enhanced peripheral sensitivity to prolactin in normoprolactinemic women have been suggested to cause anovulatory menstruation and LPD. This has been the basis of administration of bromocreptine to normoprolactinemic women with ovulatory defects. However, these reports were not based on controlled randomized trial and the result of such approach is less marked than the beneficial effect of the use of bromocreptine in hyperprolactinemic patients. (See under treatment of anovulation).

8. **Endometriosis** (see later under Endomewtriosis). Early endometriotic change can be detected by laparoscopy.

9. **Subtle uterine cavity abnormalities**

Minimal intrauterine adhesion may be missed in hysterosalpingography (HSG), particularly when a big volume of the dye is injected without screening by fluroscopy. This

is the basis for performing office hysteroscopy in all cases of unexplained infertility. The value of this practice depends upon the care exercised in performing HSG.

10. Subclinical genital tract infection

Infections in the upper genital tract result in tubal or peritoneal abnormalities, which are detected on investigating tubal factor. In addition, postinflammatory obstruction of the epididymis or vas can result in azoospermia. However, in the past decade, there has been concern on the effect of subtle, subclinical genital tract infections in couples with unexplained fertility i.e. without producing anatomical changes in the duct system. Interest has centered on *mycoplasmas* and *chlamydia trachomatis* infections. These infections may result in subtle changes not detectable in the routine evaluation of infertile couples i.e. unexplained infertility.

a. Mycoplasma

Mycoplasma is unique microorganisms with some characteristics of both bacterias and viruses. They are of a size similar to large viruses, but can survive and reproduce in cell free media as bacteria. The main species infecting the genital tract of men and women are *Ureaplasma urealyticum, and Mycoplasma hominis*. They are mainly transmitted by sexual intercourse.

Subclinical myoplasma infection in the male or female genital tract has been suggested to explain some cases of unexplained infertility. This has been based on demonstration of *U. urealyticum* in the semen and/or in the cervical discharge of a high percentage couples with unexplained infertility. Subsequent treatment with doxycycline or tetracycline was followed by pregnancy in some of these couples. These finding have not been confirmed in subsequent controlled trials.

b. Chlamydia

Chlamydia is obligate intracellular organisms that produce characteristic cytoplasmic inclusion bodies in host cells. It needs to be grown in cell cultures like viruses. The most important chlamydia infecting man is *chlamydia trachomatis*. The human diseases caused by chlamydia include trachoma, inclusion conjunctivitis, lymphogranuloma venereum, nongonococcal uretheritis in men and women, and cervicitis, a salpingooopharitis, pelvic peritonitis.

C. Trachomatis account for 20–30% of the cases of salpingitis seen in Scandinavia and the United States.

Recently, subclinical infection with chlamydia has been implicated in unexplained infertility and in failure of conception in IVF programs. Consequently, it

has been suggested that all couples with unexplained infertility should be treated by an empiric course of antibiotics such as doxycycline. However, no clinical controlled studies confirming this approach exist.

11. Implantation failure

Factors influencing endometrial receptivity to the embryo are receiving great attention nowadays. Among the many postulated markers of endometrial receptivity are the adhesion molecules, the cathedrins and integrins. Deficiency in such factor has been suggested to contribute to unexplained infertility.

Current Treatment Options used for unexplained infertility

Most of the forementioned etiological factors postulated to account for unexplained infertility have not been proven by reliable controlled clinical trials. Therefore the treatment of unexplained infertility has remained empirical and involves one or the other of the following empiric options:

1. ***No treatment:***

The spontaneous cumulative pregnancy rate (that is, without therapy) in couples with unexplained infertility who were followed up for two seven years has been reported to range from 30% to 60%. Better outcome is expected in younger patients and women with shorter periods of infertility. Therefore, an expectant management can be discussed with younger patients, and a period of waiting of some two years is a reasonable course of action. Older women (above 30 years old) are better managed by more active, again empiric methods:

2. ***Intrauterine Insemination***

The available evidence indicates that IUI alone has not been proven to benefit couples with unexplained infertility.

3. ***Clomiphene citrate plus IUI***

Timed IUI after ensuring that the ovaries have been adequately stimulated by clomiphene have been shown to improve pregnancy rate. Clomiphene if initiated early in the cycle, on day 2 or day 3 and continued for 5 days will ensure increased follicular recruitment. The improved rate per cycle was significantly greater only when two or more mature follicles were stimulated per cycle (as diagnosed by transvaginal sonography).

4. ***Human menopausal gonadotrophins with or without IUI***

HMG controlled hyperstimulation with or without IUI improve the cycle fecundability. The latter approach gives superior results.

5. ***Assisted Reproduction Technologies (ARTs)***

Couples with unexplained infertility who fail to respond to superovulation + IUI, are generally advised to undergo assisted reproductive technologies (ART). IVF/EF failures were reported to be higher in the group of unexplained infertility relative to tubal factor group. Whether ICSI is a better option for cases of unexplained infertility remains to be validated. These interventions should not be delayed until the wife has reached 35 years.

8. In Vitro Fertilization and other Assisted Reproduction Technologies (ARTs)

The successful extracorporeal ***(In Vitro)*** fertilization of human embryos was first reported more than two decades ago. The British team of Steptoe and Edwards was the first to report a pregnancy after *In Vitro* fertilization (IVF) of human egg and was the first to achieve the birth of *an* in *vitro* fertilized baby (Marry Louese). This birth occurred on July 25, 1987. Since then, many thousands of pregnancies have been achieved worldwide by this approach. The IVF/ET technology has ramified to other methods of associated fertilization and conception, which are collectively known as, assisted reproduction technologies (ARTs). These include mainly:

IVF/ET: In Vitro Fertilization (IVF): extraction of oocytes, their fertilization in the laboratory, transcervical transfer of embryo (ET) into the uterus.

GIFT: Gamete Intrafallopian Transfer: the placement of oocytes and sperm into the fallopian tube.

ZIFT: Zygote Intrafallopian Transfer: the placement of fertilized oocytes into the fallopian tube.

TET: Tubal Embryo Transfer: the placement of cleaving embryos into the fallopian tube.

POST: Peritoneal Oocyte and Sperm Transfer: the placement of oocytes and sperm into the pelvic cavity.

SUSI: Subzonal insertion of Sperm by microinjection (1–15 sperm).

ICSI: Intracytoplasmic Sperm Injection under microscopy. (of a single spermatozoon).

Surrogacy: The fertilized oocyte is transferred and carried in the uterus of a surrogate (a substitute) mother when the genetic mother has no uterus.

Gamete Donation: is resorted to when either (or both) parent cannot generate gametes of their own.

The original aim of IVF was to bypass blocked tubes, but it is now increasingly used, together with other ARTs for other types of infertility, including male factor and unexplained infertility, endometriosis, gamete (ovum) donation and surrogacy. The latter two forms of ART are not accepted in the Egyptian practice on ethical and religious ground. In other countries, ova are donated to women who have ovarian without follicles (e.g. women with premature menopause), and sperm for couples with uncorrectable azoospermia. Surrogacy refers to transfer of an IVF produced embryo of a couple to a surrogate mother when the genetic mother have no uterus e.g. in women with mullerian aplasia.

The Brussels group headed by Van Steirteghem pioneered the techniques of ICSI and demonstrated fertilization rates of more than 50% of oocytes that had a single sperm injected into its cytoplasm. ICSI have recently received a great enthusiasm, and a clinical pregnancy rate of 30% or more has been reported.

Indications of IVF: Choice of subjects:

Due to the inconvenience, hazards and cost involved in ARTs, they are resorted to when other alternative interventions carry a poor prognosis, or are not possible and when the particular ART has a reasonable chance of success. The chance of success of the IVF and other ARTs has to be considered in comparison of a fecundability of about 25% in a single cycle in a normal couple. The indications of ARTs include:

A. Tubal disease

IVF essentially performs the functions of blocked tubes. Although it is reasonable to offer surgical therapy to young women with mild tubal or peritoneal abnormalities (see under Tubal Factor Infertility), IVF is the treatment of choice for patients who are poor candidates for pelvic reconstructive surgery, such as those with combined proximal and distal tubal disease or severe distal tubal disease. Patients who have persistent tubal obstruction after surgery or fail to conceive within 2 years following surgery are appropriate candidates for IVF. Resort to IVF should not be long delayed until the female partner gets elderly; this should be made before the patient gets into her late thirties.

The determinants of success of IVF include:

1. Mainly the ***age*** of the female partner. In successful IVF programs, where take-home baby rates can be in the range of 25% per trial (beginning) for women 36 year or younger, for women over 39 the figure is in the 10% range. The decreased success in elderly women is due to all the following factors: a) decreased response to gonadotrophin stimulation ending in few ova available for fertilization and transfer; b)

lesser chance of successful fertilization; c) decreased pregnancy rate per-embryo transfer; and d) increased abortion rate.

2. ***Elevated FSH levels*** in the early follicular phase. A common experience is that successful pregnancy is rare when the FSH level on the cycle day three is above 20 IU/L. Remember, however that the specific hormone level indicating poor prognosis may vary slightly from one lab to the other depending on methodological variations in the technique of measurement, and may be, the levels vary from one cycle to another (therefore, the elevated FSH levels is better documented in two cycles).
3. ***A level of estradiol of 80 pg/ml or higher*** on day three of the cycle also indicates poor prognosis of IVF. This is indicative of tendency to entry of more than one follicle in the phase of follicular dominance. High E_2 levels indicate poor responsiveness to the negative estrogen feedback response of the hypothalamus.
4. In another attempt to estimate the prognosis for pregnancy success in IVF programs, the clomiphene challenge test has been utilized. Exaggerated FSH production after clomiphene administration indicates a poor prognosis. Clomiphene citrate, 100 mg/day, is administered on cycle days 3 to 7. Serum FSH levels are measured on days 7 to 10 and compared to baseline levels from cycle day 2 or 3. An elevated FSH response of 26 mIU/ml or higher is associated with poor pregnancy results.
5. The presence of a hydrosalpinx may compromise the chance of success of embryo transfer. The fluid in the hydrosalpinx is periodically emptied into the endometrial cavity. This may flush away the transferred embryos. This has been the basis of salpingectomy or proximal ligation of the tube in women who have hydrosalpinx and who are being prepared for IVF/ET.

B. Unexplained infertility: IVF/ET is increasingly used for couples with unexplained infertility with reasonable success rate. The success is influenced by the same factors described under tubal factor infertility; but is generally less than the success rate of IVF/ET in tubal factor infertility.

C. Endometriosis: IVF is resorted to in infertile couples with pelvic endometriosis that have failed to respond to other therapies. Individuals with mild to moderate endometriosis do well in IVF programs. Results comparable to those obtained in tubal factor infertility are reported in cases of early and moderate disease. The results with severe endometriosis, on the other hand have not been as good: Decreased numbers of stimulated follicles have been experienced, and even when comparable numbers of embryos were transferred, the pregnancy

rate has been low. This indicates the existence of certain, not fully determined biological factors contributing to infertility in presence of pelvic endometriosis.

D. Male infertility: The limited success of various treatments of male infertility has resulted in great demand for use of IVF to overcome the problem. However, the fertilization rate has been much lower than with tubal factor infertility. In order to improve the chances of fertilization, attempts have been made to isolate the best sperm from the ejaculate by the use of Percoll gradients. However, it remained that in andrological infertility only 20–30% of the inseminated cumulus-oocyte complexes are fertilized, which is much lower than 60–70% fertilization rates in patients with tubal infertility. The chance of success of IVF is meager if the numbers of progressively motile spermatozoa with normal morphology are low in the ejaculate.

These poor results have stimulated attempts to help the sperm to penetrate into the ovum by partial zona dissection (PZD), subzonal insemination (SUSI) and intracytoplasmic sperm injection (ICSI). The good results of ICSI reported by the group of Van Steirteghem, in Belgium has created great interest in the procedure, which is now widely utilized for men with grossly defective sperm quality. The sperm could be successfully obtained from the ejaculate (even with centrifugation); or by needle aspiration of epididymis or testis; or by testicular biopsy. Success has been achieved in some cases of obstructive and non-obstructive azoospermia. The success rate of ICSI is much higher than IVF in all types of male-factor infertility. The high fertilization rate obtained by ICSI has resulted in its utilization in non-male factor infertility. However, controlled trials have not demonstrated superiority of ICSI over conventional IVF procedure in non-male factor infertility. Cryo-frozen embryos have been kept for use in future cycles, should the first transfer fails.

IVF/ET procedures

A. Stimulation protocol: Follicular phase: Superovulation

Experience with IVF/ET has demonstrated the need to retrieve a good number of ova, to ensure successful fertilization and transfer of 3 to 4 fertilized ova to the uterus in order to achieve the best pregnancy rate. The ovary needs to be hyperstimulated to produce the required population of dominant follicles. A number of hyperstimulation regimens have been used which depended on clomiphene, human menopausal gonadotrophin (HMG), purified FSH and recently recombinant FSH (produced through molecular biology technology). The response of the ovaries needs to be monitored. When the desired hyperstimulation is achieved, HCG is administered as a source of LH activity similar to the preovulatory LH

peak. This results in the final maturation of graafian follicles before the ova (usually eight) are retrieved.

In the late 1980s, many programs started using gonadotrophin-releasing hormone (Gn RH) agonist for pituitary down-regulation prior to the initiation of gonadotrophin therapy. This approach have resulted in the following advantages: 1) ensured that the ovary is in a resting phase prior to hyperstimulation, thus obviated the development of a cycle with a single dominate follicle; 2) obviated the occurrence of premature ovulation, which had previously resulted in the cancellation of a good number of stimulated IVF cycle; 3) increased the number of oocytes available at the time of follicle aspiration; 4) allowed the clinician to adjust the time of initiation of HMG stimulation enabling him to schedule the time for follicular aspiration. As a result of these merits, routine use of the Gn RH agonists has been advocated. However, the use of the agonists had the disadvantages of 1) increased the number of HMG ampoules needed to stimulate follicular growth; and 2) necessitated the support of the luteal phase. The advantages have outweighed the disadvantages, and the combination of Gn RH agonists and exogenous gonadotrophins represents now the most commonly used method of controlled ovarian hyperstimulation for the various ARTs.

Down-regulation is achieved by the daily use of a number of Gn RH agonists including leuprolide acetate (Lupron) or Triptorelin (Decapepetyl) used as subcutaneous injections, or nafarelin (Synarel) or buserelin acetate (superfact) used as nasal sprays. There is no real difference in efficacy of these preparations. The agonist is started in the middle of the luteal phase of the preceding cycle. The menstrual period usually arrives on schedule (but may be occasionally missed), and a quiescent ovary can be demonstrated by thin endometrium on sonography, and by low serum estradiol (<40 pg/ml). These are usually achieved 10 to 20 days after initiation of the agonist. Then HMG stimulation is then started. The dose of HMG is usually 225–300 IU/daily (3–4 ampoules) by intramuscular injection, except in women with PCOS when a lower dose is used. The dose is adjusted in a step-up fashion as indicated by sonographic and estradiol monitoring. The Gn RH agonist is continued during induction of ovulation, albeit in half of the daily dose and up to the day of injection of HCG.

Purified FSH (Metrodin) have been produced by the chemical removal of LH from the FSH-LH combination normally present in HMG. The pure FSH is evidently favored in patients with PCOS, which have high level of endogenous LH, and increased ovarian androgen secretion. However, the special advantage of pure FSH over HMG in the usual RVF cases has not been established in randomized trials.

More recently recombinant human FSH has been produced by modern biotechnology. However, it costs much more than HMG and pure FSH of urinary origin. Controlled trial have not, so far, confirmed the superiority of recombinant FSH over pure FSH or HMG to warrant the increased cost. It has to be remembered that a small amount of LH is required to increase FSH receptors on the granulosa cell. It is noteworthy to indicate that recombinant LH and HCG are also being tested and may replace HCG extracted from placentas.

Patients who respond poorly to Gn RH agonist-HMG protocol can be treated with a shortened Gn RH agonist protocol that utilizes the initial agonistic phase of the pituitary response to augment ovarian stimulation. In this "flare" protocol, the agonist is started on Day-2 of the cycle and HMG is started on day 3 to 4.

Attempts to use Gn RH antagonistic analogs have been slow mainly because of allergic side effects and local histamine release. The antagonists are the more logical approach to down-regulate the pituitary in a short time and without the initial flare. The problem of adverse reactions to Gn RH seems to have been almost overcome, and there are a number of preparations ready to go into the market. The antagonists can prevent LH in a short time, or their administration can be initiated when the follicle has reached a certain diameter or E_2 has reached a certain level. The antagonist can be given as a single dose on day 8 of stimulation or in repeated daily doses starting from day 7 of the menstrual cycle.

Poor responder to ovarian hyperstimulation

Some 10–30% of the cancellation rate of IVF cycles result from inability to attain adequate ovarian response. This occurrence may be predicated by high early follicular FSH and estradiol or by an inadequate clomiphene challenge tests (see above). Five approaches have been so far utilized for theses poor responders (see above), but without a significant improvement:

1. Increase the HMG dose, or change to pure FSH or to a mixture of the two.
2. Use of the flare protocol of Gn RH agonist.
3. Lower the dose of Gn RH agonists or use the antagonists.
4. Omit Gn RH agonist altogether.
5. Administration of growth hormone in conjunction with HMG. Growth hormone stimulates the IGF-I by granulosa cells, which stimulates responsiveness of follicular structures to FSH.

B. Monitoring Ovarian Response

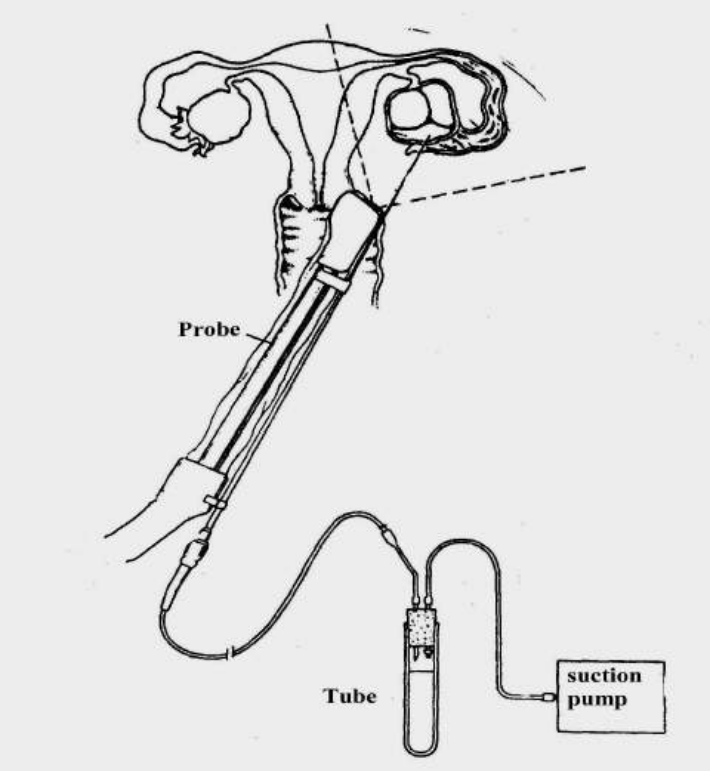
The success of IVF depends upon adequate follicular preparation and the timing of HCG administration. Monitoring of follicular growth is achieved by transvaginal

sonographic measurement of the size of the developing follicles and the measurement of serum E_2 levels. The minimum goal of stimulation is achieving of a leading follicle of at least 17 mm diameter, and at least 3 or 4 other follicles of 14 mm or greater combined with E_2 levels of approximately 200 pg/ml *per each of large follicles of 14 mm or greater*. If this degree of stimulation is achieved, HMG is stopped and a single dose 5,000 to 10,000 IU of HCG is injected on the day after the last HMG injection to induce the final stages of follicular maturation. The time interval between HCG and retrieval of ova is usually 34–36 hour; longer intervals up to 39 hours may allow for better maturation of oocyte, but slightly increases the chance of spontaneous ovulation (if Gn RH is not being concomitantly given). At the time of HCG administration, the endometrial thickness should be at least 8 mm as measured in the anteroposterior plane by transvaginal sonography. Thinner endometrium is associated with lower pregnancy rates.

Cancellation of the cycle by avoidance of HCG injection may be considered if the ovaries are markedly, hyperstimulated (>25 follicles) or E_2 level is higher than 5000 pg/ml, to avoid the risk of hyperstimulation syndrome. Aspiration of the follicles doses not protect against OHSS. The avoidance of pregnancy during the stimulated cycle through cryopreservation of all embryos is another approach, which can substantially decrease the risk of severe OHSS. These embryos can be transferred during a subsequent unstimulated cycle. The risk of hyperstimulation can also be reduced by lowering the HMG dose in predisposed patients (e.g. with PCOS) and by using progesterone instead of HCG injections to support the luteal phase after ET.

C. Oocyte retrieval

Ultrasonically guided vaginal oocyte retrieval is the standard method used for retrieval of oocytes (Figure 13). It is usually done 34 to 36 hours after HCG injection. The procedure can be an outpatient one done under fentanyl intravenous injection and occasionally under short-acting anesthetics. Periovarian adhesions do not cause difficulty in retrieval and on contrast may, facilitate it by fixing the ovary in the Douglas pouch. A number-16 needle is placed down a sterile needle guide that is attached to the upper side of the vaginal ultrasound transducer. A line on the monitor screen indicates the path the needle will traverse once it enters the abdominal cavity and the ovary. Usually one puncture of each ovary is needed to allow aspiration of all follicles larger than 14 mm. Controlled suction is provided by a special suction pump. The tubes containing the follicular fluid are immediately placed in a controlled environment at 37° C. The follicular fluid is then examined under a dissecting or invert microscope, and the oocytes are identified and placed in the culture medium.



Infertility Figure 13: Oocyte retrieval

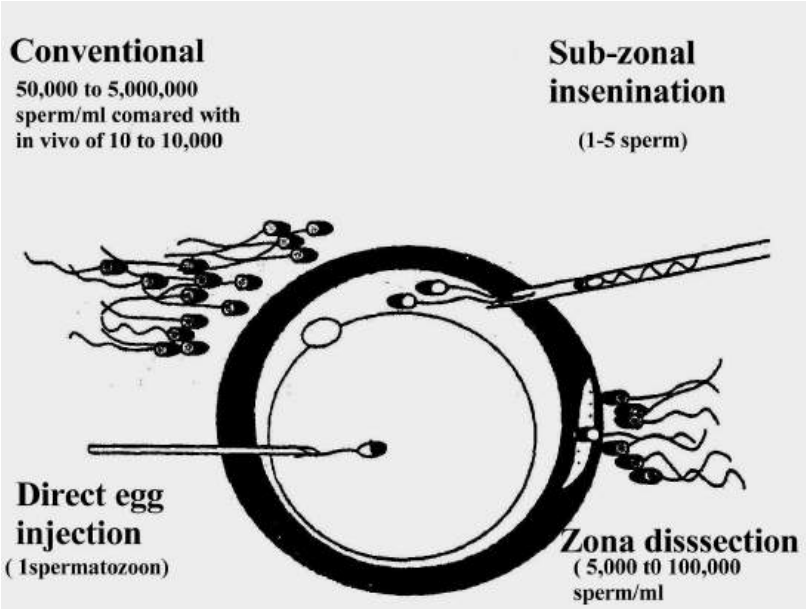
D. Oocyte culture and fertilization in vitro

The oocytes within the cumulus mass are usually incubated for 4 to 6 hours before addition of sperm. This ***preincubation*** increases the chance of maturation of the ovum. Maturity of the oocyte is determined by the morphology of the surrounding cumulus-corona cell complex (the granulosa cell are not closely packed around); or by the presence of the germinal vesicle (nucleus) and the first polar body.

The medium commonly used for in vitro fertilization is usually Ham's F 10 or human tubal fluid (HTF) that is usually supplemented with the patient's serum. In vitro fertilization is achieved in an incubator that ensure a constant temperature of 37 °C, in an atmosphere containing 5% CO_2, which produces a pH of 7.4 within the culture medium.

Semen is generally obtained on the day of follicle aspiration after a minimum of 48 hours of sexual abstinence. Sperm are prepared by washing, centrifugation, overlaying the sperm pellet with fresh media and retrieval of the sperm that swim up in the media (wash-up technique). Isolation of the most motile sperm can be accomplished by Percoll gradient for semen specimen containing a high percentage of poor sperm. Approximately 50,000–100,000 motile sperm (and much higher for male factor cases) are added to each dish containing an oocyte (Figure 14).

The day after insemination, the cumulus cells that remains attached to the zona pellucida are removed by microdissection, and the oocyte is examined for evidence of fertilization (the presence of two pronuclei), and the beginning of cleavage.



Infertility Figure 14: Different types of ARTs

E. Embryo transfer

Embryos have been transferred successfully at any stage from the pronuclear to the balstocyst, although most commonly, they are transferred when the development is between the 4 and 10 cell stage, approximately 48–80 hours after retrieval. Transfer of more than one embryo (up to four) increases the chance of pregnancy, but in general, no more than 4 or 5 embryo are transferred to limit the risks of multiple pregnancy. The multiple pregnancy rates with transfers of more than one embryo is approximately 30%. This risk is lower with advancing age. Since women over 40 have decreased per-embryo implantation, it is advisable to transfer a high number of embryos in them. The ability to resort to fetal reduction to limit the number of continuing fetuses has lessened slightly the concern over multifetal pregnancy. Embryos that are not transferred can be cryopreserved and transferred in later cycles if the initial cycle proves unsuccessful.

Embryos are generally transferred to the uterus via the cervix. Individuals in whom the cervix does not allow the passage of the transfer catheter (a rare occurrence) can have a tubal transfer via laparoscopy or minilaparotomy. To obviate the rare occurrence a “ dummy ” transfer is done at the time of follicle aspiration. The path of the canal is thus identified in order to minimize trauma during transfer. The transfer is done without anesthesia, but

sedation with diazepam can be helpful. Antibiotic prophylaxis is achieved with two oral doses of doxycycline, 100 mg, given 12 hours and 1 hour before the procedure. The patient is placed in the lithotomy position. A semirigid catheter containing the entire embryos to be transferred is used and is passed through the cervical canal, and the embryos, in ***small volume*** of 10–20 μl of culture medium, are placed ***0.5 cm below the fundus.*** The catheter is checked after transfer to ensure it contains no embryos. The patient is kept in a Trendelenburg position for 2 hours after the transfer.

Before the embryo is transferred to the uterus it can be subjected to genetic study. This is resorted to if genetic evaluation of one or both parents has indicated an abnormality or trait (see in section on Genetics). The usual method for preimplantation genetic diagnosis is the removal of a single cell from the 6-8 cell embryo (blastomere biopsy) for DNA amplification by PCR and analysis with fluorescent probes specific for chromosomes 13, 18, 21 and the X and Y chromosomes or for certain specific genes. Trisomies, and X monosomies, embryonal sex, and a number of single gene defects predisposing to diseases like cystic fibrosis, sickle cell disease hemophylia, Duchene muscular dystrophy and at least 15 other syndrome can be diagnosed. This obviates the need for invasive prenatal sampling procedures. The blastomere biopsy does not affect implantation and development of the embryo.

F. Luteal phase support

The endometrial receptivity plays a major role in the success or failure of embryo implantation after IVF-ET. There is concern about the occurrence of luteal phase defect after hyperstimulation of the ovaries. This can be contributed to by aspiration of granulosa cells along with the ova. The possibility of LPD is particularly present when Gn RH agonists are administered; the down regulation of the pituitary can persist during the luteal phase, and there will be insufficient LH to support the luteal phase. The possibility is prophylacticaly managed be administration of natural progesterone either in the form of daily or twice daily injections of 25 mg or by the twice-daily vaginal placement of 200 mg tablets of micronized progesterone. Progesterone is more advantageous than repeated injections of HCG to support the luteal phase, since the latter will increase the chance of occurrence of OHSS. Progesterone is continued up to the 10^{th} week of gestation or when repeated serums HCG assays are negative. Determination of the level of β-HCG is done on days 9 and 12 after the transfer. If positive, they confirm the occurrence of implantation. The gestational sac(s) can be seen by transvaginal sonography 4 weeks after the transfer.

Outcome of IVF/ET

Pregnancy rates in clinical trials reported after IVF are variable, depending upon selection of cases and because of small sample size in clinical trials. Overall, clinical pregnancy is expected in 23% per retrieval and 26% per embryo transfer. Of these, there is a spontaneous abortion rate of about 19% and ectopic pregnancy rate of 4.4%. The outcome in the from of take-home babies can be in the region of 19% per oocyte retrieval and 26% per embryo transfer. (These are the figure National IVF Registry of the USA in 1993, better outcome have been reported since then).

Thus, on per-cycle basis, IVF results are similar to the fecundability of natural conception cycles in the general population. The cumulative pregnancy rate determined by life table analysis progressively increase with repetition of trials of IVF/ET for the same couple up to six times.

The high ectopic pregnancy rate (4–5%) is explained by the abnormal hormonal environment resulting from hyperstimulation. It necessitates careful surveillance after ET to defect this serious complication as early as possible. Heterotopic pregnancy occurs in about 1% of IVF pregnancies.

The multiple pregnancy rate after IVF is about 30%, one sixth of these (5% of the total) are triplets or more.

The abortion rate after IVF is not above the general incidence except in elderly patients or in those with PCOS.

So far, there has been no increase reported in congenital anomaly rates in IVF siblings.

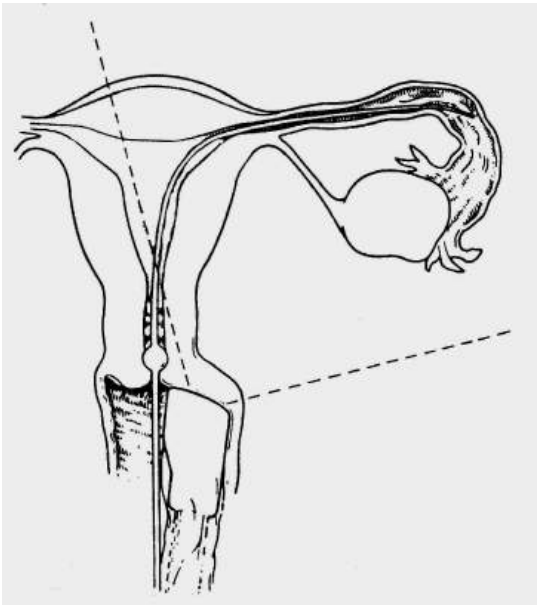
Alternative Techniques of Assisted Reproduction

Several variation of the basic methodology have be used in ARTs including:

1. **Natural cycle IVF:** The aim of using natural cycle instead of hyperstimulated cycle is to diminish the expense and inconvenience and the hazards of OHSS and multiple pregnancy. Timely administration of HCG is usually done and its timing depends upon monitoring the natural follicular growth by vaginal sonography and E2 level. However, the success rates are lower than in the hyperstimulated IVFs particularly with women 40 years old or more and with male factor infertility. In these latter two situations the availability of more ova for fertilization and of embryos to transfer are important. Natural cycle IVF is an option that may be offered to the choice of the couple.
2. **Gamete Intrafallopian tube transfer (GIFT)**

   GIFT and similar procedure (ZIFT, POST, and TET) are alternative to IVF-ET in all non-tubal cases of infertility, and allows for the placement of oocytes and sperm (or the zygotes or embryos) in the fallopian tube or in its near vicinity. The theoretical advantage is following the path of nature. The transfer to the tubes is frequently done by laparoscopy or

minilaparotomy. These techniques have not demonstrated distinct advantages over IVF/ET. Transcervical fallopian tube cannulation for tubal placement of sperm and embryos is a possible alternative, which is still under development. The tube is cannulated either blindly (tactile), or with the help of ultrasound or hysteroscope (Figure 15). Also direct intraperitoneal insemination (DIPI) by washed sperm has been also attempted with occasional successes. After establishment of ICSI and its high success rate in male infertility the use of GIFT and similar techniques have diminished markedly.



Infertility Figure 15; Gamete Intrafallopian tube transfer (GIFT)

3. Intracytoplasmic Sperm Injection (ICSI)

A number of micromanipulation techniques have been utilized in order to facilitate the access of the sperm into the ovum under the invert microscope (Figure 14). These micromanipulation techniques include the opening of a " window " in the zona pellucida to allow ingress of sperm (partial zona dissection, PZD), and injection of sperm into the perivitelline space (subzonal insemination, SUSI) or directly into the cytoplasm of the egg (intracytoplasmic sperm injection, or ICSI). The Brussel group headed by Van Steirteghem pioneered the techniques of ICSI and demonstrated fertilization rates of more than 50% of oocytes that had a single sperm injected into its cytoplasm. ICSI have recently received a great enthusiasm, and a clinical pregnancy rate of 30% or more has been reported. The method of ICSI serves most male factor infertility. Sperm are obtained from the ejaculate, occasionally after centrifugation. Success has been achieved with sperm obtained from the epididymis from cases obstructive azoospermia. In addition, success has been obtained with

sperm obtained from the testis by needle or microsurgical biopsy (the latter is the usual approach) to obtain sperm from azoospemic men. However, it is always advisable to search for sperm in centrifuged ejaculate before proceeding to testicular biopsy in such cases. Spermatides obtained from these biopsies were also utilized with some success in ICSI. Concern about possible genetic consequence of forcing such potentially defective sperm into the ovum has been raised. However, no increase in the rate of chromosomal abnormalities has been so far demonstrated in offspring of ICSI. However, ICSI offspring from a father with the genetically determined absent vas may inherit predisposition to fibrocystic disease (a recessive trait, requiring both parent carrying the responsible gene). Recently, deletion of a certain segment of the Y chromosome at the AZFC region has been shown to be an important cause of spermatogenetic failure (present in 13% of men with non-obstructive azoospermia). These men can be helped have children through ICSI utilizing testicular biopsy. Their female offspring are normal, while the males will inherit the same Y deletion and are expected to be similarly infertile adults.

Chapter 21

AMENORRHEA, OLIGOMENORRHEA AND HYPOMENORRHEA

Contents

Definition

Amenorrhea mean without menstruation. Any patient fulfilling the following criteria should be considered as having amenorrhea and be investigated:

1. No menstruation by the age of 16 regardless of development of secondary characters. Before this time she can be considered to have *delayed menarche*. This is a sort of wishful thinking depending on the observation that some girls do have their first menstruation by this age. However, such girls with delayed menarche will prove subsequently to be infertile or subfertile, and their menstruation function will be irregular. Therefore, though they are assured, they should receive proper consideration.
2. In a woman who has menstruated before, the absence of periods for the length of 3 consecutive cycles or 3 months is considered as amenorrhea.

The classification of amenorrhea as primary or secondary depends upon whether she has not or has had menstrual periods before. The etiological factors and the diagnostic evaluation are commonly the same. However, primary amenorrhea carries a worse prognosis and is more likely to be caused by faulty development of the reproductive systems. However, few cases with developmental problems of the ovaries, e.g. ovarian dysgenesis may have secondary amenorrhea i.e. they menstruate for few years only. Certain acquired conditions like Sheehan's or Ashermann's syndromes are not seen in primary amenorrhea.

The term **oligomenorrhea** is usually used to describe infrequent menstruations occurring at cycles longer than 35 days or longer than the usual habit of the patient. Infrequent menstruation and amenorrhea are essentially similar symptoms with identical causes; the difference is only one of degree.

The term ***hypomenorrhea*** is frequently used to describe the menstrual periods, which are short in duration or scanty in amount or both. This is relative to the normal habit of the individual. Bleeding that last for less than two days is however, unusual.

Amenorrhea can however, be false one, if the woman menstruate but the menstrual blood is bent up due to presence of an obstructing septum below the uterus. This condition is called **cryptomenorrhea.** The septum is frequently congenital (see under Congenital Anomalies) or rarely acquired due to traumatic injuries (including operative) of the cervix or the vagina.

Amenorrhea is *physiological* before puberty, during adolescence, pregnancy and lactation and after menopause, otherwise amenorrhea is *pathological*.

Etiology of pathological amenorrhea

Menstruation requires an intact outflow tract that connects the uterine cavity with the outside i.e. *patency and continuity* of the vaginal introitus, the vagina, and endocervix. The source of menstrual blood is the *endometrium*. This tissue is stimulated and regulated by proper quantity and sequence of steroid hormones, estrogen and progesterone produced at the *ovary*. In the latter these hormone are produced in a cyclic fashion, by the maturing ovarian follicles, the mature graffian follicle and the corpus luteum. The ovarian cycle is mainly determined by cyclic production of two *pituitary* gonadotrophic hormones, the follicle stimulating hormone (FSH) and luteinizing hormone (LH). The secretion of these two pituitary hormones is under the control of the decapeptide hormone: gonadotrophin-releasing hormone (Gn RH), which is secreted by the neuronal cells of the basal hypothalamus, and carried by the blood to the pituitary through the portal circulation connecting the hypothalamus and the pituitary. Gn RH is secreted in a certain pulsatile fashion, a feature necessary for its function. The gonadotrophins are consequently produced in a pulsatile pattern, but the physiological significance of the latter pulse is not clear. The hypothalamus is part of the brain and the secretion of its neurohormones is influenced by nervous and chemical stimuli reaching it from other parts of the brain. The influence of these higher stimuli is subtle, (but existent) in man who reproduces, usually regardless of environment but these influence are evidently operative in lower animals whose reproduction is influenced by environmental stimuli like season, weather, or light. The flow of regulation is not only in one downward direction, but there is interaction both negative and positive upward regulation in what is called *feedback mechanisms* exercised by ovarian estrogen, progesterone and inhibin. Recently, greater importance has also been recognized for local autocrine and paracrine factors in the ovaries e.g. growth factors. In addition, the hypothalamo-pituitary-ovarian-uterine axis can be influenced by certain diseased condition outside it e.g. thyroid, pancreatic and adrenal disorders and systemic disease like tuberculosis. Moreover, uterine bleeding is also influenced by focal factors acting on the endometrial blood vessels.

Therefore, in spit of discussing the etiological factors of amenorrhea under hypothalamic, pituitary, ovarian and uterine factors and other influences, there is a good deal of overlap and interplay between different groups of causes. An important example of this is the polycystic ovary syndrome, which can result from disturbance of hypothalamic, pituitary, ovarian and/or adrenal functions, the triggering point of which is not clear.

I. Hypothalamic amenorrhea

Patients with hypothalamic amenorrhea have a deficiency in the pulsatile secretion of Gn RH. Consequently hypothalamic amenorrhea is a hypogonadotrophic hypogonadic disorder. Hypothalamic problems are usually diagnosed by exclusion of pituitary lesions. There are frequently associated disorders, because the hypothalamus has centers for controlling appetite, sleep, metabolism, and fluid balance. Therefore hypothalamic amenorrhea can be associated with overeating, undereating, obesity, and sudden loss of weight. In the syndrome dystrophia adiposogenitalis (Frohlich's syndrome), genital hypoplasia is combined to obesity and sleepiness. More than one hypothalamic dysfunction may be concomitantly associated, for example, deficiency of dopamine function which is the specific inhibitor of prolactin secretion results in hyperprolactinemia; but this is usually associated with inhibition of Gn RH release in the hypothalamo-hypophyseal portal circulation resulting in amenorrhea. Both the decreased production of dopamine and Gn RH can have a common cause. Recently this hyperprolactinemic amenorrhea has been linked to increased secretion in the brain of opioids like β-endorphine which depresses production of these two neurohormones.

Hypothalamic amenorrhea can result from the following conditions:

1. ***Disease or injury in the region of the midbrain.***

   These include encephalitis, meningitis, tumors and fracture base.

2. ***Cerebral cortex influences***

   - ***Emotional upsets*** and stresses. Examples of these include stresses of exams, change of work or residence, separation from close friends, a love affair, marriage, nervous shock, death of a beloved person ... etc.
   - ***Psychosis*****:** Amenorrhea is commonly associated with certain depressive mental disorder, or can be caused by certain psychotropic **drugs**. It can follow upon electric convulsion therapy. Such therapies are frequently associated with disorder of dopmine metabolism and hyperprolactinemia.
   - ***Pseudocysis:*** In this condition the patient imagines that she is pregnant and accordingly develops amenorrhea, nausea and vomiting, breast changes, increased weight and enlargement of the abdomen due to hysterical protrusion of the abdomen. She frequently alleges that she is feeling fetal movement, and ultimately she may start to feel labor pains. Such combination of manifestations results from deep desire for pregnancy in sterile women, rarely from fear of pregnancy in women approaching her menopause. The diagnosis can be easily made by percussing the abdomen when midline

resonance is found. However, frequently the woman needs the reassurance of sonography, that her uterus is empty. The condition can be most embarrassing.

- ***Anorexia nervosa***

This is a syndrome resulting in a girl or women deliberately starving herself. Anorexia nervosa occurs frequently in young, middle or upper class females under the age of 25. The classical picture is one of secondary amenorrhea in an extremely emaciated patient whose weight is well below 45 kg. *The diagnosis depends upon the following features:*

1. Weight loss of 25% or more.
2. Aversion to food. This may begin with dieting.
3. Denial of under eating.
4. Amenorrhea.
5. Patient may induce vomiting, and has constipation.
6. Otherwise the patient has no other evident psychological problem. She may be hyperactive, perfectionist, or self-centered person, or trying to attract attention.
7. The genital tract is atrophic. Ultrasonography shows flat ovaries.
8. One or more of the following:
    - Fine downy hair (lanugo) on the face, trunk and limbs.
    - Bradycardia.
    - Low blood pressure.
    - Episodes of overeating (bulimia).
    - Vomiting.

The condition if not treated can become serious, and 7% case fatality has been reported which may result from heart failure. *Endocrine profile indicates the following changes:*

1. No response to progesterone withdrawal.
2. Low FSH and LH.
3. High cortisol.
4. Prolactin normal or occasionally high.
5. T_3 and T_4 are low.
6. The ovaries are responsive to gonadotrophin, and Gn RH injection stimulates gonadotrophin secretion.

The treatment of anorexia nervosa may prove difficult:

1. Revelation to the patient and her relatives of the relationship between amenorrhea and low body weight may initiate the patient to go back to a more normal diet.
2. Setting a program of gradual increase in the amount of food taken.
3. Encouraging the patient to develop new friends and have moderate outdoor simple exercise.
4. Psychiatric consultation is needed if the above measures do not work.

- ***Bulimia*** is a syndrome marked by episodic and secretive overeating followed by self-induced vomiting, episodic fasting or the use of laxative and diuretic. It is occasionally seen in young upper class girls and women who are suffering from societal pressure with an escape in overeating. Some of them are having depressive psychosis. Patients with anorexia nervosa may have episodes of bulimia.

3. Drugs

These include:

- Phenothiazine derivatives
- Psychotropic drugs: like trycyclic antidepressants, sulpride and other psychotropic drugs.
- Antihypertensives, particularly resperine, methyldopa and ganglion blockers.
- Antipeptics, like cimetidine.
- Drug addiction: particularly cocaine and heroine.

  Most of the above drugs act on the hypothalamus resulting in inhibition of release of both dopamine and Gn RH. Therefore, they commonly result in amenorrhea and hyperprolactinemia. They may influence other neurotransmitters.
- Hormonal contraceptives can cause secondary amenorrhea particularly the use of progestogen-only contraceptives. The injectables like DMPA or NET-EN can disrupt menstrual rhythm causing either prolonged or frequent menstruation or amenorrhea. The incidence of amenorrhea tends to increase with prolonged use. The menstrual disturbance may persist for an average of 3 months after the end of term of the last injection due to persistence of the progestogen source in the depot site for some time. Women vary in the their rate of metabolizing the progestogen. The minipill produce similar disruption of menstruation, but since they are typically used during breastfeeding, the menstrual irregularities particularly the amenorrhea are better

tolerated, as it is usually considered physiological during lactation. With Norplant, the menstrual disruption tends to improve with passage of time; after the first two years, more than 50% of users have regular monthly bleedings. The menstrual disruption caused by the minipill and Norplant, ends directly after termination of use.

Use of combined oral contraceptives (COCs) is rarely associated with missing a period or two. Rarely, discontinuation of COCs is followed by a period of amenorrhea of some month (post-pill amenorrhea). This occurrence is not related to the length of time during which the woman has taken the pill; it seems that some women have a hypothalamic-pituitary system which is unusually sensitive to the inhibition which these combined pills produce. The incidence of post-pill amenorrhea is less than 1% and it seems to have decreased with the use of low dose formulations. The condition usually resolves spontaneously. If it persists for more than 6 months the following possibilities need to be considered:

a. Pregnancy.
b. The amenorrhea is a return of a menstrual disturbance that was present before the use of the contraceptive.
c. Hyperprolactinemic amenorrhea, due to other cause.
d. The patient has grown older during pill use and entered in premature (or occasionally timely) menopause.

Therefore, in patient with persistent post-pill amenorrhea a full diagnostic workup should be made.

4. Obesity

Obesity can be associated with amenorrhea. But unless associated with psychological disturbance it cannot be considered to have a hypothalamic disorder. However effective weight reduction of an obese woman is frequently followed by return of regular menstruation.

On the other hand under eating is rarely associated with amenorrhea except in anorexia nervosa which has additional important features that suggest a hypothalamic disorder. Starvation in adults, such as during wars or famines can also be followed by amenorrhea. It is not always clear however, whether it is the lack of food or the stress of the situation that caused amenorrhea.

5. Frolich's syndrome

It is a rare, genetically determined condition that is described as dystrophia adiposogenitalia. It is characterized by amenorrhea, usually primary, genital hypoplasia and gross obesity and sleepiness.

6. Physical exercise and amenorrhea

This association is rarely seen in our culture, which does not value much neither slim body or exercise. Competitive female athletes, as well as women engaged in strenuous recreational exercises (like jogging or running) and women engaged in other demanding activity such as ballet dance have a significant incidence of menstrual irregularity and amenorrhea. They have higher incidence of anovulatory cycles and luteal phase deficiency. These women are having hypothalamic dysfunction similar to that of women with anorexia nervosa. A low gonadotrophin level is combined to high prolactin and cortisol level. However, there is none of the other psychological background in athletic amenorrhea, there is no denial of under eating. It is not clear what is the pathogenesis of this exercise related amenorrhea. The possibilities are:

a. The stress of competition produces a hypothalamic disturbance.
b. Underweight: The theory of the need for a critical mass of fat in the body for the hypothalamo-pituitary-ovarian axis to function normally (Frisch's theory) is possible; but does not apply to all cases. Suboptimal and supraoptimal amount of bodily fat may impair estrogen metabolism.
c. Increased production of endorphines (brain opiates) after such repetitive exercises can actuate suppression of hypothalamic secretion of dopamine (hence hyperprolactinemia), and of Gn RH (hence the amenorrhea). Some runner describe a state of augmentation of mood i.e. euophoria "runner high" that may lead to their indulgence in the exercise.

The condition is easy to treat once the woman recognizes the condition, and simple weight gain may reverse the amenorrhea. The element of stress and easing down the exercise may need special care to achieve.

7. Amenorrhea and Anosmia: Kallman's Syndrome

This is a rare genetically determined condition much commoner in males than females, where there is combination of deficiency in Gn RH production together with absence or extreme weakness of smelling. This defect is a consequence of the failure of

migration of both olfactory axonal and Gn RH producing neurones of the hypothalamus from the embryonal nasopharynx to the brain. The cells that produce Gn RH originate in the nasopharynx and migrate during embryogenesis along cranial nerves, which connect the nose and the base of the brain. The condition can be inherited or sporadic, and is mostly caused by an X-linked gene on the short arm of the X chromosome (hence it is commoner in males).

In the female the condition presents as primary amenorrhea, infantile sexual development, low gonadotrophins, a normal female karyotype, and the inability to perceive oders. Often the affected individuals are not aware of their olfactory defects. Sonography shows flat ovarian and a small uterus. Magnetic resonance imaging demonstrates hypoplasia or absence of olfactory sulci in the rhinencephalon. Other neurological abnormalities may be associated like defective hearing, cerebral ataxia, cleft palate and may other bone defects.

The amenorrhea can respond to gonadotrophin stimulation and ovulation can be induced and the patient can get pregnant. However, clomiphene citrate is not effective.

8. Unexplained hypothalamic amenorrhea

It is occasionally seen when a hypogonadotrophic amenorrhea has none of the above explanation. They can be caused by isolated deficiency in Gn RH production.

II. Pituitary Amenorrhea

Primary pituitary amenorrhea (not caused by hypothalamic deficiency) is mainly caused by tumors, usually adenomas. However, the anterior pituitary can be destroyed by infarction secondary to spasm and ischemia caused by postpartum hemorrhage. Tuberculomas, gummas, and fat deposits have been reported as cause of pituitary compression leading to hypogonadotrophic amenorrhea. Nearby lesions such as aneurysm of the internal carotid artery and obstruction of the aqueduct of Sylvius can compress the pituitary gland and cause amenorrhea.

1. Pituitary adenomas

Tumors of the anterior pituitary are generally benign and grow slowly; malignant tumors are exceptionally rare. Adenomas of the pituitary gland are quite common. In autopsy series the prevalence of pituitary adenoma ranged from 9% to 27%. However, they are usually silent, being small and nonfunctioning and may be discovered incidentally on X ray or CAT or MR imaging of the skull. They are usually microadenoma (less than 10 mm in diameter). Adenomas will have clinical significance if they are functioning i.e. producing hormones or when big (macrodenoma)

threatening by pressure neighboring structures; mainly the optic chiasma. Prolactin secreting adenomas, prolactinomas are the most common pituitary tumor, accounting for 50% or more of symptomatic adenomas. Adenomas may less commonly produce growth hormone causing acromegaly; ACTH causing Cushing's disease; or TSH causing secondary hyperthyroidism. All these types are associated with amenorrhea, which is usually the first clue to the disease.

In the past, pituitary adenomas have been grouped according to the staining characters of their cells as eosinophilic, basophilic or chromophobe adenomas. Presently such classification is not warranted and is replaced by a functional classification, e. g. prolactin-secreting adenoma.

With the utilization of sensitive and specific immunoassays for prolactin, and the increased sensitivity of imaging techniques like CAT and MRI, the association of amenorrhea and small tumors of the pituitary has become a relatively common clinical diagnosis. As many as one-third of patients with secondary amenorrhea can have pituitary adenoma; and if galactorrhea is also present, 50% will have an abnormal sella turcica. The clinical symptoms do not always correlate with prolactin level. This can be due variation of functional capacity of the adenoma, and the heterogeneity of the prolactin molecule in the circulation (the latter point is discussed in the chapter on induction of ovulation). However high levels of prolactin of > 100 ng/mL are commonly associated with amenorrhea and frequently with an adenoma. Very high levels of $\geq$ 1000 ng/mL are associated with macroadenomas.

Diagnosis of pituitary adenomas and hyperprolactinemia:

1) *Anovulation/amenorrhea:* women with hyperprolactinemia can progress from normal ovulation to an inadequate luteal phase to intermittent anovulation, to total anovulation to complete suppression and amenorrhea. These manifestations are similar to those seen during lactation, but the mechanism of their occurrence has not been completely elucidated. Hyperprolactinemia whether tumorous (caused by prolactinoma) or nontumorous, e.g. drug induced, is associated with inhibition of the pulsatile secretion of Gn RH which is the cause of the various ovulatory and menstrual dysfunction. The hyperprolactinemia and hypogonadism are both, most probably caused by a common denominator, which can be probably the brain opioids which cause inhibition of the two hypothalamic functions of release of dopamin (the prolactin inhibiting factor) and Gn RH. However, treatments that lower prolactin secretion restore ovarian function. This is true whether the treatment consists of surgical removal of prolactinoma or suppression of prolactin secretion by dopamine agonists like bromocreptine.

2) Two third of patients with hyperprolactinemia have *galactorrhea* which can vary in degree from expression of drops of opaque white secretion on pressure, to spirt of milky secretion on pressure, to an engagement of breast with milk. Some cases of hyperprolactinemia even with ovulatory disturbance or amenorrhea can have *no galactorrhea*. On the other hand, at least one third of women with galactorrhea have normal ovulatory menses and normal prolactin levels.

3) *Breast discomfort* is usually associated and can be the presenting symptom.

4) *Pressure symptoms* can result from upward growth of a macroadenoma to compress the optic chiasma. This causes blurring of vision and loss of vision in the temporal field of one or both eyes. This is a rare occurrence. Prolactinoma causes headache but rarely causes rise in intracranial tension. Other tumors in this region are more likely to produce these effects than the prolactinoma. These include craniopharyngeoma (usually marked by calcification seen on X-ray), meningeoma, gliomas, metastatic tumors and chordoma.

5) *Diagnostic imaging*

a. Simple coned-down lateral and anteroposterior X-ray view can show ballooning of sella turcica diversion of the cleinoid processes surrounding the sella, rarefaction of its wall, double floor (due to rarefaction of one side of the floor). However, double floor is a normal variant of the floor of the sella turcica and cannot be taken as an indication of presence of a tumor unless the sella is enlarged and the bone is rarified. Simple X-ray can diagnose the majority of macroadenomas, but microadenoma will need other methods. However, simply coned done lateral X-ray is quite enough for follow-up in most cases.

b. CAT scan with dye intensification of the pituitary tissue can recognize small tumor (microadenoma = <10 mm in diameter).

c. MRI can delineate the tumor both in the saggital and corneal planes and demonstrate its nearness to the optic chiasma.

The latter two methods can be used to make the initial diagnosis, but simple coned lateral X ray film can accomplish all what is required in periodic follow-up at a much lower cost.

2. Other causes of hyperprolactinemia

Hyperprolactinemia is present in 30% of cases of secondary amenorrhea. It has proved to be commoner than the old-syndromes of amenorrhea/galactorrhea, which were called as Chiarrie-Frommel syndrome and Forbe's syndromes; names, which are no longer used.

Hyperprolactinemia amenorrhea can be caused in addition to pituitary tumors by the following conditions:

1. *Physiological hyperprolactinemia*

- During pregnancy.
- During breastfeeding.
- Coitus.
- Frequent nipple manipulation, this can be in search for galactorrhea in an obsessed woman.
- Stress: The stress of repeated venepuncture during taking the sample can raise the level above the normal (20 ng/mL).

2. *Psychological disturbances* e.g. depressive psychosis, anorexia nervosa and Bulimea.

3. *Drugs* acting mainly at the level of hypothalamus (see above).

4. *Empty sella syndrome*

This occurs if there is congenital incompetence of the sellar diaphragm that allows an extension of the subarachnoid space into the sella turcica. Due to pressure of CSF the pituitary gland is flattened and separated from the hypothalamus; the portal system of circulation around the pituitary stalk is compressed freeing the pituitary from the inhibiting effect of dopamine. Hyperprolactinemia galactorrhea and amenorrhea can consequently, result. However, the condition does not progress to pituitary failure. The sella wall may be ballooned or rarified thus suggesting the presence of adenoma on a coned-down X ray view. The condition can be diagnosed by CAT and MRI. Given the present diagnostic imaging, the syndrome can be present in 10% of cases of amenorrhea/Galactorrhea. Empty sella can rarely be acquired due to radiotherapy, surgery or infraction of a pituitary adenoma. The condition is amenable to medical treatment by dopamine agonists and gonadotrophin therapy.

5. *Hypothyroidism*

Amenorrhea can be the result of hypothyroidism. This can result from hyperprolactinemia caused by increased production of thyrotrophin releasing hormone. Other clinical evidence of hypothyroidism includes intolerance to cold,

constipation, psychomotor retardation, mental slowness, decreased energy, slow speech, low-pitched voice, and pretibial edema. The condition is confirmed by raised TSH level (and low T3 and T4 if the first is elevated). The treatment is oral administration of thyroxin beginning with small dose of 50 μg and increasing every 4 week usually up to 150 μg.

6. *Functional hyperprolactinemia* is a diagnosis of exclusion, and its incidence depends upon the vigilance of exclusion of organic cause mainly microadenoma. About 30% of cases of amenorrhea/galactorrhea can be considered functional. However repeat yearly or every other year imaging can demonstrate the development of an adenoma that has not been previously recognized.

Treatment of prolactin secreting adenoma:

This is discussed under Treatment of Anovulation, but the management of prolactinoma can be summarized as follows:

1. Patients with microadenoma having symptoms of amenorrhea, infertility, and troublesome breast tenderness are treated by bromocreptine or other dopamine agonists. The smallest possible does should be used an the treatment is continued until the goal is achieved. If recurrence occurs the treatment is reinstituted. Women not interested in pregnancy can safely use COCs; they do not cause enlargement of the tumor. This can give in addition to contraception the required hormone replacement therapy needed for maintenance of bone integrity. Follow up consists of a yearly or two yearly prolactin measurements and a coned down X ray imaging.
2. Asymptomatic (detected during a CT scan) microadenomas need only the follow-up : every one or two years.
3. Patients with macroadenomas are better treated by bromocreptine. The smallest possible dose is used first and increased progressively. The dose can reach 15 mg daily. The prolactin level is a good tumor marker, but coned X ray should be done every 3 to 6 month until the desired reduction of size of the tumor is achieved. Thereafter, the dose is gradually reduced to maintenance dose, which can be maintained indefinitely. Patients with adenomas are more tolerant to the side effects of dopamine agonists. Withdrawal of treatment results in recurrence of hyperprolactinemia and enlargement of the tumor. Follow-up is effectively achieved by 6 monthly coned-down lateral view until the condition stabilizes, thereafter repeated at yearly intervals.

4. Surgical treatment by trans-sphenoidal approach and utilizing microsurgery is nowadays utilized for cases that do not respond to medical treatment. This preference of starting with medical treatment is based on the following disadvantages of surgery: a) incomplete cure in 50%, b) high recurrence rate, c) may result in complete ablation of the pituitary gland (panhypopituitarism). Surgery may be followed by radiotherapy, which also increases the chance of panhypopituitrism including diabetes insipidus.
5. No harm is usually expected if the woman gets pregnant. Rarely however, enlargement of the tumor can occur and may start to press on the optic chiasma. The patient should be kept under observation for her field of vision, if this start to be affected, bromocreptine can be started again to check the pregnancy-induced growth.
6. No harm results from breastfeeding.
7. Contraception can be offered by the IUD while the patient is under dopamine agonists or low dose COCs if not being such treated.

3. Sheehan's Syndrome (less commonly called Simmond's Syndrome)

Sheehan's syndrome is panhypopituitarism affecting all the trophic functions of the anterior pituitary. This syndrome is characteristically caused by ischemic nercrosis of most of the anterior pituitary, which results from arteriolar spasm occurring at the time of severe postpartum hemorrhage. The condition does not complicate hemorrhagic shock in non – pregnant women or men. Two theoretical explanations are possible for the special vulnerability of parturient woman: The first, is the enlargement of pituitary gland during pregnancy until it reaches to near the maximal limit of its blood supply, a situation that does not permit diminution. The second is that normally during labor the blood supply to the pituitary gland is modified to the advantage of the posterior lobe. When spasm occurs, therefore, the posterior lobe is spared and the anterior lobe is affected. The risk of developing the syndrome depends upon the speed and efficiency with which blood loss is controlled and replaced. The chance of developing Sheehan's syndrome can be as high as 50% for severe postpartum hemorrhage and shock. This syndrome is commonly seen in our practice reflecting the poor emergency obstetric care.

The fully developed syndrome occurs when more than 95% of the anterior pituitary is destroyed. The first manifestation is failure of initiation of postpartum lactation (or engorgement of the breast had the offspring been dead). This is due to failure to secrete prolactin. Later on, the patient will develop amenorrhea, loss of libido and genital tract and breast atrophy due to deficiency of gonadotrophins. As a result of secondary hypothyroidism, the patient becomes apathetic, sensitive to cold and may have slow staccato slurred speech. The skin can be rough and

cracky. Insulin tolerance is reduced and spontaneous hypoglycemia may develop. Signs of secondary adrenal cortical failure include absence of axillary sweating, loss of axillary and pubic hair, and decrease in skin pigmentation. The last mainly explains the striking pallor of these patients. The pallor is also contributed to by anemia, which is caused by prior blood loss and lack of the pituitary erythropoietic factor. Due to suprarenal cortical failure, the patient becomes vulnerable to any acute stress, like that caused by an accident or operation. This acute stress precipitates *suprarenal crisis* characterized by hypotension, hypothermia and hypoglycemia. There is usually no loss in weight.

The blood levels of FSH and LH are low (occasionally low normal levels may observed). TSH, ACTH, estrogen are considerably reduced. Although dormant and looks flat on sonographic imaging, the ovary retains its potential for responding to exogenous gonadotrophin, and ovulation and conception can occur. If the woman does have another pregnancy, the manifestations of the syndrome can improve. Partial destruction of the pituitary gland can lead to incomplete syndrome, or its delayed onset, or to the recovery of the functions after some months or years of quiescence.

Sheehan's syndrome is generally treatment by replacement of deficient target gland hormones. This is a lifetime therapy. The first hormone that needs to be replaced is cortisol, after giving this for some weeks, thyroxin can then be introduced. In case of beginning with thyroxin, a suprarenal crisis can be precipitated. Estrogen replacement therapy (better with natural estrogens like conjugated equine estrogens) is given either continuously or intermittently to allow for a monthly menstruation. A progestogen should be added for 10–12 days per month to counteract the proliferative effect of estrogen on the endometrium. HMG can be used to induce ovulation if pregnancy is desirable. With proper care these unfortunate women can be helped to resume reasonably normal life.

III. Ovarian Amenorrhea

In this group, the hormonal disturbance causing amenorrhea appears to arise in the ovary i.e. primary hypogonadism. This is usually hypergonadotrophic. The group comprises the following conditions:

1. Deficient gonadal development (Chromosomal abnormalities)(Gonadal Dysgenesis):

Thirty to forty percent of women presenting with primary amenorrhea have demonstrable chromosal anomalies causing problem in gonadal development. Chromosal anomalies can rarely be the cause of secondary amenorrhea, but with a much lower incidence. In the latter cases the chromosomal abnormality is less pronounced resulting in

formation of a limited amount of ovarian tissue, which will expire after some years of function. The commonest chromosomal abnormality associated with abnormal development of the gonads is 45 XO; less commonly mosaics containing this line plus 46 XX and less commonly mosaics with 45 XO / 46 XY. Deletion of the short or the long arm of one X chromosome of 46 XX individual can result in less pronounced ovarian abnormality.

Turner's syndrome is the classical syndrome associated with a karyotype of 45 XO or a masaic containing this cell line. The primary cause is non-disjunction of the sex chromosome during myeosis, the single X chromosome being maternal in the majority of cases. This chromosomal abnormality usually results in *streak ovary* (or rather called streak gonad), which appears as a white band lying in the back of the broad ligament and consisting of connective tissue containing no ova. The internal genitalia being always female i.e. mullerian, but are markedly hypotrophic.

The embryological pathogenesis of the streak gonad is as follows: Initially primordial germ cells appear in the genital ridge of the early embryo in the normal way but, due to the chromosomal abnormality they *expire quickly*. They are therefore unable to organize or maintain other tissue elements in the gonad that becomes replaced by fibrosis tissue. The condition is thus called gonadal agenesis or dysgenesis, the designation ovarian cannot be specifically used, because, it is unknown whether the absent chromosome would have been an X or Y. The dual complement of two sex chromosomes is required for development of the primordial gonad into testicle or ovary. In the absence of the Y chromosome the phenotype is female; albeit the imperfect female of Tuner's syndrome. Rarely the gonadal defect is less complete (usually determined by less pronounced chromosomal abnormality) and a few ova are found in the ovary at birth but these disappear in childhood or early in reproductive life. In order to embrace the multitude of chromosomal abnormalities and variation in the development of the gonad. These conditions are called *gonadal dysgenesis*. This term embraces a range from typical pure for to an otherwise normal female with premature menopause. The latter are described as mixed gonadal dysgenesis (see also under Normal and Abnormal Sexual Differentiation)

Many of the 45 X embryos are aborted but those who are not become deformed and, in addition to having streak gonads, present the features of Turner's syndrome at or after birth. The syndrome has been characterized long before its chromosomal basis was recognized. Being without a Y chromosome, all affected individuals appear female, and their incidence is 0.2 per 1000 live baby. The diagnosis is often made in childhood by the parents observing certain associated somatic defects. Occasionally the condition is made in

adolescence because of failure of development of secondary sex characters and absence of menstruation.

The girl is short, always being less than 150 cm. The genitalia, both external and internal are female but, in the absence of ovarian stimulation remain small and infantile. Breast buds fail to appear, and chest is broad and flat, shield-like. No pubic and axillary hair develop or are sparse. Other physical anomalies which are often but not always present include: a short wide neck occasionally webbed; cubitus valgus (i.e. exaggerated carrying angle), low set ears, low occipital hair line, deformities of fingers and toes, exaggerated epicanthic folds, cardiovascular anomalies (e.g. coarcitation of the aorta) renal anomalies color blindness, and multiple nevi on the skin. The mentality is usually normal.

The levels of estrogen in blood is very low, those of gonadotrophins may be raised (but may be high normal). These patients rarely complain of flushes. However, enhanced osteoporosis is likely to occur.

The management is by hormone replacement therapy; estrogen and progesterone should be given. This usually results in *little change in the breast or body contour and does not cause any menstruation.* However, this therapy should be continued-lifetime to protect the bones from osteoporosis. Psychological support is usually required.

All the patients with gonadal dysgenesis should be submitted to karyotyping. This is not just for academic perfection. Forty percent of individuals who appear to have Turner's syndrome are mosaics or have aberration in the X or Y-chromosomes. Mosaics with a Y chromosome in their karyotype require excision of the gonadal area because the presence of testicular component within the gonad is 1) a predisposing factor to malignant tumor formation and 2) may lead to virilization. Mosaics with 45 XO / 46 XX may appear normal female albeit short and infertile and go in the menopause early. Deletion of part of the X chromosome in otherwise 46 XX individual can develop streak ovaries only, or alternatively, the bodily deformities of Turner syndrome.

In conclusion gonadal dysgenesis is an important cause of primary amenorrhea. It results from abnormality in the sex chromosome, usually taking the form of 45 XO karyotype, streak gonads and Turner's syndrome. However, less typical or mixed forms of gonadal dysgenesis can occur.

2. Premature ovarian failure i.e. premature menopause

Approximately 1% of women will experience ovarian failure i.e. menopause before the age of 40. This means early depletion of ovarian follicles or their diminution below a

certain critical mass. The etiology of the condition is unknown. Occasionally it is a familial trait, but it is no always so. It can be caused by an autoimmune condition resulting in enhanced ovarian atresia with lymphocytic infiltration. It can be one of the variant of ovarian dysgenesis. It can be caused by Mumps related oophoritis or prior exposure to X-ray.

The condition will present with amenorrhea or oligomenorrhea that has no other explanation and is confirmed by repeated demonstration of high levels of gonadotrophins, on 2–3 occasions at least 3 months apart (with FSH $\geq$25 IU/L; and LH $\geq$40 IU/L). Vaginal sonography will show persistently flat ovaries. In view of occasionally, though rare, resumption of normal function, one cannot be certain that these patients are sterile forever.

3. Resistant Ovary Syndrome

These rare patients with amenorrhea who has elevated gonadotrophins despite the presence of some ovarian follicles. These patients rarely respond to trial to induce ovulation by gonadotrophins, even with high doses. They may rarely benefit from down-regulation of pituitary function by Gn RH agonists followed by HMG treatment in big doses. However the conception rate is very low, and the success rate of ART is also very low, probably because of poor quality ova produced.

4. Effect of Radiation and Chemotherapy

The effect of radiation is dependent upon the age and the X ray dose. The sterilizing dose of X ray is in excess of 150 rads; with >250 rads the risk becomes high (a single diagnostic X ray to the pelvis delivers $\leq$30 rads). The effect is more marked if the exposure occurs in elder patients. The effect can appear later in life in the form of premature menopause. However, a patient who develops radiation amenorrhea can occasionally resume normal ovarian function and may conceive. In such case there is no increase in the incidence of congenital anomaly in the offspring.

Alkylating agents are very toxic to the gonads. As with radiation, there is an inverse relationship between the doses required for ovarian failure and the age at the start of therapy. Methatrexate treatment for trophoblastic neoplasia seems to be less dangerous.

5. Virilizing ovarian tumors are rare but should be suspected when development of amenorrhea is associated with bodily manifestation of virilization. They can be confirmed by vaginal sonography and MRI.

6. Polycystic ovary syndrome

This condition is discussed with ovarian amenorrhea because originally the pathogenesis cycle was thought to begin with abnormality in ovarian steroidogeneses. Though this can be occasionally the case, it is not always so; the pathology may have its origin in the hypothalamus, pituitary, adrenal or in the peripheral body fat. *Recently polycystic ovary is considered as a result not the cause of anovulation* i.e. polycystic ovary emerges when a state of anovulation persists for any length of time. The condition is quite common, the characteristic changes can be found in 75% of anovulatory women. Because there are many causes for anovulation, there many causes of polycystic ovary syndrome.

The first description of the syndrome is credited to Stein and Leventhal in 1935 when they described a symptom/sign complex associated with persistent anovulation comprising amenorrhea or oligomenorrhea, slightly enlarged and polycystic ovaries, which have a smooth pearly, colored and thickened capsule. The syndrome was described to be associated with obesity and mild virilism.

The classical picture is now considered to represent one group in a bigger symptom/sign complex, which is associated with persistent anovulation, which is called polycystic ovary syndrome (PCOS).

- **One or more of the following clinical features** can be associated with polycystic ovaries include:
    1. Chronic anovulation (most constant feature).
    2. Subfertility.
    3. Amenorrhea.
    4. Oligomenorrhea.
    5. Dysfunctional uterine bleeding.
    6. The abnormality is usually a primary one, usually starting by late menarche.
    7. Obesity, mainly trunkal, (android obesity): Waist: hip ratio more, 0.85.
    8. Acne.
    9. Hirsutism: usually mild to moderate.
    10. Slight hypertrophy of the clitoris.
    11. Male-type alopecia; temporal recession and thin hair on the top of the head.
    12. Increased incidence of maturity-onset diabetes mellitus, associated with increased insulin resistance.

13. *Acanthosis nigricans* = a gray-brown velvety discoloration of the skin, usually of the chin, neck, groins, and axillae. This is particularly common in patients with insulin resistance.
14. Increased incidence of abortion.
15. Increased risk cardiovascular disease like hypertension and myocardial infarction.
16. Increased risk of endometrial and, perhaps, breast cancers.
17. ***None of the above***. Approximately 25% of normal women will demonstrate the ultrasonographic finding typical of polycystic ovaries (necklace appearance).

- The **structural changes in the ovaries** associated with polycystic ovary syndrome include the following:
    1. The size of the ovary is slightly increased; maximally to 2 to 3 times the normal size. However, the enlargement is not necessarily found.
    2. The thickness of the tunica (outermost layer) of the ovary is increased. The ovary is characterized by a smooth pearly-white capsule (ping-pong-ball appearance). It was erroneously thought in the past, that thick sclerotic capsule acts as a mechanical barrier to ovulation. A more accurate concept is that this structural change is secondary to persistent anovulation.
    3. There is increase in the number of cystic, growing or atretic, follicles of a diameter less than 8 mm. Each ovary may contain up to 20–100 of such cystic follicle; they are specially concentrated under the surface of the ovary; hence the ***necklace appearance*** on ultrasonography. They are lined by theca cell.
    4. There is increase in the thickness and density of the stroma of the ovary. This increased stromal tissue contributes to increase production of ovarian androgens.
    5. Usually no corpus luteum is present, but it may be rarely found.

- ***Endocrine criteria associated with PCOS:*** *The following endocrine changes can be found in patients with PCOS, but not necessarily all of them:*
    1. In contrast to the characteristic picture of fluctuating hormone levels in the normal cycle, a steady state of gonadotrophins and ovarian steroids can be found with persistent anovulation.
    2. High levels of LH but low-normal levels of FSH. The LH pulse amplitude and frequency are both increased. The high LH: FSH ratio ($\geq$3) is a most consistent endocrine abnormality found in PCOS.

3. High levels of the androgen of ovarian origin: testosterone, androstenedione, dehydroepiandrosterone (DHEA) or dehydroepiandrosterone sulphate (this sulphate mainly is increased if there is an adrenal cortical element in the syndrome, since DHEA sulfuration is produced at the adrenals).
4. Moderately high estrone levels; this rise is contributed to by peripheral conversion of androgens. The estradiol levels are in the normal range seen early in the follicular phase.
5. High level of 17-α hydroxyprogesterone (17-α HP).
6. Low progesterone, with levels in the follicular phase range.
7. Reduction in circulating levels of sex hormone binding globulin; this is an effect of increased androgens on hepatic synthesis of the protein. Consequently there is a increase in the free testosterone (biologically active) is expected.
8. Hyperinsulinemia, increased insulin resistance and may be noninsulin-dependent diabetes mellitus. The patient with increased hyperinsulinemia and insulin resistance are obese, and may have hypertension, acanthosis nigricans and high androgen levels; and are expected to be clomiphene resistant.

   There is indication that hyperinsulinemia is rather the cause than the effect in this association between insulin resistance and high androgen levels. After normalization of androgens with Gn RH agonist treatment, the hyperinsulin response to glucose tolerance testing remains abnormal in obese women with polycystic ovary. The possible mechanism for this effect is that the increased insulin will bind to and activate the ovarian insulin like growth factor I (IGF-I) receptors. The IG FI, through a paracrine or autocrine effects, enhance the LH effect in the production of ovarian androgens. Insulin can also inhibit secretion of SHBG.

   Hyperinsulinism is associated with abnormal lipid metabolism in the liver that increases the incidence of hypertension and predisposes to coronary arterial diseases.
9. *Patients with PCOs respond to progesterone withdrawal*, denoting that there is no deprivation of estrogen. On the contrary, the persistent, and unopposed estrogen can cause endometrial hyperplasia, and increases the risk to endometrial cancer.
10. PCOs readily respond to the antiestrogen clomiphene citrate and to ovarian wedge resection or the recently used laparoscopic surgery – (see under Ovulation Induction).
11. There is a growing trend for considering PCOS as a general badly risk of multiple components and for reaching consequences not limited to infertility.

- ***Etiology and pathophysiology of PCOS***

Though it is possible to elucidate explanations of the association of the various **clinical**, **structural** and **endocrinological** manifestation of PCOS given above, it is not possible to elucidate whether the initiating lesion is in the hypothalamic, pituitary level or within the ovary itself. There is no doubt that most women with PCOS have exaggerated secretion of LH in association with increased secretion of ovarian androgens, but the initiating event remains unclear. The relationship between hyperinsulinemia and androgen excess is now well established. However, hyperinsulinemia is not present in all cases, therefore it may aggravate but dose not cause the syndrome.

It is most unlikely that we shall find one single cause, genetic or environmental for this very common syndrome. One group of patients, those with evident virilization show a familial aggregation. But other forms of the syndrome are not showing familial tendency.

- **Diagnosis of PCOS**

Besides the clinical manifestations and demonstration of the persistent anovulation, the condition is usually diagnosed by ultrasound appearance (preferably utilizing the vaginal probe). The polycystic ovary is typically larger than normal (although not always). The most consistent feature is the peripheral ring (or necklace) of small follicles 2–8 mmin diameter, in association with increased amount and density of ovarian stroma. The picture is distinct from multicystic ovary, which shows larger cystic follicular cyst without stromal hyperplasia (this does not mean PCOS). A thickened capsule may be occasionally noted in PCOS.

The value of the hormone measurements (see under endocrine changes) in blood is rather confirmatory but is not always needed. They are particularly needed in women with hirsutism and other manifestation of virilization, in order to diagnose and adrenal contribution and associated insulin resistance. The value of a single measurement of LH and FSH is of doubtful (except for exclusion of hypergonadotrophic amenorrhea). Progesterone withdrawal test is useful. Prolactin level is measured if there is suspicion of an associated hyperprolactinemia (galactorrhea or nonresponse to progesterone withdrawal). Measurement of androgen levels is needed in patient with virilization, they may direct to the need of use of corticosteroid to inhibit an adrenal contribution.

- **Management of PCOS**

1. ***If infertility is a problem,*** clomiphene is usually an effective treatment (see under Management of Anovulation; the management of clomiphene failure is discussed there). If

HMG/FSH therapy is required, care must be exercised since women with PCOS are at higher risk of ovarian hyperstimulation. It is recommended in these cases to start with very low doses of HMG/FSH and increase the doses very slowly. The use of pure FSH or recombinant FSH have been advocated for this condition because of relative freedom of an LH component (see under Management of Anovulation) however up till now there is no solid evidence that these newer preparations are more advantageous. The addition of Gn RH analogue treatment may improve HMG results.

2. Simple weight loss restoring the proper weight for height body mass index often restores ovulation. This is particularly needed in obese patients, with virilizing manifestations and hyperinsulinism. The advice of a deitition may be needed. Certain oral antidiabetics may help in weight reduction (see under Anovulation). Metformin is given in dose of 500 mg twice daily. It can help reduce weight and diminish insulin resistance and LH levels and can result in resumption of ovulation.
3. Laparoscopic surgery may be considered (ovarian wedge resection revisited; see under Induction of ovulation). Laparoscopy approach result in a pregnancy rate of 40% to 70%. Drilling usually result in temporary effect. This approach has less likelihood of causing adhesions than BOWR but does not completely obviate the risk. Therefore, this laparoscopic management is only resorted to after failure of other measures.
4. Patients with PCOS have a grater than normal chance of early abortion. PCOS is an important cause of habitual abortion (see under this heading).
5. ***For PCOS patients who are not interested in pregnancy,*** the low dose combined oral contraceptive pill (COC s) is the best treatment. Their use has the following benefits:
    a. Suppress ovarian androgen production.
    b. The estrogen component increases SHG levels.
    c. Alleviate acne.
    d. Checks or improve hirsutism.
    e. Produces regular withdrawal bleedings.
    f. Protection of the endometrium from hyperplasia and carcinoma.
    g. Effective and safe contraception.
6. Women with marked acne and hirsutism can usually be successfully treated with a combination contraceptive pill containing instead of the progestogen, cyproterone acetate plus ethinytestradiol (Diane–35, Schering). In marked cases 100 mg of cyproterone acetate "Androcur, Schering" can be added daily during the last 10 days of taking Diane 35.

7. Patients with evidence of adrenal contribution to the hyperandrogenism can receive suppressive does of corticosteroid (see under treatment of anovulation).
8. Patient with insulin resistance needs treatment with oral antidiabetics. There are also reports of some beneficial effects of such therapy in PCO cases that are not showing such evidence. These treatments can occasionally result in resumption of ovulation.

IV Uterine Amenorrhea

1. Mullerian Agenesis :

Total Mullerian agenesis means complete lack of development of the Mullerian duct with absence of the uterus and most of the vagina (Mayer – Rokitansky – Kustner – Huster syndrome). This is a relatively common cause of primary amenorrhea, more frequent than congenital androgen insensitivity and second only to gonadal dysgenesis. Normal ovarian function is usually associated with mullerian agenesis, as evidenced by normal feminine appearance and normal secondary sexual characters and biphasic body temperature chart. The karyotype is normal. The condition is sporadic; very rarely present in sisters. *Thirty percent of patients have urinary tract abnormalities* in the form of an absent kidney or a horseshoe kidney, ectopic kidney or doubled ureter. Ten percent have skeletal anomalies mostly involving the spine (e.g. spina bifida).

Ultrasound will confirm absence of the uterus and exclude cryptomenorrhea. Usually there is no point to additional confirmation by laparoscopy except when ultrasound picture is nonconclusive. Because of similarity with androgen sensitivity, karyotyping is usually needed.

- Dyspareunia or apareunia is the real problem.
- Surgical reconstruction of the vagina has given the poorest results. Many operations have been described for the purpose. The skin graft whether partial or complete thickness graft usually contracts again.
- Progressive penile dilatation by an active young husband is the o way that can work. The couple may be contented with the sexual pleasure of interlabial intercourse. On rare occasion the frequent, insistent attempt of unknowing young husband resulted in dilatation of the urethra, which is used for the purpose, but with an associated weak control on urine.
- The patient can be provided with special vaginal dilator that can be self-used.
- Genetic offspring can be achieved by collection of oocytes from the genetic mother, IVF by the father sperm and placement of embryos into a surrogate carrier in setting where this is permitted. Surrogacy has not been approved in Egypt and other Moslem countries.

- Cases with lower partial mullerian agenesis are having cryptomenorrhea, and should receive surgical correction to establish continuity and mobilize the functioning uterus down to the vaginal pouch.

2. Androgen Insensitivity Syndrome; (Testicular Feminization):

This is third common cause of primary amenorrhea, after gonadal dysgenesis and mullerian agenesis. Androgen insensitivity is a male pseudohermaphorditism, the individual is a male because of having 46 XY karyotype and because of having testicles. However, the individual is phenotypically female with a vulva and the secondary sex characters of a female, albeit with absent or scarce pubic and axillary hair. There is no vagina, uterus, and tubes. The gonads are testicles.

The testes produce normal or increased amounts of testosterone but due to deficient concentration of the intracellular receptor of testosterone in the target organs the effect of this hormones are lacking. Alternative explanation is that the receptor hormone (testosterone) complex is perceived intracellular as estrogenic stimulus; explaining the feminine secondary sex characters. There is no deficiency of testosterone but there is insensitivity to the hormone or the male hormone has a heterosexual influence. The name androgen insensitivity should replace the old one of testicular feminization; the gonad present histologically is a testicle. Due to lack of androgenic action in utero, the wolffian system does not develop, and the external genitalia is of female type. However due to the normal *in utero* production of antimullerian hormone (mullerian duct suppressive hormone), mullerian agenesis results; hence the absence of the tubes, uterus and vagina. The condition is maternally transmitted by an X-linked recessive gene. Therefore a similar condition is frequent in "sisters" of the affected individual.

There is no ambiguity in the genitalia at birth, the individual is registered and reared as a female. However, two thirds of the patients have inguinal hernia, which can be bilateral. These frequently contain the testicles. At puberty feminine secondary characters will develop normally except for scarcity of pubic and axillary hair. The girl looks normal however, she present usually for amenorrhea and scarcity of bodily hair. The height is normal or more than usual. The external genitalia is normal. There is commonly an inguinal hernia. A mass like a testicle is felt in one or both inguinal region or the testes are completely undescended. There is increased (5%) incidence of malignant tumor in these testicles hence they should be removed at the age of 16–18 years after the full development of the secondary sex characters.

The karyotype is 46 XY, buccal chromatin body negative; testosterone and estradiol are normal for a male. LH is normal or raised. The testicles have seminiferous tubules but mostly with sertoli-cell only.

The condition simulate mullerian agenesis because of absence of the uterus and upper vagina in a phenotypically a female patient, but with the following differences:

Table 1: Difference between Mullerian Agenesis and Androgen Insensitivity

Feature	Mullerian Agenesis	Androgen insensitivity
Karyotype	46 XX	46 XY
Heredity	Not present	Family aggregates, X-linked maternal transmission: 25% are affected offspring and 25% carrier.
Sexual hair	Normal	Sparse or absent.
Hernia	Not predisposed to	70% of patients.
A mass like a testicle	Not felt	May be felt in the inguinal region.
Testosterone	Normal female	Normal or slightly elevated male levels.
Other anomalies	Frequent	Rare.
Gonadal neoplasia	Does not occur	5% incidence of malignant tumor.

Incomplete androgen insensitivity can occur, and these can be associated with enlargement of the fallus and heavy musculine built, but these are present in addition to the feminine features. (see under Sexual Differentiation).

The ***Management*** of androgen insensitivity is essentially similar to mullerian agenesis with the addition of the need for the removal of the gonad in the former case. The gender identity should be enforced rather than negated; the individual is much better as a female hereditary dispute is possible. Incidentally, the individual is insensitive to any amount of androgens administered.

3. Asherman's Syndrome

This is secondary amenorrhea due to destruction and fibroses of the endometrium; amenorrhea trumatica. Intrauterine adhesions (IUA) can bridge between the walls of the uterine cavity and may obliterate its lower part or its whole. Part of the endometrial surface may be fibrosed without adhesion. Curiously, when only the lower part of the uterine cavity is obliterated the upper part does not function and hemometra is most exceptional.

Typically the condition follows upon overzealous curettage in treatment of incomplete abortion or postabortive bleeding, frequently in presence of infection of the uterine contents. Consequently the basal layer of the endometrium from which regeneration normally occurs is removed, and the bare infected myometrial surfaces adhere together. The adhesions are to start with flimsy but later on get fibrosed. Less commonly a similar condition may develop after severe puerperal sepsis. Such cases should be differentiated from Sheehan's syndrome; with IUAs the ovarian function are normal. A similar condition may result from extensive endometrial tuberculoses, less commonly from bilharziasis. Rarely; IUA may be secondary to operations like myomectomy and exceptionally cesarean section when the anterior wall is sutured to the posterior.

The condition presents with secondary amenorrhea or diminished menstrual blood flow, repeated abortion and premature labor and infertility. The condition can be suspected from HSG but the final diagnosis and assessing the prognosis depends upon hysteroscopy (see under Diagnosis of Infertility).

In the past the condition was treated by dilatation of the cervix and blind breakage of adhesions by the endometrial curette. Presently, the condition is treated by operative hysteroscopy when the adhesions are broken under vision by diathermy-connected scissors or laser. Postoperatively an IUD is placed, and the patient is put under broad-spectrum antibiotics. Cyclic estrogen and progestogen treatment (e.g. Prempack–C) containing conjugated equine estrogens and provera are used for 3–6 months to enhance the generation of any residual endometrial rests. (See under management of Uterine Factor Infertility).

V. Amenorrhea due to general disease

1. Thyroid disturbance

Both hyperthyroidism and hypothyroidism can depress ovarian and menstrual function. ***Hyperthyroidism*** whether primary or secondary causes amenorrhea, when the endocrine disturbance is marked and can be clinically suspected. The increased thyrotropin may act on the process of feedback between the ovaries and the hypothalus-pituitary axis. The management is usually medical but surgery is sometimes needed. ***Hypothyroidism*** can cause either dysfunction uterine bleeding or amenorrhea. The menstrual disturbance may occur while the hypothyroidism is still subtle. Primary hypothyroidism increases the production of thyrotrophin releasing hormone (TRH) from the hypothalamus that enhances the production of prolactin by a direct action on lactotrophes. Hyperolactinemia is commonly associated with anovulation and amenorrhea, usually with galactorrhea.

Maintaining a high index of suspicion of thyroid dysfunction will allow recognition of slow low toned speech, suborbital buffeness, coarse scaly skin, slow pulse and low blood pressure as indicative of hypothyroidism. TSH measurement should be done early in the investigation of secondary amenorrhea when it can be higher than normal. Treatment by thyroxin (T_4) is highly effect in restoration of menstruation and ovulation.

2. Diabetes mellitus

Insulin-dependent diabetes that develops early in life is associated with amenorrhea if not adequately controlled. Maturity onset diabetes depending on enhanced insulin resistance can be part of PCOS. (See under this heading).

3. Adrenal cortex

a) The chronic administration of corticosteroids can disturb ovarian function and cause amenorrhea.
b) Adison's disease is usually associated with amenorrhea, correctable by corticosteroid therapy.
c) Adult adrenogenital syndrome or Cushing's syndrome cause amenorrhea associated with virilization.
d) Some cases of PCOS are having an element of minimal adrenal hyperactivity, which will evidence by increased level of DHEA-S. These can benefit from the addition of a small does of corticosteroid to clomphine treatment (see under treatment of anovulation).

4. Chronic illnesses

a) Pulmonary tuberculosis produces amenorrhea. It can be an early symptom of active disease. The tuberculous organism is said to producing toxins that may interfere with the reproductive axis at yet undetermined level. Cure of the chronic infection is followed by resumption of menstrual. Genital tuberculosis (which is usually a postprimary affection) can be also associated with amenorrhea.
b) Grohn's disease is rare cause of amenorrhea.
c) Malabsorption syndrome as steatorrhea can cause amenorrhea but usually after producing evident wasting.
d) Anemia is never in itself, a cause for amenorrhea.

Diagnostic Work up of Amenorrhea

General considerations:

1. Investigation should precede giving treatment. Amenorrhea can be a feature of an important disease.
2. A girl not having menstruation at the expected time and up to the age of 16 should be assessed for development of secondary sexual characters. If these show the beginning of pubertal manifestations (like breast budding and appearance of pubic and axillary hair) she should be examined to *exclude cryptomenorrhea*. If this is excluded any elaborate investigation should be deferred to beyond this age of 16. This girl can have a late menarche; no harm will happen if further diagnostic work is deferred to this age. However, if the secondary sex characters are completely lacking in a girl of 14, investigation for late puberty should be started, particularly if she is of a short stature or showing evidence of gonadal dysgenesis.
3. Primary amenorrhea after the age of 16 year with normal secondary sex characters should raise suspicion of mullerian agenesis or androgen insensitivity. In both there is no uterus that can be demonstrated by abdominal sonography. There are some clinical differences between the two conditions, but the ultimate differentiation will need buccal smear and karyotyping.
4. After excluding cryptomenorrhea, Mullerian agenesis, gonadal dysgenesis, and androgen insensitivity the diagnostic workout of primary amenorrhea is essentially the same as that for secondary amenorrhea.
5. There should be no fixed plan for investigation; the steps should be guided by clinical findings.
6. Clinical assessment: A wealth of information can be gained from careful clinical assessment, which can reduce the cost and trouble of elaborate investigations e.g. Sheehan's syndrome can be fully diagnosed from the history and Asherman's syndrome can be suspected.

   History:

   - Personal history can suggest or exclude pregnancy or suspect menopause.
   - The previous menstrual habit: While the onset of hyperprolactinemic amenorrhea is secondary to a period normal menstrual function, patients with PCOS are usually giving history of late menarche and primarily irregular menstruation.
   - Has there an abnormal development in the woman's life preceding the amenorrhea?
   - Has she had postpartum hemorrhage?

- Has she had curettage for postabortive bleeding?
- Is she breastfeeding?
- Has she been taking hormonal contraception?
- Is she having hot flushes?
- Is she receiving any medication?
- Is she having galactorrhea?

Examination:

- Short stature.
- Obesity-particularly android obesity.
- Secondary sex characters.
- Hair distribution.
- Galactorrhea.
- Manifestation of thyroid disturbance.
- The appearance of the vulva and vaginal, and the length of uterine cavity suggest the functional capacity of the ovaries.

7. ***Special Investigation***

Two investigations should be an early part of the diagnostic workout: vaginal ultrasonography, and hormone withdrawal test:

a. ***Vaginal or abdominal sonography*** will serve exclude pregnancy, assess the size of the uterus, show the characteristic changes of PCOS and assess the thickness of the endometrium. It can demonstrate a previously unsuspected small ovarian tumor. It can be used to assess response to various lines of treatment. Failure of follicular development after clomiphen and or gonadotrophin therapy should indicate a premature ovarian failure and suggest the need for gonadotrophin measurement.

b. ***Hormone withdrawal tests***: in primary amenorrhea a 21 day treatment with estradiol/levonorgestrel preparation (Cyclo-Progynova, Schering) and repeated after 7 days intervals for 3 successive months is enough test of the responsiveness of the endometrium. In general, it will be found that if no withdrawal bleeding occurs the uterus is extremely hypoplastic, or absent.

In secondary amenorrhea, when the uterus must be inherently capable of bleeding, its failure to respond to an adequate estrogen stimulus may mean, pregnancy, psychogenic amenorrhea, (e.g. Anorexia nervosa) hyperprolactenemia, effect of drugs, or marked IUAs.

Progesterone withdrawal test is in the form of given 5 mg of medroxyprogesterone acetate (provera) daily for 5 days. Response by withdrawal bleeding (of any amount) indicates that the endometrium has been under the effect of estrogen for sometime i.e. indicating that the amenorrhea is associated with partial ovarian failure. Positive progesterone withdrawal test is typical for PCOS. Failure of progesterone to produce withdrawal bleeding indicates that ovary is quiescent due to either hyperprolactinemia or primary ovarian failure.

c. ***Hormone assays:*** three hormones are commonly measured in the diagnostic workout of amenorrhea:

- ***Prolactin***: It specially needed if progesterone withdrawal test has been negative or if galactorrhea is present. Most of the labs consider valves above 20 ng/mL as abnormal. However significant hyperprolactinemia can be present without galactorrhea. If the level of prolactin is above 100 ng/mL, a prolactinoma is usually present.
- ***FSH*** level above 20 mIU/mL is abnormally high and indicate hypergonadotrophic amenorrhea and less than 5 mIU/mL is low and indicate hypothalamic amenorrhea. The abnormal level in one blood sample is not adequate and it needs to be repeated on two or three occasion.
- ***TSH***: High TSH indicates primary hypothyroidism and is usually associated with low levels of T_3 and T_4.
- ***Other hormones*** may be measured in special situations including LH, androstendione, DHEA, DHE-S, 17 hydroxyprogesterone, insulin, cortisol, … etc.

d. Imaging of the pituitary fossa

A lateral coned-down X ray can diagnose the majority of macroadenomas. If there is no abnormality detected one can directly proceed to bromocreptine treatment of cases of hyperprolactinemia. If this simple X ray can only miss a microadenoma (which is very common and its progression to a bigger tumor is associated with lack of response in the clinical marker, prolactin). The more accurate imaging by CAT scanning and MRI is better reserved for cases that show abnormality in the X ray study (see under pituitary adenoma).

8. ***Ophthalmological examination*** to assess the field of vision and the eye fundus are needed in patients with large adenoma of the pituitary.
9. ***Karyotyping:*** is required when gonadal dysgenesis or androgen insensitivity is suspected. It can indicate chromosomal deletion in some instance of early ovarian failure.
10. ***Pelvic examination under anesthesia*** and laparoscopy can be used to assess the genital tract in a virgin.
11. ***Hysteroscopy*** should be utilized to confirm, assess the extent and treat IUAs.

    Other investigations are needed under special circumstances ***e.g. X-chest, blood sugar, MRI of the adrenals, … etc.***
12. ***Other investigations are needed under special circumstances*** e.g. X-chest, blood sugar, MRI of the adrenals, … etc.

Treatment of Amenorrhea

1. Treatment of the cause (see above).
2. ***Induction of ovulation*** if infertility is the problem (see under induction of ovulation).
3. ***If contraception*** is required low-dose COC is a good treatment that can achieve besides the cyclic bleeding, the purposes of hormone-replacement therapy, prevention of osteoporosis and arterial diseases, protection from endometrial hyperplasia (if there is continuous availability estrogen as in PCOS) and ensure monthly bleeds.
4. If contraception is not required and all what is needed is monthly bleeding and hormone replacement therapy, cyclic administration of a natural estrogen like estradiol valerate is more advantageous than the synthetic estrogen, ethinylestradiol (EE) present in COCs. Natural estrogen are much less active than EE and their metabolic effects are much less marked. Usually estradiol is administrated for 21 days; during the last 10 days of which a progestogen like levonorgestrel is added. This is followed by 7 days interval before repeating the treatment. This result in monthly withdrawal bleeding. This is frequently required to assure the patient of her normality.

Chapter 22

ENDOMETRIOSIS

Contents

- General pathology
- Pathogenesis and predisposing factors
- Clinical picture
- Treatment
    - Of infertility associated with endometriosis
    - Of cases presenting for pain and other symptoms

      Medical

      Surgical

Definition

Endometriosis indicates the presence and proliferation of endometrium in sites other the uterus. The ectopic endometrium is usually found in other pelvic organs but sometimes in more remote sites.

Endometriosis shares certain pathological features with adenomyosis; which is however a distinct pathology. The two conditions are different pathological entities and in fact are not associated together. They arise in different ways and the finding of one is almost diagnostic of the absence of the other. In adenomyosis, (sometimes described as endometriosis interna) the myometrium is invaded by endometriosis from within. These outgrowths of the endometrium produce surrounding thickening of the fibromuscular tissue in the uterine wall. The thickenings of the myometrium stimulate fibromyomas but differ in having no pseudocapsules around. Pelvic endometrium may involve the peritoneal covering of the uterus, i.e. from without as a result of spread and adhesion to other pelvic structures affected by endometriosis. These belong to endometriosis.

The following discussion concern endometriosis; adenomyosis is discussed elsewhere (Tumors of the Corpus Uteri).

General Pathology of endometriosis

An endometriosis lesion has the typical appearance of endometrium. Both glands and stroma are present, but the relative amounts of each vary. The presence of endometrium in the ectopic sites promotes a fibrous reaction in the host, which is usually diffuse. Sometimes it is encapsulated as in the ovary where there can be a localized endofibroma or endometriotic cyst.

The ectopic endometrium resembles the uterine mucosa in that it is subservient to ovarian hormones. It therefore typically only proliferates when the ovaries are active and atrophies after the menopause. The islets of ectopic endometrium show the cyclical changes of the menstrual cycle and, during pregnancy, its stromal cells exhibit decidual reaction. Since there is no outlet for its menstrual discharge, blood and debris collect within the tissue to from cysts. With each menstrual episode, the collection increases in size, but continual absorption of some of the fluid causes the blood to become inspissated and dark colored to produce a "tarry" or chocolate cysts. As the cyst grows, its endometrial lining is progressively destroyed and is replaced by granulation tissue or by pseudoxanthoma cells rich in blood pigments. This may result in difficulty in recognizing the endometriotic nature of the cyst containing this chocolate material. This is because old hemorrhage in any ovarian cyst, functional or neoplastic, will get similarly inspissated and may be wrongly diagnosed as endometriosis. In the latter, however, the pathology is multifocal and is associated with fibrosis.

Rupture of endometriotic cysts, even small ones, is common, scatters their contents, which include endometrial cells on other peritoneal surfaces, which leads to the development of further areas of endometriosis. The peritoneum reacts sharply by development of dense adhesions. Adhesion and fixation are also encouraged by the fact that endometriosis infiltrate adjacent structures.

Although it is generally recognized that the condition usually becomes quiescent with the cessation of ovarian function, but the condition frequently "burns itself out" with time and become quiescent before the menopause. Indeed the lesions frequently have a limited phase of activity, after which it becomes burnt out to leave merely adhesions and a few tarry cysts. One of the conditions, which favor retrogression, is pregnancy.

No matter how extensive the endometriosis, the fallopian tubes usually remain patent. This fact is of great importance from the standpoint of the retrograde menstruation theory of origin of endometriosis.

After the advent of laparoscopy and its frequent use in infertility, certain early stages of endometriosis are increasingly diagnosed. These early lesion appear as raised or puckered patches which lacks the luster of the surrounding peritoneum or looks red or brown. There is

growing conviction that such early lesions are possibly more active metabolically and generate humeral and cellular factors influencing fertility (Vide Infra).

Sites

Endometriosis can occur anywhere in the body as have been found even in tissues of the arm, leg, pleura, lungs, diaphragm and kidney, however, it is usually confined to the organs and tissues of the abdomen and pelvis at or below the level of umbilicus. ***Visceral lesions are usually multiple****:*

- ***Ovary***

The ovary is the commonest site and is involved in 40 % of cases. The lesions are usually bilateral. It sometimes takes the form of multiple "burnt match head" spots on the surface of the ovary. Sometimes it takes the appearance of chocolate cysts, which disorganize the ovary and are surrounded by dense adhesion. An endometriotic cyst can reach the size of a fetal head, but is rarely larger. It is usually difficult to remove the cysts intact out of surrounding adhesions.

- ***Pelvic peritoneum including the Douglas and uterovesical pouches:***

The peritoneum of the pouch of Douglas is the second common site, and a lesion there is often associated with lesions in the ovaries. In fact, it may represent secondary seedlings from ovarian lesions. The tarry cysts cyst are usually small, no bigger than a pea and are surrounded by puckering and thickening of peritoneum and by adhesions. These adhesions may obliterate the uterorectal space, fixing the uterus in retroversion.

- ***Outer coat of the uterus***

Endometriosis of the pelvic peritoneum and ovaries usually gets adherent to the uterus and endometriosis can involve the superficial layers of the uterus. These are not an adenomyosis.

- ***Uterosacral and Round Ligaments***

The uterosacral ligaments are commonly involved by endometriosis. The lesion can spread down the rectovaginal septum causing extensive puckering and induration of the posterior fornix and the lower part of the rectoovaginal septum. Lesions in this septum can occur without an overlying involvement of the peritoneum of the Douglas pouch. Endometriosis can involve the round ligament in either its pelvic or inguinal canal portion. In the latter case, it forms an abdominal wall swelling that undergoes periodical swelling and pain with menstruation.

- ***Fallopian tube***

Endometriosis of the outer surface of the fallopian tube occurs as a part of endometriosis in the pelvic peritoneum. Endometriosis in the endosalpinx is not seen; may be due to presence of cilia, which prevent endometrial cells from settling in the tube.

– ***Vagina and vulva***

Endometriosis of the posterior vaginal fornix usually represents a spread from deposits in Douglas pouch. It cause thickening and puckering in the affected area, and may ulcerate and periodically discharge blood. It can be mistaken for carcinoma. Endometriotic deposits can occur in scars of episiotomy or of a gynecological operation.

– ***Intestines***

The rectum and pelvic colon can be involved by spread from ovarian and peritoneal endometriosis. The rectum can be implicated by endometriosis in the rectovaginal septum. The appendix, cecum, ileum and omentum are possible sites. Endometriosis of the intestines causes fibrotic thickening and puckering of the outer wall, often with stricture formation. The mucosa is usually intact and the affection does not cause bleeding per rectum and cannot be visualized by sigmoidoscopy.

– ***Bladder and ureter***

Endometriosis of the bladder and ureter is usually invasion from an outside lesion.

– ***Abdominal wall***

Endometriosis can develop in abdominal wall scars following operations on the uterus or tubes. The operations, which are most likely to be followed by these endometriotic deposits, include myomectomy, hysterectomy, removal of pelvic endometriosis, cesarean section and tubal sterilization. A similar condition can follow appendectomy. Endometriosis occurs spontaneously in the umbilicus or inguinal canal without other peritoneal deposits. In these sites, it causes a swelling that becomes bigger and more painful during menstruation. It may appear blue and may ulcerate and bleed during menstruation. The surrounding tissues get fibrosed and indurated.

– ***Lungs and pleura***

Endometriosis in these sites is extremely rare. It can result in cyclic pleuritic pain, hemoptysis and hemothorax.

Pathogenesis of endometriosis

Many theories have been proposed to explain endometriosis but non of them can explain the development of the disease in all the sites. The disease may have more than one mechanism of origin:

1. Transplantation of exfoliated epithelium - retrograde menstruation

The menstrual blood contains viable epithelium, which can be grown in culture. Retrograde menstruation via the fallopian tube into the peritoneal cavity has been seen in laparoscopy done during menstruation cycle. However, the implantation of menstrual

effluent on ectopic sites requires certain predisposition. Sampson has proposed the theory of retrograde menstruation long time ago. Points that may support the theory include:

1. The tubes remain patents in most cases of endometriosis.
2. The most frequent site of endometriosis the ovaries, peritoneum of the Douglas pouch and uterosacral ligament are the possible site of spillage of retrograde menstruation.
3. The stationary structures in the pelvis, as the ovaries and ligaments are more likely to implicated than continually motile structures like intestinal loops.
4. The cul-de-sac is the most dependant part in the peritoneal cavity, and it is a site of common involvement.
5. Areas of endometriosis have been noticed in girls with cryptomenorrhea.

2. Serosal cell metaplasia

The theory (associated with the name of Ivanoff) is based on the fact that the uterus develops from an outgrowth from celomic cells which forms the mullerian duct. It is postulated either that embryonic cell rests capable of differentiating into mullerian tissue remain in and around the peritoneum of the pelvis and the surface of the ovary, or that adult cells in these sites retain the potential to differentiate into endometrium. A similar mechanism has been proposed to explain the histopathology of certain ovarian neoplasias. The serosal metaplasia theory can explain the ectopic endometrium in most of the abdominal sites. Endometriosis outside the peritoneal cavity can be explainable by the presence of vestigeal tongues of celom accompanying the down-growth of the mesodermal urorectal septum and perineum. It is said that even limb buds receive tongues from the celom.

3. Lymphatic and vascular embolism

There is evidence that tiny fragments of endometrium can be detached into lymphatic and venous drainage of the uterus. Under undetermined influences, such emboli can implant in ectopic sites like the umbilicus (known to be richly communicated to the lymphatics of the pelvis) or in distant organs as the lungs or limbs.

All the three mechanisms may be operating, but the development of endometriosis in certain women require certain predisposition, the nature of which is still not understood.

Predisposing factors

Endometriosis is nowadays more commonly diagnosed than in the past. This is because of higher index of suspicion and more frequent use of laparoscopy in investigation of infertility. Widely varying figures have been reported on the prevalence of endometriosis, and a rough estimate is that 3 – 10 % of women in the reproductive age group and 25 – 35 % of infertile women have endometriosis.

Endometriosis and myomas are commonly associated and have common predisposing factor:

1. Age

Active endometriosis is seen most commonly between the age of 30 and 40 years. However, it can occur at any age even in teenagers.

2. Race and class

The disease was considered a disease of white affluent women; Negroes were thought to be less frequently affected. However, recent data suggest that the difference, if any is not dependant on racial factor but rather on social influences including, delayed marriage and childbearing and longer birth intervals, in which effluent women. This coupled to ready access to diagnostic service.

3. Infertility and endometriosis

About 70% of affected women are infertile. This does not always mean that endometriosis is the cause of infertility. In reality the available information, suggest an association rather than a causal relationship. Alternatively, endometriosis may be a consequence of infertility; a prolonged interval of uninterrupted ovulatory menstrual cycles rather than reproductive failure predispose to endometriosis.

Endometriosis can contribute to infertility by either anatomic or biochemical metabolic influences.

a) Anatomical distortion include 1) periovarian and peritubal adhesions interfering with the pickup of the ovum; 2) peritubal adhesion interfering with tubal motility critical for the events of fertilization and transport of the fertilized ovum to the uterus.

b) Potential metabolic effects of endometriosis on fertility have been recently proposed including:

1. Increased prostaglandin production in the peritoneal fluid by the ectopic endometrial deposits. This can influence tubal peristalsis important for ovum transport; in addition to interference with ciliary current. The prostaglandins may reach to the tubal fluid and influence the contractility of the muscle surrounding the interstitial portion of the tube, which influences the transport of sperm and ovum.
2. Altered cell-mediated immunity has been suggested in many publications to be contributing to infertility associated with endometriosis. Peritoneal macrophages are increased in associated with endometriosis; including cases with early endometriosis. The macrophages may engulf sperm and diminish their availability at the fertilization site. An increased number of macrophages trigger cellular activation and cause release of cytokines, which could be toxic to the gametes or early embryos.

3. ***Ovulatory disturbance*** are rare in association with endometriosis. By contrast, most observations have indicated that the disease is almost present exclusively in women who go in long intervals of ovulatory menstrual cycles without conception. Luteinized unruptured follicle (LUF) syndrome is suggested to be commoner in association with endometriosis but the evidence are not strong.
4. The suggestion that endometriosis is associated with increased chance of abortion has not been validated.

The importance of these potential metabolic effects of endometriosis has been subject of a great debate. It has been the basis of offering surgical and medical treatment of endometriosis for infertile women with minimal to moderate disease without anatomic disturbance. However, the evidence so far available does not support that such treatment enhance the chance of pregnancy. At present, it is better to consider these couples with mild to moderate endometriosis to have *unexplained infertility*, and they can be treated accordingly without the delay, expense, inconvenience and complication of surgical and medical treatment of endometriosis.

Clinical picture of endometriosis

▪ *Symptoms*

The severity of symptoms does not always correlate with the severity of the pathology. There may be no symptoms, even when endometriosis is extensive. The explanations for this are: by the time, the lesion is discovered it may have become inactive for several years; and that not all endometriomata menstruate.

1. Dysmenorrhea

Dysmenorrhea is suggestive of endometriosis if it begins after years of painless menstruation. The pain may be diffuse in the pelvis but can be localized to one side or is felt in the rectum. The pain comes on gradually for few days before the period, but is more severe during menstruation when there is bleeding in closed spaces. It can reach a maximum at the end of menstruation. Thereafter, the pain subsides gradually, but may persist during most of the cycle. The pain of endometriosis in localized body sites, like in a scar, is localized to the tumor itself.

2. Abnormal menstruation

Abnormal uterine bleeding is present in 60 % of cases of endometriosis, and can take the from of menorrhagia, polymenorrhea and polymenorrhagia. It frequently indicates ovarian involvement.

3. Dyspareunia

Deep-seated dyspareunia is particularly likely when there is endometriosis in the Douglas pouch, uterosacral ligament and rectovaginal septum, and when there is fixed retroversion flexion.

4. Pain during defecation

This occurs when there is involvement of the rectovaginal septum and is particularly noticeable during menstruation.

5. Infertility

Subfertility is commonly associated with endometriosis (see above). Endometriosis is increasingly diagnosed during laparoscopy done for infertility.

6. Tumor formation

A noticeable tumor can be present if endometriosis involves an abdominal or perineal scar. The tumor enlarges with menstruation and may ulcerate and bleed.

7. Acute abdominal pain

This may result from rupture of an endometriosis cyst. It is particularly likely to occur at the time of menstruation, and may be mistaken for disturbed ectopic or acute appendicitis. Careful analysis of previous and present history suggests the diagnosis of endometriosis. Laparoscopy is usually needed to reach the diagnosis.

8. Other symptoms

General ill health can be associated with endometriosis. Intermittent pyrexia, especially at the time of menstruation. Frequency, strangury (painful desire to micturate) and sometimes hematuria may be caused by endometriosis in the urinary tract. The association with menstruation suggests the diagnosis.

▪ *Physical signs*

Small multiple lesions may produce no physical signs. Larger lesion cause pelvic masses, which are tender, indurate, and are usually ill defined. A fixed tender retroversion of the uterus is suggestive particularly in the absence of any history of genital tract infection. Shotty masses in the Douglas pouch may be felt.

Diffrantial diagnosis:

The diagnosis of endometriosis may be first made during investigation of infertility by laparoscopy. *Symptomatizing endometriosis has to be distinguished from the following conditions:*

- Chronic salpingoophoritis : The two condition share many symptoms and signs. In chronic inflammatory disease, dysmenorrhea is mainly premenstrual and diminishes with menstrual flow.

- Benign adnexal cysts
- Uterine Myomas
- Malignant disease of the ovary
- Carcinoma of the vagina
- Carcinoma of the rectum and colon
- All cases of acute abdomen
- Rupture of a tarry cyst
- Disturbed ectopic

Aids to diagnosis :

1. CA-125 Assay

CA-125 is a cell surface antigen found on the derivatives of the celomic epithelium (which include endometriosis) and it is a useful marker in monitoring of patients with epithelial ovarian carcinoma. In addition, serum CA-125 levels are often elevated in patient with endometriosis, and correlate with both the degree of disease and response to treatment. The assay cannot be used for screening since it is not specific; it can be elevated in early pregnancy, acute pelvic inflammatory disease, myoma and menstruation. However, measuring of CA-125 can help to differentiate endometriotic lesions from benign adnexal cysts.

2. Diagnostic imaging

Ultrasonography and magnetic resonance imaging can be helpful in diagnosis of ovarian chocolate cyst. The density of the chocolate fluid content can be appreciated by both methods. However, neither method is conclusive of endometriosis.

3. Laparoscopy

Laparoscopy is usually the ultimate method used to confirm the diagnosis of endometriosis; the lesion can be magnified on the video monitor. All too often, the clinician fails to observe endometriotic lesions because of a preconceived expectation limited to the classic black powder burn appearance. Lesions can be red, white, blue or black. Adhesions, peritoneal puckering band patches of peritoneal defects, and tanned, non-glistening areas can prove by biopsy to contain endometriotic deposit. However, the clinical significance of these minimal lesions for infertility is not certain, unless there is anatomical distortion of the tubes and ovaries.

Staging systems

There have been several attempts to classify the extent of the disease as seen on laparoscopy or laparotomy. However, there has not been a widely accepted classification system because of the variability of the association of symptoms and clinical consequences,

and the pathology found; and variability of the course taken by the disease. The American Fertility Society (AFS) classification is the most widely used classification but is highly subjective.

Treatment of Endometriosis

The management approaches may differ according to the clinical presentation. The framework of management is as follows:

1. ***Treatment of infertility associated with endometriosis:***
    a. When there are anatomical distortion of the pelvic viscera, surgical treatment; either with laparoscopic or laparotomy microsurgery is needed.
    b. Without anatomical distortion of pelvic viscera:
        i. Expectant management, or treat as cases of unexplained infertility, or.
        ii. Hormonal suppression therapy *is rarely* resorted to, together with surgery.
    c. Assisted Reproduction technology: when the above measures have failed.
2. ***Treatment of pain associated with endometriosis***
    a. General measures.
    b. Hormonal suppression therapy.
    c. Surgery, which can be either.
        i. Conservative.
        ii. Ablative; hysterectomy plus ovarian ablation.

1. Treatment of infertility associated with endometriosis

a. Anatomical distortion of pelvic viscera

- When endometriosis results in mechanical distortion of pelvic viscera surgical correction is indicated. This can be achieved by either operative laparoscopy, or laparotomy and microsurgical correction. The former approach is usually possible and preferable. The same principles used for postinflammatory tuboperitoneal disease should be utilized. These include the use of gentle manipulation, minimal tissue destruction, use of operative magnification, avoidance of desiccation, and the use of powder free gloves, i.e. use of all measures to prevent postoperative adhesion formation (See under treatment of tuboperitoneal-factor infertility).
- The tubes are usually patent but there may be endometriotic adhesions to ovarian capsule, pelvic sidewall or the uterorectal pouch, so that the tube cannot pick up the ovum. These adhesions can be best dealt with by operative laparoscopy. When only the posterior cul-de-sac is involved with adhesion, their removal is not necessary, as

this will not increase the chance of conception, and their removal may induce formation of new adhesions, which can involve the tube.

- The ovary is the most common site of pelvic endometriosis. This can take the form of superficial implants, adhesion of the ovary to the sidewall of the pelvis or other viscera, or intraovarian endometriosis, which produce chocolate cysts (endometriomas). The adhesions should be broken and surface implants cautarized. The endometriomas (chocolate cysts) are excised via the laparoscopy or laparotomy. They usually rupture during removal. Every attempt should be made to remove the whole of the cyst wall. Occasionally, the lining of the endometrioma is so densely adherent that it cannot be removed, requiring cautarization or vaporization to destroy all viable endometrial tissue in the cyst wall. It is usually unnecessary to suture the capsule. Aspiration of the content is not enough. Every attempt should be made not to sacrifice normal ovarian tissue. Recurrence of endometriosis after adequate surgery is usually uncommon (2–20 %).
- Salpingitis isthmica nodosa (SIN) can be a feature of endometriosis (or rather adenomyosis) of the uterotubal junction. This results in proximal tubal block which is demonstrated by hysterosalpingography and. At laparoscopy, the SIN shows localized thickening of the juxta-uterine portion of the tube. Usually there is no other involvement of the rest of the tube. These cases may respond to hormonal suppression treatment, which can be followed by establishment of tubal patency. If hysterosalpingography demonstrate the tube is still blocked, fluroscopic or hysteroscopic proximal tubal cannulation can be tried.
- *If diagnostic laparoscopy demonstrates extensive endometriosis.* Preoperative hormonal suppressive treatment for 2–3 months by danazol or Gn RH agonists can facilitate subsequent surgery.
- It is generally better to allow the couple to attempt having pregnancy after the surgery without delay. The chance is higher within the first postoperative year. Rarely this chance needs be partially wasted by use of postoperative hormonal suppressive treatments.

b. Endometriosis without anatomical distortion of the pelvic viscera

- Although there is no doubt that the endometriotic lesions will need treatment if they are causing pain and or dyspareunia, there is a great controversy about whether these treatment improves fecundability of infertile couple, when the disease dose not mechanically distort the anatomy of pelvic viscera. Controlled trials have not so far, provided evidence that surgical or medical treatment of such early cases increase fecundability. The proponents of active management of minimal or moderate disease give two arguments in support of their view: 1) The first is that the metabolic effects of

endometriotic may reduce the chance of conception. The second rationale for active treatment is to stop progression of early disease. This is usually not the case. Current recommendation is to *manage such cases with minimal lesion associated with infertility in the same way as cases of idiopathic or unexplained infertility*. Recommendations of using hormonal suppression treatment come from trials involving patient with painful disease. Usually these cases can be managed by controlled ovarian hyperstimualtion and IUI.

- ***Assisted reproduction technology*** by IVF/ET or GIFT can be utilized for difficult and resistant cases. Resort to such approach should not be long delayed until the patient get in her forties. The results are much better in early and moderate cases than in advanced cases. Recent series have demonstrated that results of ARTs are not inferior to those obtained in comparable infertility cases with post-inflammatory tubo-peritoneal factor, or cases of unexplained infertility without endometriosis. However, the result of ARTs is inferior in cases with advanced pelvic endometriosis.

2. Treatment of endometriosis presenting for pelvic pains

a. General nonspecific measures

- Before specific treatment directed to endometrium is initiated certain nonspecific therapies can be tried including analgesic, treatment of constipation and use of non-steroidal anti-inflammatory drugs during the second half of the cycle. The lattes diminish the formation of luteal phase prostaglandins, which contribute to dysmenorrhea. *If acceptable, pregnancy is encouraged;* it gives a prolonged period relief if not a complete cure.
- If the idea of pregnancy is not acceptable, the patient can benefit from cyclic *combined oral contraceptive* that prevent the luteal-phase increased production of uterine prostaglandins.

b. Hormonal suppressive therapy

Three ways can be used to temporarily suppress ovarian function and the cyclic stimulation of ectopic endometrium:

i. "pseudopregnancy" : the *continuous use of combined oral contraceptive* to relieve the pain due to endometriosis results, like the occurrence of pregnancy, in pseudodecidual changes in the endometriotic deposit which is followed by atrophy. This treatment should be continued for 6 – 12 months, and immediate relief of pain is not to be expected. The treatment causes irregular episode of bleeding which progressively diminish with time, usually giving place to long episodes of amenorrhea. It can give the patient a good relief of pain that usually persist for

some months or years after its discontinuation. The metabolic side-effect are not important and not more than the rare problem associated with intermittent use of oral contraceptive, and are generally less important than the side-effects caused by other forms of hormonal suppressive treatment.

Similarly, the *continuous use of progestogens* alone can result in a similar state of pseudopregnancy. The drug that has been most commonly used for this purpose is orally administered medroxyprogesterone acetate (Provera) 30 mg daily. Some women go in a mild depression with continuous progestogen treatment, and hence, they should be used with care in women with history of clinical depression. There is tendency for weight gain. If oral therapy proves be not effective or acceptable, a shift is made to injectable depot medroxyprogesterone acetate (DMP) giving in doses of 150 mg injections at 3 monthly intervals. The patient should be told that the duration of effects of these injectable may overlast their use by several monthly. Continuous treatment with progestogen disrupt menstrual pattern and can result in prolonged unpredictable episodes of, usually slight bleeding or of amenorrhea. The ovarian suppression may result in atrophy of the vaginal lining and dyspareunia, which can be helped by estrogen local creams.

One advantage of the above two types of pseudopregnancy induction is that they are much less costly than the other two types that will be discussed below.

ii. Danazol

Danazol is a derivative of testosterone that has been in use for some time for endometriosis. It relieves the pain, prevents progression of the disease, and causes atrophy of ectopic endometrium. Originally, danazol was thought to be "antigonadotrophin", however, it has been found not to suppress basal gonadotrophin but it prevents the midcyclic FSH and LH peaks. Hence, it will *prevent* ovulation and *produce* amenorrhea. It does not suppress estrogen levels and has *mild* androgenic effect. Danazol decreases the hepatic production of sex hormone binding globulin and the lipid carrying, high-density lipoprotein. Danazol thus, induces a state estroginized anovualtion with mild androgenization, similar to that associated with polycystic ovary syndrome.

Danazol is given orally, two 200 mg tablets daily. Because of the high cost of the drug, smaller doses have been tried but are not always effective. The treatment is continued for 3 to 6 months. Amenorrhea frequently results, but occasionally episodes of irregular bleeding occur. Danazol is definitely anabolic; it increases body weight due to increase in muscle mass (rarely observable). It has a mild virilizing effects as shown in increased acne, increase in growth of sexual hair but very exceptionally notable hirsutism. It decreases HDL cholesterol; and therefore

its use needs care in dyslipidemic women. Danazol is metabolized in the liver and should be used with caution in patient with hepatocellular damage.

Danazol is an expensive drug, much more costly than pseudopregnancy agents. As a result, it is not always the first choice.

Recurrence of symptoms is expected in at least 30 % cases after discontinuation of treatment.

iii. Gonadotrophin-releasing hormone agonists

Gn RH is a decapeptide that has a short half-life time because it is rapidly cleaved between aminoacid 5-6, 6-7 and 9-10. Analogues of Gn RH have been produced by substituting the aminoacid number 6 and/or replacement of the C-terminal glycine-amid. These substitution inhibited degradation of the peptide prolonging its action resulting in long-term agonists. Such prolongation of action results in an initial "flare" response to the agonist, which is followed by inhibition of gonadotrophin secretion due to the loss of the physiological puslatile pattern. If the administration of the agonist is continued a state of temporary hypogonadism is produced similar to the one that prevailing after menopause. This produces suppression and atrophy of the endometrium and the endometriotic deposits. A number of analogues have been produced that are administered either as a nasal spray (Buserelin), subcutaneous daily injections (Leuprolide or Decapeptyl) or depot intramuscular monthly injection (depo-decapeptyl) or as small biodegradable subcutaneous monthly implants by prepackaged syringe (Goserelin = Zoladex).

Two to four weeks after initiation of Gn RH agonist therapy, the estradiol level drops to levels below 40 pg/ml. This is a temporary "medical oophorectomy" resulting in marked regression of endometriotic tissues and masses. The treatment is continued for 3 to 6 months.

The treatment with Gn RH agonists has a number of disadvantages:

- It is costly.
- It is attended with climacteric manifestations in the form of vasomotor hot flushing and atrophy of the vagina and dyspareunia.
- It results in decrease of bone density, i.e. osteoporosis. Six-month course can reduce the density of trabecular bones by 6–8 %. After discontinuation of treatment, part of the loss is regained but not completely replenished. Recently an "add-back" treatment has been tried, in the form of simultaneous administration of estrogen-progestogen similar to that used for postmenopausal hormonal replacement therapy. The add-back treatment is needed when Gn RH-analogue is continued for more than 3 months. This effectively relieves the

flushes, and it is still to be seen whether this reduces osteoporosis. The results so far, did not show that this add-back treatment diminishes the beneficial effect on endometriotic deposit.

- Gn RH agonist therapy is associated with changes in the lipogram similar to that seen after the menopause i.e. a decrease in HDL-cholesterol. However, the effect is much less marked than that associated with danazol treatment.
- The beneficial effect of Gn RH on endometriosis is temporary; it provides suppression rather than cure of the disease. The cumulative 5-year recurrence rate can be as high as 50 %.
- In well-designed clinical trials, treatment with Gn RH agonists has not increased pregnancy rates in women with infertility associated with minimal or moderate endometriosis.

iv. Gestrinone

Gestrinone, a 19-nortestosterone derivative. It use decreases the secretion of FSH and LH and has a similar beneficial effect to danazol. It is administered only twice weekly.

c. Surgical treatment

Tumors on the body surface are best excised. Deep-seadet lesions call for surgery when 1) symptoms are acute, 2) when the diagnosis is in doubt, 3) when the tumor masses are large, 4) when hormonal suppression therapy has failed, 5) and when there is no immediate plan of having pregnancy. Surgical treatment can be either in the form of either conservative resection, or ablative treatment entailing hysterectomy and bilateral salpingoophorectomy.

i) Conservative resection

A “conservative resection” of endometriotic tissue is defined as a surgical procedure designed to reduce or eliminate endometriosis but to preserve the option of future childbearing. It can be accomplished by laparoscopic or conventional open surgery. Preoperative hormonal suppressive treatment can reduce the amount and facilitate the surgical effort. This involves resection or vaporization of all visible endometriotic implants and removal of endometriotic cysts in the ovary.

Denervation of pelvic viscera at the time of conservative resection of endometriosis has been used to improve the pain relief. This can be achieved by transecting the uterosacral ligaments or performing a presacral neurectomy. However, these carry risk of injury to the ureters or bowel and may produces bladder dysfunction.

ii) Hysterectomy

If the patient is over the age of 40 year it is often best to remove the uterus and both ovaries if the endometriosis is widespread and severe. If the ovaries are removed, there is no need to risk injury to the bowel or other structures by attempting to excise every fragment of endometriosis; it will regress by its own. Hormonal suppressive treatment can be given for patients who have had incomplete ablation of endometriosis.

In younger women, every effort should be made to conserve ovarian function, and the appropriate treatment is to excise as much as possible and thereafter to treat the patient medically (see above).

After hysterectomy and oopherectomy, hormonal replacement should be in the from of continuous estrogen treatment. The possibility of this reactivating endometriosis is a remote one and should not routinely deprive the patient of the benefit of such hormonal replacement.

Chapter: 23

ABNORMAL UTERINE BLEEDING

DYSFUNCTIONAL UTERINE BLEEDING (DUB)

Contents

Introduction:

Abnormal uterine bleeding is one of the commonest causes of gynecological consultation. There are many possible causes for uterine bleeding, and the differentiation

between them should proceed in a methodological way. The main groups of causes comprise complications of an early unsuspected pregnancy, lesions in the genital tract (mainly the uterus) which can be traumatic, inflammatory and neoplastic, benign and malignant; and lastly dysfunctional uterine bleeding. The emphasis in the diagnostic plan varies with age of the patient:

- ***In infant and young children:*** bleeding is rare and can be caused by:
  - vulvovaginitis of children.
  - Foreign body.
  - tumors (rare, and probably malignant).
  - precocious puberty.
- ***In adolescent*** teenagers, dysfunctional uterine bleeding (DUB) is the commonest possibility, however complications of pregnancy, and blood coagulatory disturbances should be ruled out.
- ***In childbearing period,*** complications of pregnancy should be the first possibility, but iatrogenic bleeding (caused by contraceptives) and DUB are possible.
- ***In women above the age of 4,0*** dysfunctional uterine bleeding is the first possibility but bleeding can be caused by myomata, complications of pregnancy and malignant neoplasias.
- ***In postmenopausal women,*** malignant neoplasia should be ruled out, but the iatrogenic bleeding resulting from HRT is nowadays the commonest diagnosis.

The diagnostic workup can be also influenced by the clinical type of bleeding.

The more irregular the bleeding is, the more likelihood of organic cause.

Clinical types:

The following terms are commonly used:

Dysfunctional uterine bleeding (DUB) is abnormal uterine bleeding with no demonstrable organic cause, genital or extragenital. It is evidently a diagnosis of exclusion.

Cyclic uterine bleeding:

Cyclic uterine bleeding is the bleeding occurring at the time of menstruation. It can be either:

1. ***Menorrhagia*** **(hypermenorrhea):** prolonged and/or excessive uterine bleeding (usually greater than 80 mL) occurring at regular intervals at the time of menstruation.
2. ***Polymenorrhea*** is cyclical bleeding which is normal in amount but occurs at too-frequent intervals of less than 21 days or less than the usual rhythm of the patient.
3. ***Polymenorrhagia*** is cyclical bleeding which is both excessive and frequent.

Acyclic uterine bleeding:

This comprises bleedings occurring apart from a recognized menstruation. It comprises either:

1. ***Metrorrhagia*** is uterine bleeding occurring at irregular but at frequent intervals, the amount can be variable.
2. ***Menometrorrhagia*** is a uterine bleeding that is prolonged and/or excessive, and occurring at irregular intervals.
3. ***Intermenstrual bleeding or breakthrough bleeding*** is the bleeding that occurs between recognized menstrual bleedings. *Intermenstrual spotting* is sometimes used to describe the blood loss that is so light and infrequent that no pad is used.
4. ***Postcoital bleeding or contact bleeding*** is used to describe bleeding or spotting that follows upon intercourse or manipulating the genitalia during douching or self examinations (frequent practice in our culture).
5. ***Metropathia hemorrhagica*** is a term used to describe a clinical situation in which an episode of amenorrhea of some 8 to 10 weeks is followed by an episode of long and/or heavy uterine bleeding.
6. ***Perimenopausal*** *bleeding* is used to describe abnormal bleeding occurring in a woman above the age of 40 years who has not yet had an established menopause.
7. ***Postmenopausal bleeding*** is the bleeding occurring more than one year after the last menstruation in a woman above the age of 40 years or after established menopause (absence of menstruation for more than 12 months).

In general, acyclic uterine bleeding often indicates ovarian dysfunction while cyclic bleeding indicates a lesion enlarging the uterine cavity, e.g., myoma or adenomyosis.

Causes of abnormal uterine bleeding:

A. *General systemic diseases*

These are uncommon cause of uterine bleeding and include the following diseases:

1. ***Coagulation disorders and increased capillary fragility.*** Uterine bleeding can be the first indication of such disorders, but are usually associated with bleeding from other sites of the body like nose and gums. The disorders include:
   a. Idiopathic thrombocytopenic purpura. There is thrombocytopenia and/or defective platelet aggregation. These patients may benefit from corticosteroid therapy and need platelet transfusion. Some need splenectomy.
   b. Iatrogenic thrombocytopenia related to intake of drugs or toxins.
   c. Hypersplenemia (usually associated with splenomegaly).
   d. Leukemia.
   e. Severe sepsis e.g. infected burns.

f. von Willebrand's disease. This is the commonest inherited coagulopathy. The inheritance pattern of von Willebrand's disease is through autosomal dominance; 50% of the offspring of the patient will be affected but with variable penetrance. It is due to deficiency in von Willebrand factor (vWF) which has two important functions in hemostasis: It serves as a bridge between platelets and damaged endothelium of broken capillaries, and it prevents the degradation of factor VIII which is vital to the normal coagulation process. There are three major types of von Willebrand disease. In type 1 disease (80% of the cases), there is deficiency in the levels of normal functioning vWF. In type 2 disease, the levels of vWF may be near normal, but there are abnormalities in function. In type 3 disease (very rare), there is a complete or almost complete absence of vWF from the circulation. The condition is diagnosed by measurement of vWF in blood and assessment of platelet function (aggregation).

The prevalence of von Willebrand disease is about 1% of the European population, and 20% of adolescents hospitalized due to menometrorrhagia can have the abnormality. In many of the patients with type 1 and 2 diseases the symptoms may be very mild, but these individuals are at increased risk for impaired clotting and heavy bleeding during menstruation, or associated with injuries, surgery or dental procedures.

Mild cases can be treated by an analog of vasopressin but marked cases will need infusion of blood products. The latter carry increased risk of viral hepatitis and HIV transmission.

g. *Anticoagulant therapy* does *not* cause uterine bleeding.

2. Hypothyroidism

Hypothyroidism may be associated with abnormal uterine bleeding in the form of menorrhagia or polymenorrhagia. The condition should be suspected when no organic lesion is found for the bleeding and before considering the abnormality as dysfunctional. The condition is suspected when the patient has stigmata of hypothyroidism, like lassitude, sensitivity to cold, slurred speech, pretibial edema and galactorrhea. The condition is confirmed by measuring T3, T4 and TSH in the blood. Recently attention has been directed to subclinical hypothyroidism, which can be diagnosed by an exaggerated response to thyrotrophin releasing hormone TRH, i.e., in spite of a normal bloodTSH level, TRH causes excessive rise in TSH. Menorrhagia associated with hypothyroidism is improved after thyroxin treatment.

Hyperthyroidism, on the other hand, is associated with hypomenorrhea oligomenorrhea or amenorrhea.

3. ***Liver disease*:** Liver cirrhosis is associated with excessive uterine bleeding because of reduced capacity of the cirrhotic liver to metabolize estrogen, and because of inadequate production of coagulation factors. It has to be remembered however, that the periportal fibrosis, the type of cirrhosis secondary to schistosomaisis is late to affect hepatic cellular functions, and therefore is late to cause abnormal uterine bleeding.
4. ***Psychological disturbance*:** Acute psychological upset may precipitate one or two episodes of abnormal uterine bleeding. This may follow exposure to stressful situation in school or work, or in marital or personal life. The condition is commonly seen in adolescents. Chronic psychological imbalance can be associated with menorrhagia or menometrorrhagia, or an alleged prolonged bleeding can be a way of escaping husband's attention. The bleeding can be caused by the associated unovulation and exposure to unopposed estrogen all the time. They can also operate through disturbing the autonomic control of uterine blood vessels. These can cause chronic pelvic congestion manifested by pelvic heaviness, congestive dysmenorrhea, and menorrhagia. In rare cases the uterus may be symmetrically enlarged due to myometrial hyperplasia.
5. ***Heart disease does not cause abnormal uterine bleeding.*** Against common belief, hypertension does *not* affect menstruation.
6. ***Iatrogenic causes.*** These are important causes of uterine bleeding in practice.

a. *Combined oral contraceptives* can cause "breakthrough" intermenstrual bleeding or spotting in about 20% of early cycles of use. Irregular use of the pill is expected to cause irregular menstruation. However, if the bleedings are persistent or develop *de novo* after normal bleeding pattern during earlier use, an organic cause for bleeding should be excluded.
b. *Progestogen-only contraceptives* like the minipill, injectables and Norplant *usually* result in abnormal uterine bleeding. This takes the form of irregular, prolonged, and rarely excessive bleedings. They can also cause of amenorrhea. With progestogen-only injectables continuation of treatment usually results in progressive diminution of occurrence of excessive bleeding, but usually with its replacement by amenorrhea. Continuation of Norplant use, in contrast, is usually associated with progressive normalization of the bleeding pattern; and after the first year of use more than two thirds of continuing users will have acceptable monthly bleeding.

This troublesome bleedings during the use of progestogen-only contraceptives is difficult to manage. A number of approaches have been tried including the administration of a small dose of ethinyl estradiol, simultaneous use of low-dose COCs, use of prostaglandin synthetase inhibitors and Tranexamic acid (a

fibrinolytic inhibitor; the latter two) can be given during bleeding episodes. None of these measures had a conclusive benefit. The failure of hormonal treatment to stop these bleeding abnormalities may be explained by diminution of estrogen receptors in the endometrial elements as a result of continuous availability of the progestogens, or development of abnormal endometrial vasculature..

The best approach for the management of bleeding irregularities associated progestogen only contraceptives is a conservative one. This takes the form of reassurance, after exclusion of organic causes. The user should be encouraged (but not pressed) to bear with abnormality awaiting spontaneous improvement or replacement by amenorrhea (in case of injectables). If this proves unacceptable with the patient, she can discontinue the use and then shifted to another contraceptive. It has to be remembered however, that while normal menstruation will be resumed upon discontinuation of the minipill or removal of the Norplant implants, in the case of injectables resumption of normal menstruation may take some 3 to 6 months after the end of the term of effectiveness of the last injection to become evident.

c. *The IUD* can cause menorrhagia or intermenstrual bleeding or spotting during the first two or three months following the insertion. If these bleedings were excessive, proved persistent or developed *de novo*, this indicates misplacement or displacement of the IUD, and point to the need of the IUD removal or replacement.

d. *Sterilization*. The effects of tubal ligation on menstruation are still not certain. It has been clinically observed that tubal sterilization is followed by increased incidence of dysmenorrhea, menorrhagia or polymenorrhagia. Controlled clinical trials yielded conflicting results varying from no association and an association between prior tubal ligation and abnormal uterine bleeding. There are a number of possible sources of confounding effects e.g. the perimenopausal menstrual irregularities, and of patient and physician bias. It has been suggested that techniques of tubal sterilization, which entail damage to a big segment of the tube by diathermic cauterization, are more likely to cause uterine bleeding than techniques, which involve minimal damage to the tube (and ovarian vessels) like the use of the tubal ring or clip. However, there have been reports on increased incidence of post-sterilization hysterectomies. These should not be taken to confirm cause effect relationship.

e. *Other hormone therapies* might have been used for other indications like climacteric symptoms, premenstrual tension syndrome, dysmenorrhea and acne; and the use may result in abnormal bleeding.

f. *Other medications* may be associated with abnormal uterine bleedings if used for a long time, including corticosteroids and tranquilizers. These disturb the hypothalamo-pituitary control of ovarian function. Ginseng, an herbal root has a weak estrogenic

effect. Ginseng may be used as a general tonic for a long time and can disturb menstruation.

B. *Pregnancy complications*

These are common causes for bleeding and should be considered in the differential diagnosis of abnormal uterine bleeding. The pregnancy state is frequently unsuspected, concealed, or overlooked. The mistake can result in serious implications, particularly if the diagnosis of undisturbed or chronically disturbed ectopic or of trophoblastic neoplasia are overlooked. It is a good rule that a young woman presenting for any gynecological complaint is "pregnant until proved otherwise". Vaginal sonography, pregnancy test or quantitative HCG assays are helpful, and may need to be repeated.

C. *Abnormal uterine development*

Menorrhagia is not uncommonly present with doubled-cavity uterus due to enlargement of the bleeding surface.

D. *Traumatic causes*

- Trauma to the uterus or other parts of the genital tract may result from attempt to induce abortion.
- A foreign body can be inadventally introduced in the vagina by a playing young child.
- A pessary or an IUD might have been forgotten in the genital tract by an old dementiated lady.

E. *Displacement*

Retroversion flexion of the uterus does not itself result in abnormal uterine bleeding. However, a fixed tender retroverted flexed uterus can be associated with abnormal uterine bleeding which is actually caused by the pathology that has resulted in this displacement, e.g., salpingo-oophoritis, or endometriosis.

Uterine prolapse can cause menorrhagia due to increased congestion of the uterus. It can cause metrorrhagia if associated with trophic ulceration.

F. *Pelvic inflammatory diseases*

Salpingo-oophoritis, pelvic peritonitis or cellulitis can cause abnormal uterine bleeding in the form of menorrhagia or polymenorrhagia. These are caused by uterine and ovarian congestion. Chronic endometritis is frequently reported upon in endometrial biopsy specimens but cannot be accepted in itself as a cause of bleeding, since the endometrium is renewed monthly. Tuberculosis of the genital tract can cause uterine bleeding but is more likely to cause hypomenorrhea or amenorrhea.

Chronic cervicitis is rarely associated with bleeding, and this is usually occurring with chronic hypertrophy of the cervix and associated parametritis. Cervical mucous polyp can cause contact bleeding.

G. *Adenomyosis*

Adenomyosis is commonly associated with menorrhagia or polymenorrhagia due to enlargement of the bleeding surface and increased congestion of the uterus.

H. *Endometriosis*

When the ovaries are involved, their function can be disturbed leading to polymenorrhea and polymenorrhagia.

I. *Functional cysts of the ovaries*

These are common occurrence in the ovary but are rarely associated with disturbance of ovarian functions. They can delay the menstruation and this is followed by an episode of prolonged and/or heavy period. Rupture of a persistent corpus luteum cyst may simulate disturbed ectopic pregnancy.

J. *Uterine myomata*

This common tumor is frequently asymptomatic, but when myomata symptomatize abnormal uterine bleeding is the commonest presenting symptom: The nearer the myoma to the uterine cavity the higher is the incidence of uterine bleeding. All types of cyclic or acyclic uterine bleedings can be present. The bleeding is caused by one or more of the following mechanisms: 1) enlargement of the bleeding surface, 2) increased uterine congestion, 3) the commonly associated ovarian dysfunction, 4) associated endometrial hyperplasia, or polyposis, 5) ulceration and infection of the endometrium overlying a submucous myoma, 6) and associated endometrial cancer.

K. *Polycystic ovary syndrome (PCOS)*

Polycystic ovary syndrome can cause abnormal uterine bleeding. The rare functioning ovarian tumors like granulosa/theca tumor can cause abnormal uterine bleeding, usually postmenopausal.

L. *Other benign tumors*

Benign tumors include mainly endometrial polyps that can be, adenomatous, fibroadenomatous and myomatous and are associated with metrorrhagia, or menorrhagia. Cervical mucous polyp can cause slight bleeding.

M. *Malignant tumors*

These include cervical, endometrial, vaginal, vulval and tubal cancer. Ovarian neoplasia rarely disturbs menstruation (see later).

N. *Chronic symmetrical enlargement of the uterus*

Excessive uterine bleeding is sometimes associated with generalized enlargement of the uterus without any focal lesion. The bleeding is mainly in the form of menorrhagia, which is usually ovular. The condition forms an increasing proportion of indications of hysterectomy. The etiology of the condition is not certain. It may be caused by 1) chronic pelvic congestion which can results from sedentary life, chronic psychological stresses and anxiety states like marital disharmony, and unsatisfactory sexual relations. 2) The condition can be associated with varicosities of the pampiniform plexus of veins. 3) The condition can be associated with chronic pelvic inflammatory disease or endometriosis and fixed retroversion flexion. 4) Occasionally the condition is seen in highly parous women. Parous women tend to have heavier blood losses and slightly bigger uterus than nulliparous women, but the differences are usually not accentuated by parity order. Why some highly parous women develop abnormal symmetrical enlargement of the uterus and endometrial cavity is not clear. In the past, the condition was ascribed, without real evidence, to progressive increase in the proportion of fibrous tissue to muscle tissue in highly parous women or chronic or repeated subinvolution of the uterus. Some of these cases should represent an adenomyosis in which the endometrial element has burnt itself off.

O. *Dysfunctional uterine bleeding*

This term is used to describe uterine bleeding for which no organic cause is found. It is a diagnosis of exclusion and its frequency depends upon the definition of organic causes and the care exercised in excluding them.

Mechanisms in abnormal bleeding

The nature of dysfunction is not always certain and can depend upon abnormality 1) in the hormonal stimulation of the endometrium, and/or 2) the control of bleeding from endometrial vessels. The condition is frequently classified according to the nature of the endometrium in biopsy specimens: *Ovular* DUB is diagnosed when secretory endometrium is found, and the bleeding is ascribed to estrogen and progesterone withdrawal. This bleeding can take the form of menorrhagia or polymenorrhagia and is frequently seen during the childbearing period. It is not clear what shortens the menstrual cycle or precipitate excessive blood loss. This can depend upon abnormality in the balance of the hypothalo-pitiutary ovarian stimulation resulting in a shorter follicular phase. This condition is frequently seen with resumption of menstruation after a delivery and is frequently self-limiting. The condition can be caused by an imbalance between different kinds of prostaglandins involved in production of endometrial ischemia and in controlling blood loss from open spiral blood vessels of the endometrium.

When the secretory changes in the endometrium are incomplete or patchy the condition is described as *irregular shedding* of the endometrium, and is thought to be due to a corpus luteum deficiency or its early degeneration.

When the endometrium in the biopsy is not showing secretory changes the bleeding is described as *anovular*. On the whole, this is the commoner type. This condition is more during the years of decline of the function in women above the age of 35 years. The bleeding is usually acyclic and may take the form of metropathia hemorrhagica. The condition may be associated with follicular enlargements in the ovaries seen on vaginal sonography but not necessarily so.

Anovular bleeding usually tends to be heavier than bleeding from secretory endometrium. The heavier bleeding is secondary to high-sustained level of estrogen. In the absence of the growth limiting secretory transformation, the endometrium attains an abnormal height in absence of concomitant formation of supporting stromal matrix. This tissue is therefore, fragile and can suffer from spontaneous patchy breakage and bleeding. As one site heals, another new site breaks and bleeds. As a result of imbalance between different types of locally produced prostaglandins there is deficiency of the restrictive rhythmicity of contraction of the spiral arterioles. Progesterone is important in allowing the endometrium to compact and in increasing contractility of these arterioles. With anovular bleeding there is no tight coiling of the non-secretory endometrium similar to that, which occurs on progesterone withdrawal. DUB has not been fully explained be endocrine dysfunction.

There can be various *types of anovular non-secretory endometrium shown in the biopsy*; occasionally more than one type can be found in a single specimen. They can vary from:

1. Proliferative endometrium like that seen during the follicular phase of the cycle. In this type there is lack of the usual balance between the proportions of glandular and stromal elements.
2. Endometrial hyperplasia with increased number of glands and occasional stratification of glandular epithelium.
3. Cystic glandular hyperplasia, in which there is great variability in the size of the glands, some of them being small while some are wide, resulting in Swiss-cheese appearance under the microscope. Some of the glands can be lined by flattened epithelium while others are lined by cuboidal; some by high epithelium; with occasional sites of stratification. There is no cellular atypia.
4. Glandular hyperplasia in which there is preponderance of the glandular epithelium. The glands are more numerous than usual and appear back-to-back. The epithelium is usually high and may show occasional stratification. However they show no cellular atypia.

5. Atypical endometrial hyperplasia in which the glandular elements are not only excessive but show cellular atypia in the form of enlargement, rounding and pleomorphism of the nuclei. This form is considered precancerous and is better described as endometrial intraepithelial cancer (EIC). They differ from cancer in only absence of invasion of the stroma.

There has been incidence in which there has been progression between the above grades. However, when there are evidences of EIC the condition should be taken seriously and hysterectomy is the recommended treatment. If this is not acceptable progestogen therapy can be tried and should be shown to results in secretory transformation on repeat curettage. If the atypical hyperplasia persists or recurs the uterus should be removed.

When the endometrium is thin and poorly developed proliferative, the bleeding is described as *threshold bleeding*. This is commonly seen during adolescence and premenopause and marks the waxing and waning of ovarian function. The endometrium is under-stimulated and the bleeding represents a breakthrough bleeding.

It has to be noted however that the underlying endocrinopathy and the other mechanism involved in dysfunctional uterine bleeding are not completely understood. Increasing attention is being given to abnormalities in the vascular spaces of the endometrium. Factors influencing the development of vascular endothelium of the endometrium may be involved in the pathogenesis of abnormal bleeding.

Diagnosis of abnormal uterine bleeding

Assessment of the amount of menstrual blood loss

This is usually subjective and depends upon what the woman perceive as usual or normal for her, usually as judged from the number of days of bleeding and the number of sanitary pads (or tampons) she needs to use and soiling of clothes or bedding. The presence of blood clots is usually taken to indicate excess blood loss. The normal menstrual blood does not clot, it has already clotted and been lysed by fibrinolysis during its passage through the endometrium. The presence of clots usually indicates that the amount of blood is more than what can be dealt with by the fibrinolytic system.

Women may be influenced in considering her period abnormal or heavy by subjective variables. These include her concern about fertility and about organic diseases. She can be influenced by a general anxiety or unsatisfactory sexual life. The clinician may need to assess the amount of blood loss. Menstrual blood loss should not cause, in a patient who is consuming an adequate diet anemia or depletion of iron stores. The body can make good the normal menstrual loss of 80-ml monthly. Lowering of hemoglobin concentration or serum ferritin indicate excessive blood loss.

Assessing menstrual loss

The ***alkaline hematin method*** has been used to assess the volume of blood loss. The blood is extracted from towels, pads or tampons by soaking them in a sodium hydroxide solution, which is, examined spectrophotometriclly for alkaline hematin. The median blood loss was found to be 30 mL, but about 20% of women had loss greater than 60 ml and 11% lost more than 80 ml. Discrepancies have been observed between woman's subjective assessment and the objective measurement. These discrepancies were evident in studies of blood loss during use of the various contraceptive methods.

Abnormal uterine bleeding from the perspective of Muslim women

The Muslim women have special concerns about abnormal uterine bleeding. During menstruation, the Muslim woman is not allowed to observe the following religious functions: the prayers, fasting, pilgrimage, entering the mosque, or reading or carrying the Koran. Although she is subsequently required to fast the same number of days she missed during menstruation, she is not required to catch up on the prayers she missed. She is also not allowed to have sexual relations during menstruation. It is not widely appreciated, however, that the above rules apply strictly to menstruation and do not extend to any other abnormal vaginal bleeding, whether cyclic (i.e. prolonged for more than the usual days of bleeding) or acyclic (i.e. occurring at other times). Therefore, and due to inadequate information, abnormal vaginal bleeding is an unwelcome occurrence if it occurs in special circumstance. It is also a cause for discomfort to her husband; he can become annoyed and apprehensive if postcoital bleeding occurs. According to Islamic doctrines the abnormal bleeding is called "Estehada" (menstruation-like bleeding), and does not prevent from the above functions. The prophet Mohamed (God's prayer and peace upon him) was careful to clarify this point when he was asked about a woman whose bleeding exceeded the usual duration of her menstruation. He advised that she should act according to her own previous "habit" (one of the names for the menses in Arabic), and treat the extra days as an Estehada. The prophet said: "these are not menses, but a discharge; she should abstain during the days of her habit and then wash and can pray". The washing required after such episodes of Estehada, and before starting prayer, is a vulval wash, and afterward she wears a protective pad, and then carries out the usual Wodoa. This latter is different from the total body wash she is required to carry out after the end of the days of menstruation and after having intercourse. It is even less widely appreciated that the woman is sinning if she knows these rules but does not observe her religious duties during the Estehada. These points, which are frequently not clear in mind of some Muslim women and their treating physicians, make abnormal uterine bleeding not only a disease entity but a personal and social inconvenience, and result sometimes in over-reaction to the bleeding.

Investigation of abnormal uterine bleeding

The diagnostic workup of abnormal uterine bleeding is a systematic way of defining the cause of abnormal bleeding. The diagnostic plan is not fixed, the older the patient and the more irregular the bleeding, the greater is the need for exclusion of organic causes. Complications of pregnancy need to be excluded during the childbearing period and neoplasia in older patients (during late premenopause and after the menopause).

1- History

- Assessment of the type and amount of bleeding.
- Assessment of presence of associated symptoms like pain, vaginal discharge.
- In certain instance there is a need to exclude that the bleeding is coming from extra genital sites, being anal or urethral in origin.
- Exclude a generalized bleeding tendency. This is particularly required in adolescent patients.
- Careful exclusion of the possibility of pregnancy complication. A history of a prior period of amenorrhea is not always definite, and the pregnancy complications are very variable in their presentation particularly in the case of ectopic pregnancy and trophoblastic neoplasias. An office pregnancy test on a urine sample is usually helpful, but a negative test does not always exclude such complications; quantitative measurement of serum β-HCG and vaginal sonography may be needed; and these may have to be done repeatedly.
- Iatrogenic nature of the bleeding needs be considered.

2- General examination

- Assessment of the effect of bleeding on the hemodynamics and on causing anemia.
- Manifestation of hypothyroidism or other general diseases.

3- Hematological investigations are needed to confirm anemia and to diagnose suspected coagulapathy, particularly in adolescent girls. If hypothyroidism is suspected a thyroid function profile is needed, particularly the measurement of serum TSH level.

4- Pelvic examination

- Assessment of the uterine size, contour, consistency and position.
- Examination of the adnexae.
- Taking cervical smear for routine screening. It can detect some abnormal cells originating from the cervix, endometrium or rarely from the tubes and ovaries. However, failure to find malignant cells in cervical cytology does not exclude the presence of cancer in the corpus.
- Exclude the presence of injuries in the lower genital tract.

5- Sonography: Vaginal sonography can yield many information as regard the uterine size, presence of focal lesion (e.g. Myomata), thickness of the myometrium, endometrium, presence of polyps, adnexal swelling and the size of the uterus. Fluid enhancement by

injecting few millilitre of normal saline (sonohysterography) can help delineate uterine polyps. The use of color Doppler will *add little* to vaginal sonography in diagnosis of abnormal uterine bleeding.

6- Hysterosalpingography (under fluoroscopy)

After the wide use of sonography HSG is rarely used for this purpose. It should not be done if pregnancy or pelvic inflammatory disease are suspected and should not be done during an episode of bleeding. HSG can however show the extent of enlargement and distortion of the uterine cavity, the presence of fusion deformation in the uterine cavity, presence of a polypoidal lesion and the presence of adenomyosis. It will allow the assessment of tubal and peritoneal factor when there is concern about fertility.

7- D&C and other methods of endometrial sampling

D&C is primarily used to exclude the possibility of cancer of the endometrium. It is particularly needed in elderly perimenopausal and postmenopausal. However, it is less likely needed in young women with cyclic uterine bleeding. The incidence of endometrial cancer is 0.66 per 100,000 women aged 30-34. A lot of D&Cs are done unnecessarily in our practice. The potential benefit needs to be considered in the context of the risks associated with D&C, such as those of general anesthesia, laceration of the cervix and uterine perforation. Diagnostic curettage needs to be done with care in order not to miss a polypoidal lesion that may escape the curette, and the uterine cavity always needs to *explored by a small ring forceps* that can catch a pedunculated polyp. The curettage should be methodologically carried out around all the walls of the uterus including the fundus and the connual angles. Studies have indicated, however, that a significant proportion of endometrial lesions are not detected by D&C. The diagnoses of the histopathological type of the endometrium in cases of dysfunctional uterine bleeding will rarely influence the management except the finding of atypical hyperplasia (EIC).

Use of *endometrial brush* and *uterine biopsy* suction gun can be used as an office procedure for endometrial sampling, but they sample a limited segment of endometrial cavity.

8- Hysteroscopy:

Hysteroscopy is the "gold standard" in diagnosis of endometrial lesion because it allows a targeted biopsy. It can be done as an office procedure using a finer scope not requiring cervical dilatation. However, when prior evaluation has indicated the great likelihood of presence of some lesion, it should be planned as an inpatient procedure allowing the use of an operating hysteroscope and a distending fluid and biopsy forceps.

9- Laparoscopy:

Laparoscopy is sometimes used in diagnosis of abnormal bleeding particularly when there is a possibility of tubal (ectopic) or ovarian lesion (e.g. small functioning ovarian tumor). It is also valuable to confirm endometriosis or pelvic inflammatory conditions.

Treatment of DUB

Organic lesions are treated by specific measures. Management of dysfunctional bleeding is by either medical or surgical means and the choice depends upon the severity and length of the complaint, the reaction of the patient to the complaint, and extent of influence on her quality of life and general health. It is also influenced by the attitude of the treating gynecologist.

A. General measures:

- Severe bleeding needs besides measures to stop the bleeding, correction of blood loss. Whole blood or packed RBC transfusions may be required to make good the blood loss. Fresh blood (less than 2 days old), or platelet concentrates may be needed in special cases. Iron and other hematenics are needed to correct anemia. However, long-term conservation should not be permitted of the patient is losing more than what she can gian. In our culture women are reluctant to undergo surgical management, particularly, hysterectomy; and severely anemic women who have been bleeding for a long time are frequently seen. With improved safety and variability of the types of surgical interventions such delay is not warranted.
- Patients with hypothyroidism will have her menorrhagia improved few months after starting thyroid hormone replacement therapy: However, in the absence of hypothyroidism such treatment should not be given, as it increases the burden put on the heart already embarrassed by anemia.
- Patients with coagulopathies will benefit from replacement of deficient coagulation factor: Idiopathic thrombocytopenic purpura may undergo a remission of variable length after corticosteroid therapy. Platelet transfusion is usually needed. Patients with mild forms of von Willebrand's disease will benefit from treatment by analogs of vasopressin; severe cases need transfusion with blood products.

B. Drugs therapies:

There are three groups of drug therapy: (1) prostaglandin synthetase inhibitors (PGSI), (2) fibrinolytic inhibitors, and (3) various hormonal treatments.

1- Prostaglandin synthetase inhibitors:

- There are several, essentially similar drugs which vary only in the extent of side effects, mainly in causing gastric side effects.
- They are taken during the menses, but this needs to be repeated.
- They have been shown to result in 20-40% reduction of menstrual blood loss.
- Dysmenorrhea and pelvic heaviness may also be improved.

2- Fibrinolytic inhibitors and similar drugs:

- The usually used drug is tranexamic acid (e.g cyklokapron tablets): 1-1.5 g four times daily by mouth during the period and repeated monthly.
- They can result in 50% reduction of menstrual blood loss but not all patients will benefit. Concern about causing spontaneous thrombosis has not been substantiated.
- Drugs claimed to improve capillary fragility has been suggested for the purpose of diminishing menstrual blood loss, but without real scientific proof. They are not always effective.

3. *Hormonal treatments*

- *Estrogens*

Estrogen given in high dose orally or by injection, can be used to stop an episode of severe dysfunctional bleeding, the idea being to raise the estrogen blood level above the bleeding threshold; inducing endometrial healing. However, after waning of the effect of the estrogen an episode of withdrawal bleeding is expected and can be severer than the original episode. Therefore, it is always advisable to combine the initial estrogen with a progestogen; bleeding from progestional endometrium is milder than from estrogenic endometrium. A commonly used injectable preparation (Primosistone, Schering) is in ampoule containing 10 mg of estradiol benzoate and 250 mg of hydroxy progesterone coproate, which is given once intramuscularly. To delay the expected withdrawal bleeding and make it milder, the injection is followed by oral administration of a progestogen e.g. norethindrone acetate 10 mg (Primolut-Nor, Schering) twice daily for 10-20 days.

- *Progestogen treatment*
  - One of the synthetic progestogens can be given by mouth during the second half of the cycle (from day 15 to 25) to produce a secretory transformation in the endometrium. This can result in milder withdrawal bleeding and can diminish the blood loss in functional menorrhagia. The progestogens used for that purpose include norethindrone(Primolot-N), norethindrone acetate(Primolot-Nor), dydrogesterone(e.g Duphaston), medroxy-progesterone acetate(e.g. provera), or microonized progesterone(e.g. Utrogestan).
  - Again the effect can be partial and does not occur in all subjects.
- *Estrogen progestogen combination*
  - These can be used cyclically every month starting from the first day in the bleeding and continued for 21 days. One of two possibilities of such therapy can be utilized: The first, is to use combined oral contraceptive, and this is used when

contraception is required. The other, is to use a orally administered preparation containing a natural estrogen like estradiol valerate 2 mg for 21 days, and last 10-12 pills have an added progestogen e.g. norgestrel 0.5 mg or provera 5 mg. This type of treatment is used when contraception is not required. Such estrogen/progesterone treatment can result in formation of less stimulated progestional endometrium and when stopped, a milder withdrawal bleeding. During 3 to 6 cycles of such treatment the abnormality in the pituitary ovarian axis is inhibited, and there is a good chance that the abnormality will have corrected itself by the time it is discontinued. However, this does not always occur.

- This estrogen/progestogen treatment is the most commonly used modality used for dysfunctional uterine bleeding. Lack of response should indicate further search for an organic cause e.g. symmetrical enlargement of the uterus, uterine myoma or endometrial polyp.
- The side effects are very minimal and the treatment is affordable by most patients.

- *Danazol*
  - This is taken continuously in a dose of 200 mg twice daily.
  - It is particularly indicated if endometriosis is present.
  - It is effective; it can reduce the amount of bleeding or cause amenorrhea.
  - Side effects, include mainly weight gain, acne and rarely mild hirsutism.
  - It is an expensive treatment.
- *Gestrinone*
  - It is similar to danazol, but is given twice weekly in oral dose of 2.5 mg.
  - It is not presently available in Egypt.
- *Antiestrogens or Selective Estrogen Receptor Modulators (SERMs)*

  SERMs like Tamoxifen and Raloxifen can be used. They are given by mouth either continuously or during the first 20 days of the cycle. They induce thinning of the endometrium and can reduce the amount of blood loss. The effect is however not achieved on all patients
- *Gonadotrophin releasing hormone (GnRH) agonists*
  - This is highly effective in producing amenorrhea (see under endometriosis).
  - It is continued for 6 months.
  - It is highly expensive.
  - It can produce hot flushes and other menopausal manifestation including osteoporosis.

- If continued for more than 3 months it needs to be balanced by "add-back" therapy by low dose estrogen to prevent osteoporosis.
- Abnormal uterine bleeding may recur after discontinuation.
- It is mainly used in severe cases of uterine bleeding due to coagulapathies like ITP or von-Willebrand's disease allowing time for correction of the hematological problems, or when more definitive treatment needs to be postponed.

- *Levonorgestrel intrauterine device (also designated as system) (LNG IUS)*
  - It is good method of contraception, (commercially available under the name Miner system). An effect of the locally released progestogen (20 μg/day), the endometrium becomes atrophic. This account for the marked reduction in the amount of menstrual blood and the occurrence of amenorrhea in some users. The small amount of LNG released in the uterus has no systemic effects.
  - LNG IUS can be an effective non-surgical method of treatment of dysfunctional bleeding.

C. Surgical treatment of DUB

1. ***D&C***

Although this operation is primarily diagnostic, it is sometimes used to stop an attack of severe bleeding by removing the endometrium. If during the operation, considerable bleeding persisted after curettage, the uterine cavity can be tamponaded by the balloon of Folley catheter inflated to 30 ml. The effect of curettage is usually temporary and bleeding recurs. Repeat curettage is justifiable in young patients, but should not be the practice in women aged more 40 years, in whom the results are poor.

2. ***Laparoscopic drilling of PCOS***

PCOS can sometimes be associated with dysfunctional uterine bleeding. Clomiphene citrate treatment should be tried, but should this repeatedly fail, laparoscopic ovarian drillings may be used.

3. ***Hysterectomy***

Hysterectomy is resorted to in women with persistent dysfunctional uterine bleeding which has failed to respond to repeated trials medical treatment and who are above the age of 40 years and had completed the desired family size. The extent of resort to hysterectomy for this indication is increasing but varies in different countries. The decision to resort to hysterectomy is influenced by two main factors: (1) first is the attitude of the patient, her husband, and the community towards removing the uterus. For some it is a loss of an important part of the body and means end of sexual life and increased risk of obesity and ill health notably menopausal symptoms. (2) Second, the decision is influenced by the attitude of

the treating gynecologist and her or his willingness to proceed further with medical treatment. In the United States DUB is the indication of about 20 to 40% of hysterectomy operation, which is in itself the second common type of major surgery after cesarean section.

At laparotomy for the indication of hysterectomy for DUB it is usually advisable to open the uterine cavity before applying the severing clamps. A small previously unsuspected polyp may be discovered; this may results in saving the uterus from unnecessary removal.

The hysterectomy specimen should be pathologically assessed; the bleeding may be caused or associated with organic lesion, e.g. endometrial carcinoma.

- *Advantage of hysterectomy*

1- A definitive final treatment of abnormal uterine bleeding.

2- Removes the risk of endometrial, cervical (if the cervix is removed) and most of the risk of ovarian cancer (if the ovaries are removed).

3- Even if the ovaries are conserved, hysterectomy by itself can yield 40% reduction of risk of ovarian cancer, this benefit has been demonstrated for tubal ligation for sterilization. This might be the effect of preventing retrograde menstruation, which is said to douse the ovaries with carcinogens.

4- Concurrent removal of the ovaries may reduce the risk of breast cancer.

5- Patients with menorrhagia often have other needs - for example sterilization, relief of pain and treatment of prolapse, which may be addressed by hysterectomy.

- *Disadvantages of hysterectomy*

1- It is a major surgery. However the mortality and the morbidity have been markedly reduced, and the period of stay in hospital reduced.

2- Cost of the operation.

3- Increase the incidence of menopausal symptoms. Even when the ovaries are conserved there is a usually early onset of such symptoms due to premature failure of ovarian function. This may be due to disturbance of vasculature of conserved ovaries. Early menopause may predispose the patient to osteoporosis and coronary atherosclerosis.

4- Psychological effect: There can occasionally be a decline of sexual activity and increased incidence of depression and obesity. However, these points are not based on physiological reasons and needs validation by long-term, controlled studies.

The patient with such a "soft" indication for hysterectomy like DUB, should be adequately and faithfully counseled; she should not be pressed to have hysterectomy unless necessary (see under hystrectomy). The idea of hysterectomy should be discussed in the context of efficacy and possible effects of continuation of medical management:

- *Indications for hysterectomy in DUB*

1. Atypical endometrial hyperplasia.
2. In women above the age of 40 with completed family, when
   - she had needed D&C twice to stop an attack of severe bleeding.
   - the bleeding had caused her anemia.
   - failure of medical treatment and the bleeding is causing unacceptable social and personal difficulties.
3. Cases with symmetrical enlargement of the uterus.

However, there is still three other points that need discussion

1- does the cervix need be removed?

2- should the ovaries be removed?

3- the technique of hysterectomy.

The *cervix* is removed along with the body of the uterus, mainly to obviate the risk of cervical cancer. It may improve drainage of any possible blood ooze (this should not be left behind). Leaving the cervix behind has long been taken as a hallmark of incomplete job and an indication of incompetence of the surgeon. However, removing the cervix increases the risk of complications of injury of the bladder and ureters, of bleeding during operation and formation of vault hematoma. It can also sever the supports of the vaginal vault predisposing to inversion of the vagina. Moreover, the risk of cervical carcinoma should be rare in a patient above the age of forty who had already repeatedly shown negative cervical smears in a screening program in younger age(a service not generally available in Egypt). It has been claimed that leaving the cervix may diminish the perception of the patient of "organ loss", and help her to retain full sexual pleasure. Therefore, it may be reasonable to leave behind the cervix in hysterectomies done for non-neoplastic conditions including DUB. This is particularly so when the cervix is healthy, and when it is deeply fixed in the pelvis.

Removal of normal ovaries along with the uterus is usually considered in order to diminish the risk of ovarian cancer, a deadly malignancy that is frequently discovered at a late stage. However, removal of the uterus itself may reduce this latter risk. The argument in favor of conserving the ovaries is to maintain their hormonal functions. Early and surgically induced menopause is commonly associated with severe climacteric manifestations and with increased incidence of osteoporosis and cardiovascular disease. These risks are greater, the younger the patient at the time of the operation. HRT is rather costly, not completely free of risk, and only a small proportion of women persist with medication for the desired years required for prophylaxis against osteoporosis and CVDs. The ovary does not just make estrogen and

progesterone, but also androgens, which have a role in maintaining libido and sexual arousability. Conserving the ovaries diminishes the concern of the patient about organ loss; removal of the ovaries is equated in the mind of some women with castration. Therefore, the idea of removing the ovaries should be discussed with the patient prior to surgery, and she should be given the above information and helped to make her choice. In this litigious age, gynecologist needs to have written concent on removing the ovaries. In any case, surgeon should keep to himself the right of removing suspicious ovaries and ovaries unseperabably adherent to the uterus.

There are several ***approaches*** for removing the uterus:

a-*Abdominal hysterectomy (AH)* is still the commonly used approach. It allows exploration for associated pelvic abnormalities and adhesion. It caries the least risk of injury of pelvic structures and the easiest approach to control any inadvertent bleeding. It allows easier removal of the ovaries on one hand, and conserving the cervix on the other. However, AH entails leaving an abdominal scar (this can be made minimal and cosmetic), and a longer stay in hospital.

b-*Vaginal hysterectomy (VH):* Vaginal hysterectomy may entail less psychological stress and leaves no visible reminder. It allows repair of the pelvic floor if deficient. It has special advantage in obese women. However, it is doubtful that it entails less risk to the bladder and urters, particularly if done in absence of laxity of uterine support. VH does not allow exploration of the abdomen, and removal of the ovaries is sometime more difficult transvaginally, sometimes they are highly fixed at the pelvic brim. Certainly VH in absence of pelvic laxity needs an experienced surgeon. Such experience should be starved for because the technique is usually gratifying. The cervix is generally removed in VH, however, an operation can be done through the posterior fornix leaving the cervix in situ.

c-*Laparoscopically assisted vaginal hysterectomy (LAVH):* The increasing use of endoscopic surgery has led to this combined approach. The ovarian and may be also uterine vessels are secured and the bladder partially dissected through laparoscopic surgery. The dissection is completed from below through a circular incision around the cervix, through which the organ is removed. Advocates of this type of surgery have given favorable reports. However this approach needs equipment and experience that are not widely available, and may result in greater incidence of injuries to important structures. On the whole, LAVH will take more time (even with trained surgeon) than subtotal AH. LAVH should require longer hospital observation than most of abdominal hysterectomies (contrary to what it is said by advocates).

d-*Laparoscopic hysterectomy*. A technique has been also described for removing the body of the uterus through laparoscopic surgery ending with morcellation of the

specimen. This was followed by coring out the endocervix by the vaginal route (Simm's operation).

4. Endometrial ablation (See also under chapter on hystrectomy)

In dysfunctional uterine bleeding that is not responding to medical treatment endometrial ablation performed hysteroscopically (or by other alternatives) is an alternative to hysterectomy. Hysteroscopic removal of small myomata encroaching upon the uterine cavity is also possible through the hysteroscopy.

Endometrial ablation aims at producing amenorrhea or hypomenorrhea and is possible through a number of approaches:

a- *Hysteroscopic endometrial ablation (HEA)*

- This is done through operating hysteroscope. Both the electrical current of the resectoscope and the Nd:YAG laser has proved to be effective tools in hystroscopic management of DUB and abnormal menorrhagia associated with symmetrical enlargement of the uterus. The resectoscope entails less capital investment. However, it has possible disadvantages since it is a unipolar instrument with a potential for damaging the bowel or bladder by transmitting the current through the uterine wall or by penetrating this wall with the cutting loop. Moreover, there is a risk of troublesome bleeding if a major uterine vessel is opened by cutting too deeply into the uterine wall. Controlling such bleeding carries the risk of fluid overloading of the circulation.
- The Nd:YAG laser entails more capital investment. It has the advantages of:

1- Its probe is flexible reaching the angles of the uterine cavity.

2- It has the ability to transmit laser energy through the distending saline medium obviating the direct contact with the uterine wall. The energy penetrate the tissue to a controlled depth avoiding the risk of perforation of the wall and opening big blood vessels.

- HEA aims at either complete ablation rendering the patient amenorrheic or causing incomplete destruction causing hypomenorrhea. Preoperative thinning of the endometrium can be achieved by use of a GnRH agonist for 2 to 3 months, and this can make the operation easier. Alternatively, thinning of the endometrium can be achieved by preoperative use of COC preparation for 4 to 5 weeks.

b- *Thermal balloon endometrial ablation*

Recently, thermal endometrial ablation has been tried in treatment of DUB. The balloon thermal ablation system comprises a catheter attached to a latex balloon that it is inserted in the uterine cavity. The balloon is filled with a solution of 5% dextrose, which is heated to a certain temperature. The treatment results in uniform coagulation

of 3-5 mm of the endometrium by transmitted heat this can reduce the uterine bleeding in a significant proportion of patient (80%). The idea is to offer an easier alternative to hysteroscopic endometrial ablation. It still needs wider evaluation.

c- *Transcervical endometrial cryoablation*

This is another possible alternative to hysteroscopic endometrial ablation utilizing sudden cooling effect for inducing endometrial destruction. The procedure is carried out through a canulated uterine probe through which carbondioxide or nitrous oxide gas is channeled to its tip. This gas is suddenly cooled to - 45°C, which creates an ice, ball on the tip which cryodestroys the surface of the endometrium. The method is still under evaluation.

d- *Microwave endometrial ablation*

This is another alternative approach for endometrial ablation that is still in the trial phase. This approach utilizes microwave energy, widely used in home kitchens, to heat and cook surface endometrium.

e- *Radio frequency induced thermal endometrial ablation*

This is another approach under development, which is using electromagnetic radiations generated around a probe rotated within the uterine cavity.

Postmenopausal uterine bleeding (PMB)

Postmenopausal bleeding is an important gynecological complaint, which is increasing in frequency, particularly after the increased use of postmenopausal hormonal treatment. Traditionally, the bleeding is considered postmenopausal after the lapse of one year after the last menstruation. However bleeding in the late premenopausal years i.e. in a woman above 45 year is essentially similar to PMB and should be similarly investigated. The investigation aims primarily to exclusion of malignant or premalignant lesions.

Causes

1- Estrogen therapy:

Hormone replacement therapy is being increasingly used to treat patients with climacteric symptoms and for prophylaxis against osteoporosis and coronary heart disease. This prophylactic therapy extends for a number of years. This treatment in women with a uterus comprises the use of estrogen to which a progestogen is added during part (10-12 days) of or the whole month of treatment. The treatment is usually used continuously without periods of interruption. Withdrawal bleedings may not occur during such continuous medication, but they can occur. Women having such bleeding episodes need to be kept under gynecological surveillance aiming avoiding delay in diagnosis of malignant and premalignant

condition. The extent of resort to invasive investigation like endometrial sampling and D&C in these instances depends upon the rhythmicity of bleeding episodes, and their relationship to the time of interfaces between treatment packets (cycles); a withdrawal bleeding is expected after the end of progestogen comedication. Women with such rhythmic bleeding need not be submitted to D&C but should be submitted to repeated, six-monthly assessment of endometrial thickness by vaginal sonography plus cervical smear examinations. Women having continuous or irregular bleeding or develop bleeding *de novo* after long amenorrhea need more invasive search for an organic cause.

Other forms of estrogen therapy need also be considered since estrogens are commonly added to or contained in various types of treatments like in vaginal creams and suppositories, multivitamin preparations, and cosmetic skin creams. These can result in uterine bleeding episodes.

Ginseng, a Chinese herbal root preparation is increasing included in general tonic/antioxidant preparations. Ginseng can have a weak estrogen effect and may occasional cause PMB.

2- Malignant and premalignant lesions including

- *Endometrial carcinoma* and atypical endometrial hyperplasia can account to about 15 to 20% of cases with PMB.
- *Cervical carcinoma*. This may account to 5 to 10% of PMB.
- *Ovarian carcinoma* rarely causes abnormal bleeding, but they may do so if functioning (e.g. granulosa/theca tumors), if associated with pelvic congestion: when big, torted or encurserated in the pelvis. The bleeding can result from spread of malignancy to uterus and tubes.
- *Other types of genital tract cancer* like vaginal, vulval and tubal carcinomas are rare.

3- Benign tumors

Benign tumors rarely cause *de novo* bleeding after the menopause. Examples include myomatous polyp, benign endometrial polyps and cervical mycous polyps (a manifestation of cervicitis).

4-Dysfunctional uterine bleeding

These bleeding results from postmenopausal availability of endogenous estrogens. They can result from peripheral convention of androgens to estrogens mainly occurring in the body fat. This is expected in obese and diabetic women, which are high risk group for endometrial carcinoma. The endometrium in these cases can show any of the grades of endometrial hyperplasia including atypical hyperplasia (which is EIC). However, a significant proportion of women with PMB have atrophic endometrium. True ovular bleeding is exceptional, but may result from follicle "forgotten behind" in the ovaries.

5- Infections:

- Vaginitis - senile, trichomonas, candida infections or bacterial vaginosis.
- Endometritis - tuberculosis or senile.
- Pyometra and hematometra.
- The bleeding in these inflammatory conditions is usually slight and is usually in the form of bloodstained or infected discharge. Such abnormal postmenopausal discharge should receive equal attention as bleeding.

6- Injuries:

- Trophic ulcer of prolapse.
- Forgotten IUD or ring pessary in an old demented woman.
- Post-irradiation injuries.
- Direct trauma.

7- ***Blood dyscrasia*** is an exceptional cause of PMB**.**

8- ***Extra genital causes*** can cause bleeding, which is presumed by the patient as genital in origin. Examples include bleeding or staining of underwear that can result from urethral caruncle, urethral inversion, urethral or bladder polyp or carcinoma. This can also result from hemorrhoides, anal fissure, or anorectal tumors.

Investigation and treatment of PMB

Postmenopausal bleeding or discharge calls for immediate investigation even if it is only one episode in order to exclude malignant or premalignant causes. The presence of an apparent but not important cause for PMB e.g. senile vaginitis should not detract from completing the diagnostic workup. The situation is similar to the story of a bleeding piles or anal fissure that can delay the diagnosis of carcinoma of the rectum. The diagnostic workup include:

1- History.

2- Clinical examination.

3- Cervical and vaginal smear.

4- Transvaginal ultrasound (endometrial thickness).

5- D&C or fractional curettage.

6- Outpatient endometrial sampling.

7- Hysteroscopy and curettage or hysteroscopically guided biopsy.

The **history and clinical examination** aim at diagnosis of above listed causes. Cervical and vaginal smears are routinely done but can easily miss endometrial and cervical pathologies. Further investigation can be tailored to individual cases depending upon the

extent of suspicion of endometrial pathology. Investigation can be repeated in recurrent bleeding until the diagnosis is settled. In rare instances of persistent bleeding hysterectomy is resorted to and the whole specimen is submitted to histopathology.

Ultrasound

Measurement of endometrial thickness by transvaginal ultrasound (TVS) can play a role in screening for uterine malignancy in women with PMB. The cut-off thickness of the endometrium (double layers) is usually 5 mm. The sensitivity in detecting endometrial lesion varies between 80 and 100%, but the specificity (i.e. the ability to exclude lesions other than endometrial cancer) is low, in the region of 50%; and a subsequent investigation is needed in about half of the cases. The specificity of TVS is lower in women receiving HRT. Interoperator variability can exist and the skill of the ultrasonographer matters much.

Sonohysterography has been suggested to improve the sensitivity of the method by injected a fluid (saline or special sonographic contrast medium).

Ultrasound investigation also gives opportunity to diagnose small-unsuspected ovarian tumor.

Dilatation and curettage:

Until recently, fractional curettage under general anesthesia has been the standard investigation of PMB. Separate sampling of endocervical canal can assess the spread of endometrial cancer to the cervix. However, it is not always possible to sample all the surface of endometrial cavity during curettage and the procedure can miss a localized pathology or a polyp. D&C may be complicated by cervical injury (causing bleeding) or perforation of the uterus. Special care should be exercised in D&C done for postmenopausal bleeding, the internal as may be fibrosed and stenosed, and the uterine wall may be markedly thinned out by postmenopausal atrophy.

Outpatient endometrial sampling

There are now a number of devices for performing endometrial biopsies as an outpatient procedure (e.g. Pippelle and Vabra canulas). They entail aspiration of endometrial material via an endometrial canula, which is moved around stroking the endometrium. These procedures usually proceeded by vaginal sonographic examination. Doing both procedures have been suggested as a screening tests before or as substitutes for D&C. However, they sample a limited part of the endometrial cavity, and may miss a localized pathology. If both tests are negative, D&C or hysteroscopy can be deferred but become indicated if bleeding recurs. After the advent of hysteroscopy enthusiasm about these methods has faded.

Hysteroscopy with endometrial sampling

Hysteroscopy allows visualization of uterine cavity and detection of foci of pathology. It can be followed by D&C or combined with guided biopsy. Wherever, available hysteroscopically guided biopsy has become the gold standard for investigation of PMB.

Concern about the possibility of neoplastic implantation into the pelvic cavity by hysteroscopy have not been verified. The approach should be more widely utilized in investigation of PMB.

Chapter 24

MENSTRUATION RELATED SYMPTOMS

Contents

Dysmenorrhea

Dysmenorrhea means painful menstruation. It is one of the commonest gynecological complaints affecting about 50% of women in the reproductive age, and approximately 1% of women have pain severe enough to interfere with their daily life and incapacitate them.

Dysmenorrhea is clinically classified into primary and secondary types. In primary dysmenorrhea, the pain has its origin in the uterus and has no organic pathological cause in the uterus or the pelvis. In secondary dysmenorrhea, the pain is secondary to a pelvic pathology, like pelvic inflammatory disease, endometriosis or myomas. The clinical differentiation between primary and secondary dysmenorrhea is not always clear.

A. Primary Dysmenorrhea

Primary dysmenorrhea takes the form of pelvic pain, which is cramping i.e. with periodic exacerbations. It may radiate to inner thighs or lower back. It starts few hours before or after the onset of menstruation and lasts for one to three days. During severe exacerbations, the patient may look drawn and pale and may vomit or have diarrhea, rectal pain or tenesmus. Sometimes dysmenorrhea may be preceded or accompanied by symptoms of premenstrual syndrome (PMS) like headache, nervousness and fatigue.

Primary dysmenorrhea only complicates ovulatory cycles. Since the early postmenarchal menstrual cycles are usually anovulatory, they are therefore painless and

dysmenorrhea begins one or two years after menarche. Psychological tension tends to exaggerate dysmenorrhea, which is worse during examination periods. Marriage usually does not influence dysmenorrhea unless infertility becomes a problem. In this situation, the woman hates the monthly period and this exaggerates her monthly suffering. Usually primary dysmenorrhea spontaneously disappears in the thirties. Moreover, it is nearly always cured by pregnancy, term labor being more certain to have this effect than early abortion. The pregnancy and labor have this curing effect on primary dysmenorrhea possibly through completing the development of the myometrium and its vascular supply and by dilation of the cervix.

Mechanisms involved in primary dysmenorrhea:

The mechanisms involved in causation of dysmenorrhea are not fully clear. The pain coincides with uterine contraction, there is evidence that PGE2, and $PGF_2\alpha$ released in the endometrium causes this intense uterine contraction. These prostaglandins are released from the endometrium, which has been subjected to cyclic estrogen and progesterone effects. This hormonal sequence activates endometrial synthesis of PGE_2 and $PGF_2\alpha$ from arachidonic acid. The lysis of endometrial cell at the time of menstruation brings the prostaglandins in contact with myometrial cells.

A narrow internal os may result in an increase in the intrauterine pressure. When uterine pressure exceeds the mean arterial pressure for a prolonged tissue, uterine ischemia develops. Uterine ischemia results in accumulation of anaerobic metabolites that can stimulate the small type C pain receptors. This simulates the mechanism of anginal pain of the heart. Uncoordinated uterine contraction can result in a rise of intrauterine pressure resulting in uterine ischemia.

The diagnosis of primary dysmenorrhea depends on exclusion of pelvic or uterine pathology. The need for an elaborate diagnostic workup arises in cases resisting treatment. This includes ultrasonography, peripheral leucocytic count, sedimentation rate and laparoscopy.

The treatment of primary dysmenorrhea begins by reassurance about normality of the phenomena. Restriction of coffee, treatment for constipation, avoidance of long hours on the desk, and encouragement of outdoor exercises may help. These work in the majority of cases. Further drug therapy includes prostaglandin synthase inhibitors and suppression of ovulation.

1. *Nonsteroidal anti-inflammatory drugs:* These inhibit prostaglandin synthesis through inhibiting the cyclo-oxygenase enzymes. Drugs like Ibuprofen, Naproxen sodium and ketoprofen have been long used for treatment of primary dysmenorrhea. They are administered either orally or as rectal suppositories, but occasionally as injections during menstruation. They can produced side effects including increased gastric acidity

(heartburn), gastric ulcer, nausea, prolonged bleeding time, decreased renal blood flow and renal papillary necrosis. Most of these side effects result from inhibition of the physiologic production of the isoform of cyclo-oxygenase-I (COX-I). Recently specific COX-II inhibitors have become available which inhibit abnormal prostaglandin production without inhibiting the physiologically required prostaglandins like PGI, which is cytoprotective to the stomach. These COX-II inhibitors (e.g. Vioxx or Celebrex) will replace other nonsteroidal anti-inflammatory drugs in treatment of primary dysmenorrhea. However, they are costly.

2. *Inhibition of ovulation*: combined oral contraceptives inhibit ovulation; prevent the normal synchronal endometrial growth and differentiation, and usually results in painless menstruation. There is no harm in a girl receiving several cycles of COCs, therefore enjoying pain-free menstruations during an examination season. Persistence of dysmenorrhea after 3 or 4 cycles of COCs should raise doubt about the diagnosis of primary dysmenorrhea and call for investigation for pelvic disease.
3. *Surgical treatment* is exceptionally required and has included:
   a) Dilatation of the cervix to improve cervical drainage and prevent increase in intrauterine pressure. The dilatation should be done slowly and gradually using half-millimeter increments in the dilator in order to avoid injury of the internal os that can result in cervical incompetence. It should never go beyond number 10 dilator. The operation can be most difficult and in fact is rarely justifiable. It is sometimes not effective in relieving the pain.
   b) Presacral neurectomy is done to denervate the uterus. The operation is never justified unless simpler treatment has failed. It may be justified in severe cases where there is other pelvic pathology present i.e. when the dysmenorrhea is secondary. It can be done by laparoscopic uterosacral diathermic cautary and cutting (LUNA). Care should be exercised not injure the ureter during this procedure.

B. Secondary dysmenorrhea

Secondary dysmenorrhea is the occurrence of painful menstruation caused by pelvic abnormalities. These can be endometriosis, pelvic inflammatory disease, myoma, or pelvic congestion syndrome due to broad-ligament varicocele. The pain may be present in other times during the menstrual cycle and represent a periodic exacerbation of a constant discomfort. It takes the form of a diffuse dull aching pain in the pelvis or a sense of pelvic weight. It is often accompanied by lower backache. The pain is at its height two or three days preceding menstruation and is gradually relieved after the onset of menstruation. Therefore, the condition is linked to pelvic congestion building up premenstrually and relieved by

menstruation. The condition is sometimes called congestive dysmenorrhea. The condition usually begins several years after onset of menstruation and usually has a progressive course. Secondary dysmenorrhea may be associated with PMS.

Pelvic examination usually reveals tender adnexa, adnexal masses, tender retroverted-flexed uterus or other evidence of PID, endometriosis or myomas. The diagnostic workup comprises peripheral blood count, erhtyrocyte sedimentation rate, C-reactive proteins, vaginal ultrasonography, laparoscopy, and occasionally Doppler ultrasonography. The diagnostic workup is not always positive, pelvic congestion is difficult to see with the patient lying on her back, and subclinical or minimal endometriosis may be missed.

Treatment of secondary dysmenorrhea is directed to the cause. Non-steroidal anti-inflammatory drugs (see above) may produce partial improvement. General measures like regular aerobotic exercise avoiding caffeine, long hours on the desk, and adjustment of life responsibility may help in cases where there is no treatable cause. Hysterectomy should not be considered except rarely and after failure of other measures when there is incapacitating pain not responding to all measures and only in women with completed family size. A psychological background of chronic pelvic pain should be excluded, lest the pain should persist after removing the uterus.

Dysmenorrhea due to endometriosis and adenomyosis:

Secondary dysmenorrhea beginning after the age of thirty should raise the possibility of pelvic endometriosis or adenomyosis. The pain of endometriosis can be on one side but frequently central in the pelvis. It can be rectal in cases of uterosacral ligament or rectovaginal septum involvement. The pain can be on unusual site according to the site of affection e.g. umbilicus episiotomy or abdominal scar. The pain is usually present all through the cycle and exacerbates premenstrually, but unlike other cases of secondary dysmenorrhea, it worsens during menstruation secondary to accumulation of menstrual blood in closed spaces. The peak is reached during or at the end of menstruation; the relief thereafter, is slow and stretches for some days during the subsequent cycle. The pain may diminish after some years when the endometriosis becomes inactive (see under Endometriosis).

Adenomyosis causes central pelvic pain, which is usually not marked since the ectopic endometrial sprouts are rarely hormone-responsive.

Premenstrual Syndrome (PMS); Premenstrual Tension Syndrome (PTS) (Late Luteal Phase Dysphoric Disorder) (LLPDD):

Most women experience minor psychosomatic changes for few days preceding menstruation. These include easy fatigability, malaise, irritability, headache, or fullness and tenderness of the breasts. These menstrual molimina give way to a sensation of relief and well being once menstruation is established. However, one to five percent of women (depending on type of population) experience severe disabling premenstrual symptoms requiring treatment and often resulting in work or social impairment. Severe symptoms are particularly seen in highly-strung generally nervous women. The syndrome is particularly seen in the duration between the ages of 25 and 45 years. It is monthly repetitive in ovulatory cycles, characteristically premenstrual and relieved by establishment of menstrual flow.

Premenstrual syndrome comprises a constellation of behavioral and physical symptom. The main *behavioral symptoms* include fatigue, irritability, anxiety, excitability, insomnia, mood swings, depression, crying outbursts. The main *physical symptoms* of PMS are headache, dizziness, bloatedness of abdomen and legs, mestalgia (pain and/or tenderness of the breasts) and weight gain. Palpitation, hot flushes or sweating may occur and may be mistaken for premenopausal symptom. Appetite changes are common and may take the form craving for sweets. One or more of the manifestations of PMS may be more prominent e.g. mastalagia. The condition may be associated with congestive dysmenorrhea.

None of the symptoms of PMS is unique to the syndrome. What is pathognomic for the syndrome is the marked fluctuation of symptoms with the menstrual cycle. During the time from the fourth day after the onset of menstruation until at least day 12 of the cycle, symptoms are absent or no more frequent than in the general population. The symptoms coincide with the luteal phase and may increase in severity with the approach of menstruation and disappear either abruptly or gradually after its onset. The persistence of symptoms throughout the cycle should suggest another psychoneurotic disorder and so the prominence of certain aspects likes depression and suicidal ideation. These cases should receive psychiatric care.

In summary, the diagnosis of PMS two-step process:

1. Obtaining the prospective diary of symptom (printed forms are useful).
2. Screening for chronic psychiatric problem, such as major depression.

Etiology of PMS:

The cause of PMS is not understood. The following theories have been suggested and are the bases of a number of treatment approaches:

1. The syndrome is seen in ovulatory cycles. Fine imbalance between estrogen and progesterone (or certain of their metabolites) has been suggested to explain PMS. Inhibition of ovarian functions by long-acting GnRH analogues produces significant relief of PMS. In addition, abnormal interactions between these steroids and certain brain neurotransmitters or receptors have been suggested.
2. A popular theory is that progesterone or certain progesterone metabolites depress GABA-A receptors. The Gamma Aminobutyric Acid (GABA) is a central nervous system mediator which modulates electrolyte influx in brain cells particularly Cl- influx. Activation of GABA-A by certain drugs (e.g. benzodiazepine) produces an anaxiolytic effect. GABA is a general inhibitor of the brain. The mechanism has been suggested to explain the anxiety, tension and depression of PMS.
3. Depression of brain opiates e.g. β-endorphines during the premenstrual period.
4. Depression of serotinine, a CNS neurotransmitter. A low level of serotinine is associated with depressive state.
5. Abnormal prostaglandin metabolism in the endometrium or the brain. These can influence cellular or vascular permeability to ions or water.
6. Fluid retention, an effect of increased estrogens and progesterone.
7. Vitamin B6 deficiency.

Treatment of PMS:

Several approaches can be attempted which can vary with the more prominent feature present:

1. Trial to correct any present personal or psychological problems, which can act as the filter through which, the individual woman interprets and, in turn, expresses her symptoms. This should start by sympathetic hearing and encouragement of the patient to exteriorize her special problems and the aggravating conditions. Advice about trial to reduce the reasons for tension and trial to organize her work and home duties. Reduction of intake of alcohol, nicotine, caffeine, and salt. Regular aerobatic exercise in fresh air can be helpful.

2. A number of hormonal approaches have been tried with some success but in uncontrolled trials. These included:
    a. Administration of progesterone during the 10 to 12 premenstrual days. Natural progesterones or their derivatives are the ones to be used e.g. micronized

progesterone (Utrogestan 100mg twice daily), or dydrogesterone (Duphastone 10 – 20mg daily). Nor-testosterone derivatives are not suitable; they can cause salt and water retention. The intake of combined hormonal contraceptives has been associated with reduced evidence of PMS, but their use as a line of treatment of cases with certain symptoms should be made with care. They may aggravate symptoms like depression or bloatedness. They, however, can be given a trial.

b. Danazol, and attenuated androgen has been demonstrated to be effective in the treatment of PMS in a controlled randomized trial. This benefit may be due to suppressing ovulatory cycle.
c. Bromocreptine one tablet of 0.25mg daily during the second half of the cycle may be of help, particularly when premenstrual mastalgia is a prominent feature.
d. Temporary suppression of ovarian function by long-acting GnRH analogue has been shown to relieve the PMS. The cost and side effects prevent their use except during certain critical occasions when severe symptoms need be avoided.

3. Gamma-Linoleic acid (evening primrose oil, e.g. Primaleve Glaxo wellcome) is a dietary supplement especially useful in the treatment of mastalgia, bloating, weight gain and edema associated with PMS. It may be effective in the treatment of PMS because it alters prostaglandin production and metabolism. The dose is 3 g/day in the 10 to 12 premenstrual days. It is not always effective.
4. *Alprazolam* (e.g. Prazin 0.25mg) is a member of benzodiazepine class of psychoactive drugs. It can be effective in treatment of PMS when anxiety is a prominent feature. It acts through the GABA-A receptors. It may occasionally result in withdrawal symptoms.
5. *Fluoxetine* (Prozac 20 – 40mg daily) is a serotonin reuptake inhibitor and can be used when depression and anxiety are prominent features in PMS. Fluoxetine may produce insomnia, nervousness or nausea.
6. Mild diuretics e.g. thiazide or sprinolacton can be administered during the second half of the cycle when bloating anastalgia and edema are prominent features of PMS. The smallest possible dose should be used.
7. *Vitamin B6* in the dose of 500mg/day can be occasionally effective in treatment of PMS.
8. When depression is a marked feature in a PMS a specialized psychiatric consultation should be sought.

Other cyclic menstrual Phenomena

Menstrual Migraine

This refers to attacks of migraine occurring at the time of menses. Te headaches are localized to one area and are sever. They are usually accompanied by nausea and vomiting

and may be preceded by blurred vision or speech disturbance. The patient may report migrainal attacks at other times.

The etiology, like other cases of migraine, is cerebral vascular instability, arterial spasm or brain congestion. The menstrual timing is not adequately explainable and may be related to allergy to certain hormones or hormone products, cerebral congestion and /or edema.

Treatment includes:

- Same measure as under PMS.
- Symptomatic
- An attack may be prevented by giving, the day before the period, drugs as phenobarbitone, belladonna and chlorpromazine, singly or in combination.
- The specific treatment of the attack is ergotamine tartrate with or without caffeine that can be given intramuscularly in a dose of 0.25mg or 2 – 4 mg by mouth (e.g. Migril tablets 2 mg). To be effective, the remedy needs be given as early as possible in the attack.

Premenstrual Mastalgia

This is usually part of PMS.

Treatment includes:

- Reassurance
- Keeping the breast supported by a bra all the time
- Premenstrual restriction of salt intake or giving of a mild diuretic
- Premenstrual progesterone (see under PMS)
- Premenstrual bromocreptine administration

Recurrent (cyclical) buccal and vulval ulcerations:

Superficial small painful ulcers in the mouth or rarely the vulva may be recurrent and cyclically occur premenstrually or in the midcycle, and disappear at other times. The menstrual cyclicity is usually not strict.

The etiology of these aphthous ulcers is not clear. It can be allergic or related to certain undetectable viral infection.

Treatment is by local applications of antiseptics and astringent douching or pessaries. Improvement of general health and multivitamin and antioxidant preparations may occur. Corticosteroids can be used but beneficial effect is not always achieved.

Chapter 25

CYTOGENETICS AND MOLECULAR GENETICS,

RELEVANCE TO OBSTETRICS AND GYNECOLOGY

Contents

Human genetics is the science devoted to understanding inheritance of characters, including disease and predisposition to disease. Cytogenetic deals with the subject at the structural level as detectable under the microscope; the basic unit is the chromosome. Molecular genetic goes down to the level of molecules as studied in chemical reactions, the basic unit is DNA.

The following is meant to be a basic introduction, refreshment of memory or a summary, which concentrate on information, which have proved to be of clinical relevance.

Historical Landmarks

- In the 1860s, Mendel laid down laws for hereditary transmission, which are still holding until now.
- In the 1950s, Watson and Crick proposed the structure of DNA.
- In the 1960s, Arber, Smith and Nathan discovered the enzymes responsible for cutting and joining DNA; namely the restriction endonucleases and ligases respectively. The use of these enzymes permitted production of recombinant DNA molecule by Berg in 1972.
- In 1975, Southern developed an electrophoresis system (blot) that enabled isolation of DNA fragments utilizing radio-labeled RNA probes. This paved the way to cloning of DNA fragments or genes.
- The next development was the insertion of "plasmid" carrying foreign DNA molecules into bacteria, leading to massive replication of these molecules during division of bacteria (Recombinant DNA).
- In 1988, Mullis received Noble prize for the development of the polymerase chain reaction (PCR) a powerful tool in molecular genetics.

Basic Information

These will be dealt with in the order: chromosomes, genes, DNA.

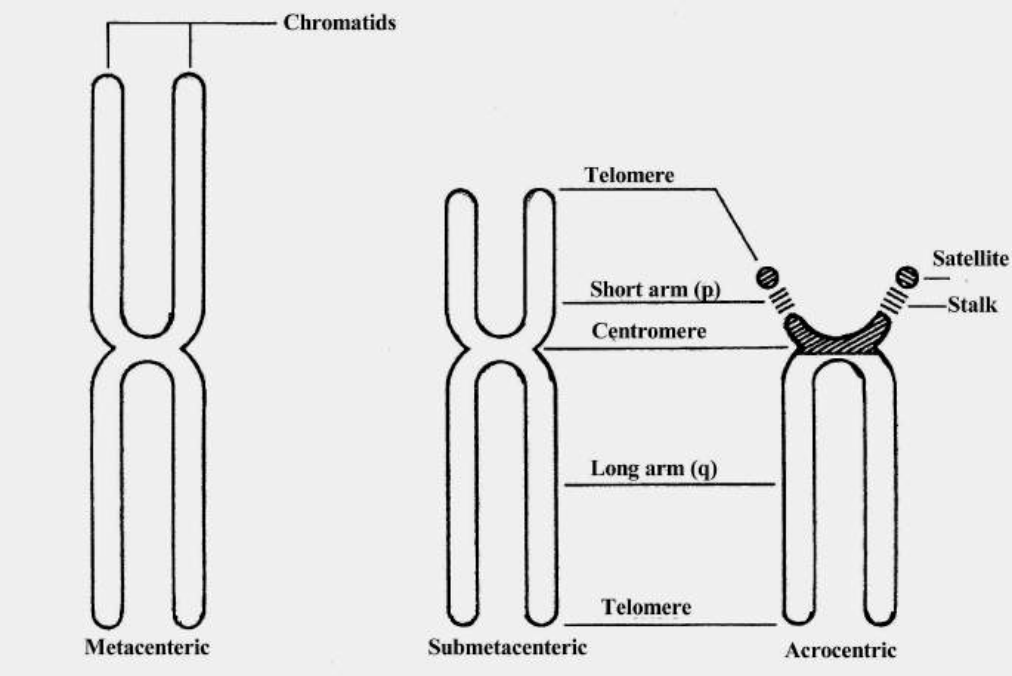
I. Cytogenetics

Chromosomes

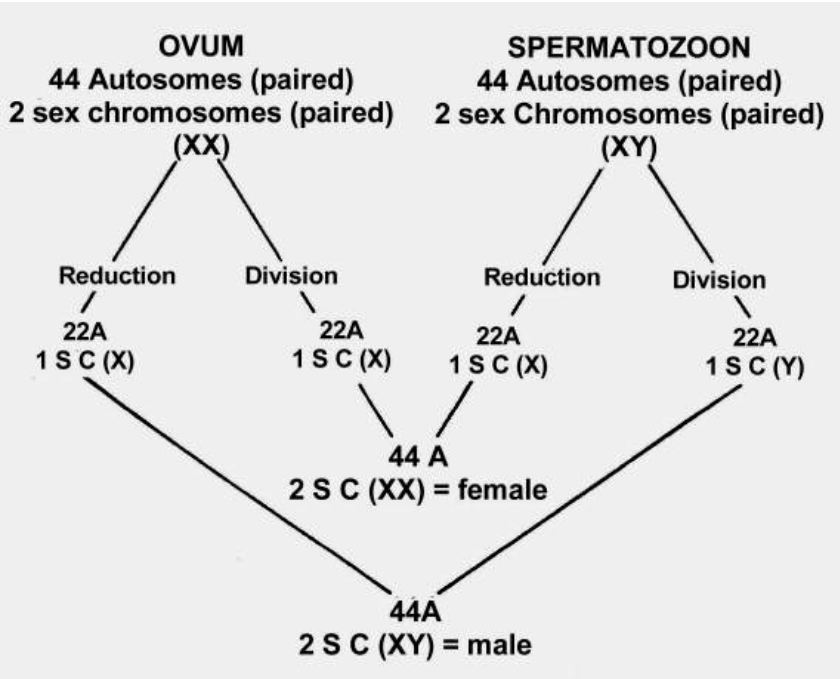
In human cells, genetic material is organized at a certain stage of the cell life cycle in condensed structures called chromosomes. These are microscopically discernible during cell division by the processes of mitosis and meiosis. During these divisions the genetic information are faithfully reproduced and passed to daughter cells.

Each species is distinguished, during the metaphase of cell division, by a characteristic chromosomal number and structure, called the karyotype. Each chromosome is composed of two sister halves, called chromatids which are held together at a point along their length known as the centromere (Figure 1). Each chromatid is replicate of the parent chromosome. The centromere divides the chromatids on a morphological basis into two arms: a short arm designated as p and a long arm designated as q. Grouping of chromosomes and their individual identification depend upon their size and the ratio of p and q arm length. Metacenteric chromosomes have their centromeres near the middle of their length, with p and q arms being nearly equal in length. Acrocenteric chromosomes have very short p arms.

Between these two extremes lie the submetacenteric chromosomes, which have their centromeres at an intermediate position. Chromosomes are also identifiable by a characteristic banding after being stained by geimsa or quinacrine dyes to produce G-bands and Q bands. These bands are produced by certain protein/DNA condensations



Cytogenetics and Molecular Genetics; Figure 1:Human chromosome morphology with delineation of landmarks. *(after Thompson MW, McInnes RR, Willard MF: Thompson and Thompson: Genetics in medicine, ed5, Philadelphia, 1991, WB Saunders)*

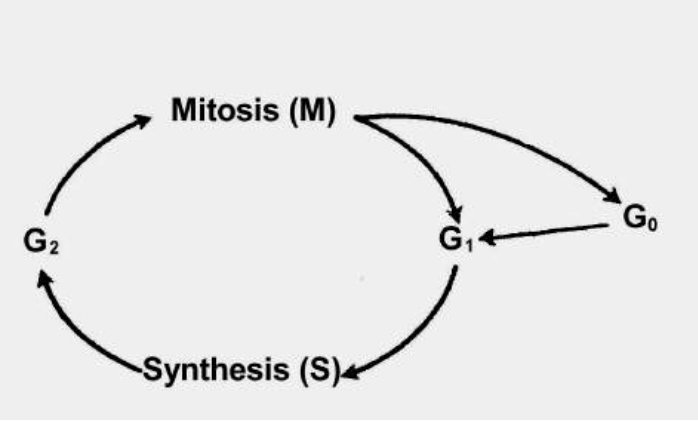


Cytogenetics and Molecular Genetics; Figure 2:*The normal distribution of autosomes (A) and sex chromosomes (sc) before and after reduction division of the ovum and spermatozoon.*

Normal human somatic cells contain 46 chromosomes, referred to as the diploid number (2n), because they comprise 23 pairs. Each pair comprises a paternal and maternal member (Figure 2). This total includes 22-paired autosomes (chromosomes carrying somatic characters) common to both females and males, and 2 sex chromosomes (determining sex specific characters). The female cells have two X chromosomes, while the male cells have one X chromosome and one Y sex chromosome. The chromosomes are identified by conventional numbers depending upon their size, location of the centromere, and the particular banding pattern.

Each chromatid contains one double stranded DNA molecule that stretches from one end to the other as a continuous molecule. The genetic information, the genes represents specific part of the chromosome situated at a specific site called the locus. Each chromosome carries thousands of genes. Each inherited character is determined by a pair of genes, one member being inherited from each parent and situated at corresponding locus in the chromosomal pair i.e. alleles. When the alleles are similar, the individual is described as homologous. When they are different i.e. determining opposite features; the individual is describes as heterogeneous. The alleles can be dominants i.e. showing their effect even if their sister alleles determine an opposite but recessive feature. Recessive genes only show their influence upon pairing with another recessive sister alleles.

Mitosis



Cytogenetics and Molecular Genetics; Figure 3: Phase of cell cycle. *M= mitosis; G1= cells preparing for DNA synthesis which takes place in S, G2= prepare for mitosis, G0= resting phase.*

Mitosis is the division process of somatic cells that ensures that the daughter cells contain the same chromosomal complement as in the parent cell. Mitosis is the last of the four phases of the ***cell life cycle*** that are designated as G1, S, G2, and M phases (Figure 3). During the M phase, mitosis takes place. This is followed by G1 phase, an intermediate phase when

the cell is preparing for DNA synthesis, which takes place in the S phase when DNA is copied. During the G2 phase, the cell prepares again for the next mitosis.

Mitosis (M phase) consists of the following stages:

- ***Prophase*** during which the two chromatids become microscopically visible, the nuclear membrane disappears, and centriole is formed. The centriole is an organelle outside the nucleus that forms the spindles for cell division. The centriole divides and the two halves migrate to the opposite sides of the cell.
- ***Metaphase*** during which the chromosomes allignes themselves in the equatorial plane of the cells. The chromosomes are now maximally condensed. The spindle is formed, consisting of microtubutes of proteins that radiate from the centromeres to the centrioles.
- ***Anaphase*** during which the division occurs in the longitudinal plane of the centromeres. The two separate chromatids move to the opposite sides of the cells by contraction of the spindle tubules.

The ultimate effect of mitosis is the formation of two daughters cells each containing the same number and types of chromosomes present in the parent somatic cell.

An additional important phenomenon occurs during mitosis, which is sister, chromatid exchange (SCE). During SCE, portions of sister chromatids of a single chromosome are exchanged. Usually an equal exchange occurs. Unequal exchange can also occur, resulting in two daughter cells that are not identical in terms of their genetic content.

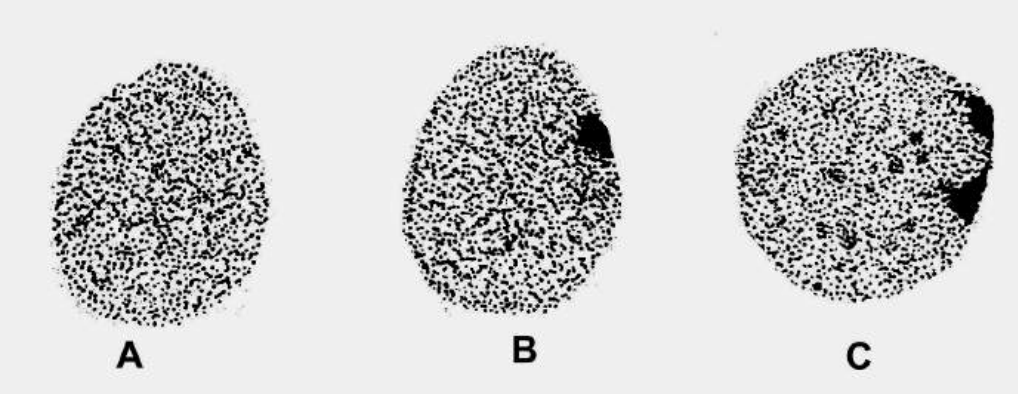
Meiosis

This is the reduction division that forms the gametes, each with haploid number of chromosomes (half of that characteristic for the species). In meiosis, one DNA replication results in two cellular divisions: In the first (Meiosis I), homologous (corresponding) chromosomes pair in the equatorial plane, but instead of longitudinally dividing they separate apart; each of the resultant daughter cell is haploid. The second meiotic division (Meiosis II) is similar to mitosis resulting in the ultimate formation of 4 haploid cells. Gamete production in males gives four functional spermatids, which mature to sperm. Females produce only one functional gamete (ovum), with the remaining meiotic products becoming the two nonfunctional polar bodies. In the oocyte production, meiosis II occurs after fertilization. An exchange of genetic material occurs between chromosomes or chromatids via chiasmata formation resulting in each gamete having a somewhat different genetic endowment e.g. the four sperm resulting from meiosis are not copies of one another.

Error in either division can be the basis of a diseased conditions (vide infra):

Cytogenetic techniques:

1. ***X-chromatin detection:*** This was the first approach for cytogenetic analysis. A chromatin aggregation is conspicuous under the nuclear membrane of the metabolic resting cells in cells containing two X-chromosomes. It is called X-chromatin or Barr's body . It is demonstrated in cytological preparations from a buccal smears. This X–chromatin is 0.7 x 1.4 u in diameter. It is present in 20–60% of the female nuclei and in none of XY males (Figure 4).



Cytogenetics and Molecular Genetics; Figure 4: Sex chromatin (Barr body). *A= the nucleus of a cell with no sex chromatin (usually of a male); B= One barr body usually a female; C= 2 barr bodies from XXX female.*

2. ***Karyotyping:*** Conventional cytogenetic analysis relies on the microscopic evaluation of chromosomes presents during the metaphase of the cell division. At this stage, the chromosomes are at their greatest condensation and are easily obtained intact from lysed cells. The somatic cells are obtained (usually lymphoblast from peripheral blood) and are cultured in presence of agents that stimulate cell growth (mitogens) e.g. phytohemagglutinin. After a period of growth, the cell division is arrested at the metaphase by adding an agent that prevents the completion of the division. The cells are lysed and the spread chromosomes are fixed identified and grouped according to the size, site of the centeromere, and usually by banding technique.
3. ***In banding techniques,*** the metaphase chromosomes are stained with special dyes for visualization under the microscope. Most commonly, geimsa or quinacrine dyes are used to produce either G-banded or Q-banded chromosomes for analysis.

   Any abnormalities in number or appearance of chromosomes are thus identifiable in the karyotype, which can be used to describe the cytogenetic basis of disease.
4. ***Molecular Cytogenetic analysis:*** In the past decade, newer techniques have been developed to evaluate chromosomal structure and function. They depend on more

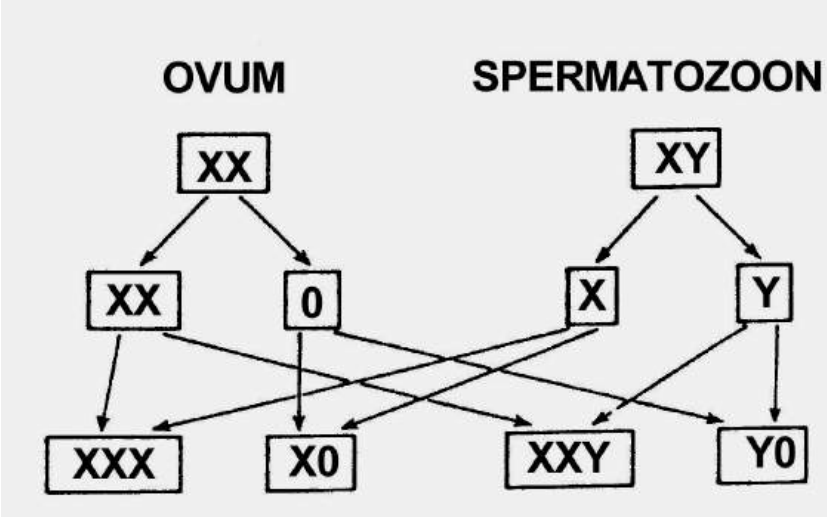
elaborate identification of chromosome segment utilizing labeled molecular probes which anneal (fix to) to specific sites on the chromosome and help their identification.

Cytogenetic bases of disease:

Cytogenetic aberration can arise during faulty meiosis or mitosis. They can belong to two categories: Those related to ***chromosomal number*** and those affecting ***chromosomal structure:***

1. Aberrations of chromosome number (*heteroploidies)* can be either those with multiples of haploid number (n) greater than 2 n (*polyploidies)*, or those with numbers that are not just the multiples of n (*aneuploidies)*.
    a. ***Polyploidy:*** Triploidy is more common than tetraploidy, and both result in early pregnancy wastage. Most often, no identifiable fetal tissue is present. Triploidy usually arises from fertilization of one ovum by two sperm, i.e. Dispermy. Tetraploidy can result from duplication of euploiploid chromosome complement during early stage of cleavage division after fertilization.
    b. ***Aneuploidy*** can result from either the failure of disjunction of sister chromosomes during meiosis I, *(nondisjunction)* (Figure 5) or an *anaphase* lag of segregation. Although nondisjunction can occur in both mitosis and meiosis, it commonly arises in meiosis. One pair of chromosomes fails to separate, and is passed to only one of the daughter cells. These results in one cell lacking both chromosomes of the pair and one cell containing an extra chromosome. Example of the formers when occurring at meiosis is 45,X individuals (gonadal dysgenesis), and example of the latter is 47XXY Klinefilter males. When occurring in early post fertilization mitosis it can result in mosaics, i.e. an individual with two cell lines. In anaphase lag, one chromosome of a pair fail to migrate as the other chromosomes during the last stages of cellular division and becomes excluded from daughter cell. This error yield one chromosomally normal cell and another missing the chromosome (i.e. monosomy, e.g. 45,X).

        Autosomal aneuploidy usually results in an early pregnancy loss. Trisomy 21 may however result in birth of an offspring with Down's syndrome. Sex chromosome monosomy (45,X) can also result in early pregnancy loss, but may result in birth of an individual with gonadal dysgenesis.



Cytogenetics and Molecular Genetics; Figure 5: Non-disjunction of the sex chromosomes of the ovum at the time of reduction division. *After fertilization the possible combinations of the sex chromosomes are* ***XXX*** *(triple X syndrome);* ***XO*** *(Gonadal dysgenesis or turner syndrome);* ***XXY*** *(primary micro-orchidism or Klinefelter syndrome); and* ***YO*** *which has never been found clinically and may be incompatible with life of the embryo.*

2. ***Structural aberrations*** involve chromosome breakage. They comprise deletions, duplications, inversions, translocations, insertions, and isochromosome and ring chromosome formations.
   - ***Deletion*** is the loss of a portion of a chromosome, due to either single or double breaks. A single break leads to the loss of the segment distal to the break, while double break excise the segment between the breaks (interstitial deletion) before rejoining of the bulk of the chromosome.
   - ***Translocation is*** the transfer of a segment of one chromosome to another chromosome. There are two types of translocation: reciprocal translocation in which two chromosomes exchange segments, and Robertsonian translocation, in which two chromosomes are joined as one. Such translocation may be balanced, with no net loss or gain of genetic material, or unbalanced. Unbalanced translocation results in congenital anomalies of the individual carrying the translocation, but balanced ones can only influence gametogenesis resulting in abnormalities in siblings. Translocation can also result in formation of new abnormal genes when the break and joining occur across the sequence of a gene.
   - ***Duplication*** arises when a chromosome includes an extra segment of chromosomal material. The aberration may result from an unequal exchange of genetic material between homologous chromosomes during meiosis.
   - ***Inversion*** takes place by a mechanism similar to interstitial deletion. In contrast, however, the acentric fragment is reinserted at the same breakage site, but in an inverted orientation. Although there is no loss of genetic material this can alter

pairing to homologous chromosome during meiosis and impair cross over of genetic material.

- ***Isochromosomes*** are chromosomes in which both arms are identical for example; two q arms may be present. They are produced by an abnormal division of the centromere in a horizontal rather than longitudinal plane, which thus separates the two arms rather than the two chromatids of the chromosome. The most common example is a chromosome is an X chromosome composed of two long arms. The gamete produced will lack the short arm, and fertilization with a normal gamete will yield a zygote monosomic for the short arm.
- ***Ring chromosome*** arises when two breaks occur on two arms of the same chromosome resulting in two terminal deletions followed by joining of the two break points.

By convention written reports on the karyotype, follow certain order. The number of chromosomes is first specified (e.g., 45 or 46), followed by the sex chromosomes, punctuated by a comma. Thus, 46, XX is the karyotype for a normal female, 46, XY is the karyotype of a normal male, and 45, X for pure gonadal dysgenesis. A description of any abnormality follows, again punctuated by a comma: The specific chromosome is noted by its number, preceded by a plus or minus sign denoting whether the chromosome is extra or missing respectively (e.g., 47, XX, +21 for trisomy 21). When there is a structural abnormality of the chromosome the abnormality is given abbreviated e.g. del for deletion, followed by the number of the chromosome involved, in parenthesis, which may be followed by more specific notation of band involvement. For example, 46,XX, del (5), (q21) denotes a deletion of chromosomal material distal to the q21 band on chromosome 5.

Indications for karyotypic studies (: cytogenetic studies)

The common indications for karyotyping studies broadly include the following:

A. Studies on the individual himself or herself

1. Ambiguity of sex at birth.
2. Delayed menarche.
3. Primary amenorrhea, some cases of secondary amenorrhea with indications of primary hypogonadism.
4. Evidence of abnormality of sexual differentiation.
5. Evidence suggesting Down's syndrome.
6. One or both parent known to be carrier of a chromosomal abnormality e.g. Robertsonian translocation.

B. Sampling of amniotic fluid, chorion or cord of the fetus

1. Advanced maternal age (Genetic amniocentesis), on amniocenthesis or cordocenthesis.
2. Congenital anomalies in previous child.
3. Congenital anomalies in previous family members.
4. Repeated pregnancy loss (abortion or combination of abortion, still birth and malformed fetus).
5. Certain neoplastic conditions e.g. leukemia.
6. Mental retardation.

These karyotypic studies indicate having the *disease* or carrying the *trait*, i.e., the probability of passing the abnormality to the offspring. The karyotype study may be replaced or reinforced by molecular biology studies (see below).

II. Molecular genetics

Molecular biology focuses upon DNA and RNA.

Structure and function of deoxyribonuleic acid (DNA)

DNA is the molecule in the chromosome responsible for coding the genetic messages transmitted during cellular division. Each chromosome carries thousands of genes which are the segments of DNA which code for specific proteins.

Each molecule of DNA consists of repeating groups of ***nucleotides***. Each nucleotide has a sugar, deoxyribose. The sugars in the nucleotides are linked together through *phosphodiester bonds* forming together the backbone of the DNA molecule. Each deoxyribose is attached, in a specific order (which gives individuality and specificity to the nucleotide) to one of four nucleic acid bases, the nucleic bases. These bases comprise two purines and two pyrimidines: The purines are adenine or guanine, while the pyridines are thymidine or cystosine. There are, therefore, four possible nucleotides.

The phosphate-sugar linkages between nucleotides are asymmetric; the phosphorus is linked to the 5- carbon of one sugar and to the 3-carbon of the following sugar. Thus, one end of the chromosome or its segments is the 5` (5 prime) end and the other the 3` (3 prime) end. By convention, DNA and its nucleotide sequences are written from the left to right, from the 5'end to the 3'end. This is in fact, direction in which transcription of DNA segments occurs. During the process of translation, the 5'end leads to the formation of the amino acid end of the coded protein; the 3'end forms the carboxy end of the protein.

If the DNA molecules of a cell were stretched out they would measure nearly 2 million meters long. However, in the chromosome a DNA molecules consists of two tightly coiled strands which form together a characteristic *double helix*. This pattern was described

by Watson and Crick in 1956. The nuclear bases are on the inside of each strand. The nuclear bases of one strand pair by hydrogen bond with those on its sister strand; the adenine specifically pairs with thymidine, and cytosine with guanin. Each DNA strand is complementary in base sequence to its fellow strand. As the cm is a measure of length, the base pair (bp) is the unit of measurement of DNA. A fragment of DNA is therefore measured by the number of base pairs; e.g., a 4,800 bp fragments (a 4.8-kb fragment).

It is estimated that the human has 3 billion bp of DNA, only small portions of which are genetically functional i.e. coding out for proteins.

DNA does not exist within the cell as a naked molecule. The nucleotide chains wind around a core of proteins (histones) to form *neuclosomes*. The nucleosomes become condensed into many bands, the bands that are recognized in the stained karyotype preparations. A variety of other proteins is associated with DNA, and these associations are important for the function of DNA in different tissues.

Replication of DNA:

Replication of DNA occurs during cell division. The process of replication of DNA begins with a separation of the double-stranded DNA helix. This occurs step-by-step initiated by certain enzyme actions. Each strand will constitute a template, which is copied during replication through the action of an enzyme, *DNA polymerase*. This produces a reciprocal copy of the strand. Each daughter molecule therefore contains one of parenteral strand and a newly formed reciprocal one. During the lifetime, the original molecules of DNA will be copied many billion times. By combining precision; with error correcting systems, errors, which affect the function of the geneses, are surprisingly rare.

Maintenance of the fidelity of genetic code is of fundamental importance in normal cell division. There are discrete checkpoints built into the cell cycle to ensure that a cell containing damaged DNA does not replicate its DNA and does not proceed to mitosis until all of the damage has been repaired. In addition, proof reading mechanism keeps DNA sequences under continuous surveillance allowing rapid detection and repair of any damage. Indeed, the presence of excessive or irreparable damage of DNA sequence will activate mechanisms leading to programmed cell death or *apoptosis* in order to ensure that errors are not passed on to daughter cells. Defects in this apoptosis programs propagate faulty DNA through immortalization of abnormal cells. Such defects contribute to cancer pathogenesis.

Gene structure and function:

It is estimated that each human cell contains 5 to 6 million genes. A gene is composed of a segment of DNA comprising a unique sequence of nucleotides (1000 on the average). The genotype of an organism represents the complement of genes (and intervening noncoding

nucleotides) contained in DNA that is inherited from the parents. The location of a specific gene on a certain chromosome is called the locus. Some of the genes are coding for related proteins or segments of dimeric protein e.g. a gonadotrophin genes coding for the α and β subunits are present on separate loci which are on different chromosomes.

Gene Expression

Expression of the encoded genetic information in the DNA occurs through the two processes of ***transcription*** and ***translation***.

The genes in the nucleus determine the production of certain proteins in the cytoplasm. This process is described as gene expression. With some exceptions, essentially one gene yields one protein. This gene expression is achieved through ***transcription*** into a ***messenger RNA (mRNA)***, which carries the genetic message to the cytoplasm where proteins are formed. Not all the nucleotides on the gene are copied in the m RNA. The gene sequence of nucleotides comprises:

Exon: The segment of the gene that yields a messenger RNA product that code for a specific protein.

Intron : The segment of gene not represented in mature mRNA and therefore, not coding for protein synthesis.

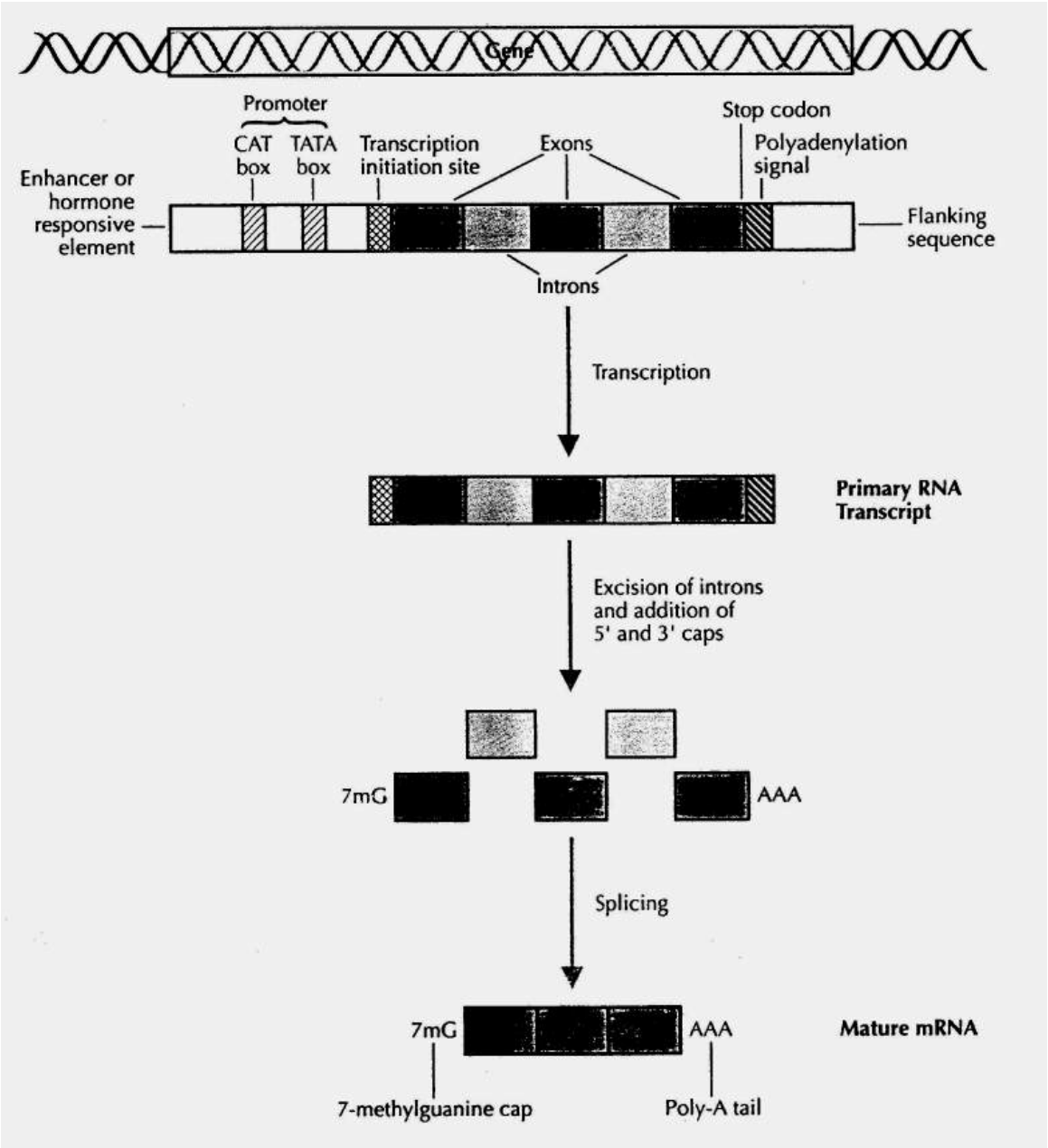
Each exon comprises a number of codons. A codon is a sequence of 3 adjacent bases in DNA (or RNA) that codes for a specific amino acid; which is therefore called the triplet codon. The polypeptide encoded by a particular gene is composed of a certain collection of these codon-coded amino acids, joined together at a certain sequence.

Genes also include *flanking sequences* which are important in gene transcription. These comprise *enhancer* and *promoter* regions present along the gene. ***Enhancer*** region initiates DNA action-for example, by furnishing a binding site for the hormone-receptor complex. The ***promoter*** sites are the actual areas where transcription begins. Only few nucleotide sequences are promoters, such as the T-A-T-A-A sequence, or TATA box, and the C-C-A-A-T sequence, or CAT box. They are situated near the start of the coding region of the gene.

The enhancer sites bind proteins that serve as a signal to regulate gene expression by either enhancing or repressing the binding of RNA polymerase in the promoter region. This is one method of creating unique cellular functions. For example, a hormone target tissue contains specific receptor proteins, which bind to the hormone, and the hormone-receptor complex binds to the enhancer site of DNA.

Three codons (UAG, UAA, UGA) act as stop codons, they stop the process of translation of RNA into protein (like a period in a sentence).

The open reading frames are the DNA segments, which are transcribed and encode for the amino acid sequence of the protein products.

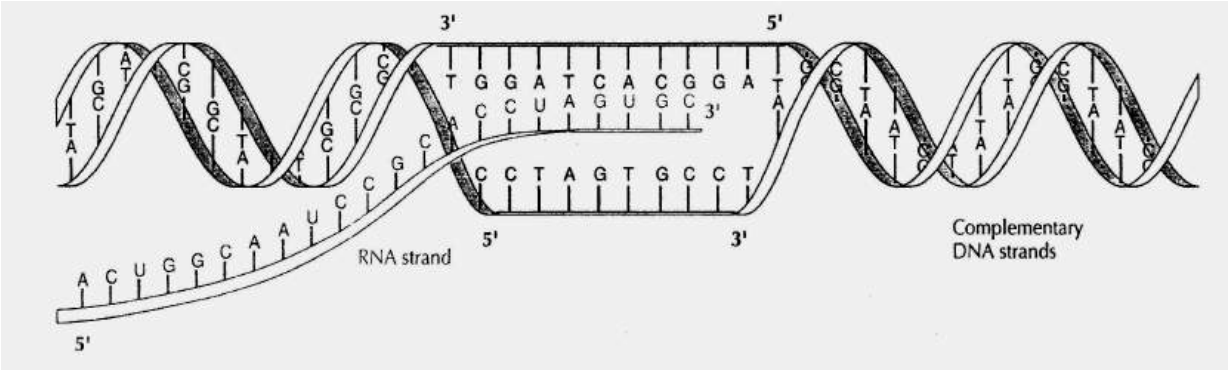


Cytogenetics and Molecular Genetics; Figure 6: A diagrammatic representation of the process of formation of mature mRNA. *(After L. Speroff, R. Glass and N. Kase; Clinical Gynecologic Endocrinology and Infertility, Lippincott, Williams & Wilkins, Paltimore, 1999).*

Gene expression: RNA:

RNA is a single stranded chain of ribose sugar to which four nucleic bases are attached: adenine, guanine, cytosine and uracil, i.e. uracil substitutes for thymidine of DNA. The transcription begins with unfolding of the double helix at the gene locus and results in a copy of one strand of DNA. Through the effect of certain a enzyme *RNA polymerase* a complementary copy of one DNA strand is formed i.e. the base sequence on RNA is in fact

similar to the sequence in the complementary sister strand which is not copied (Figure 7). Transcription of RNA begins at the promoter site and proceeds in a 5' to 3' direction. The RNA is thus formed, to begin with, of exons and introns, and latter on, the introns are spliced off. This results in the formation of the messenger RNA, which comprises complementary copies of exons only. ***The m-RNA moves to the cytoplasm*** where it is translated.



Cytogenetics and Molecular Genetics; Figure 7: Gene transcription

Translation:

The messenger RNA travels from the chromosome on which it was synthesized to a ribosome in the cytoplasm, where it directs the assembly of amino acids into proteins (translation). The specific linear sequence of amino acids is specified by nucleic bases on the codons in the exons and proceeds up until a stop codon is reached, whereupon the messenger RNA falls off the ribosome and degenerates.

The final expression of a gene may not end with the translation process. Further (post translational) processing of proteins occurs, such as glycosylation (the gonadotrophins) or proteolytic cleavage (e.g. the conversion of proopiomelanocortin, from which a number of molecules are ultimately formed; opiods, melatonine and adrenocorticotrophic hormone (ACTH).

Although the genetic information contained in each nucleated human cell is the same, difference in function of the various cell types requires that not all genes be universally and simultaneously expressed. Some of the genes must be constitutively expressed, regardless of cell type to maintain the requisites of nonspecific (common to all cells) functions of the cell. Other genes are required for only specialized functions, depending on the cell type. Changes in gene expression occur through the interaction between the nucleus, or cytoplasm and the surrounding environment. One example is the interaction between hormone – receptor complex and genetic material that initiate expression of certain genes to express themselves in a certain endocrine function -example is androgen insensitivity syndrome.

Mutation:

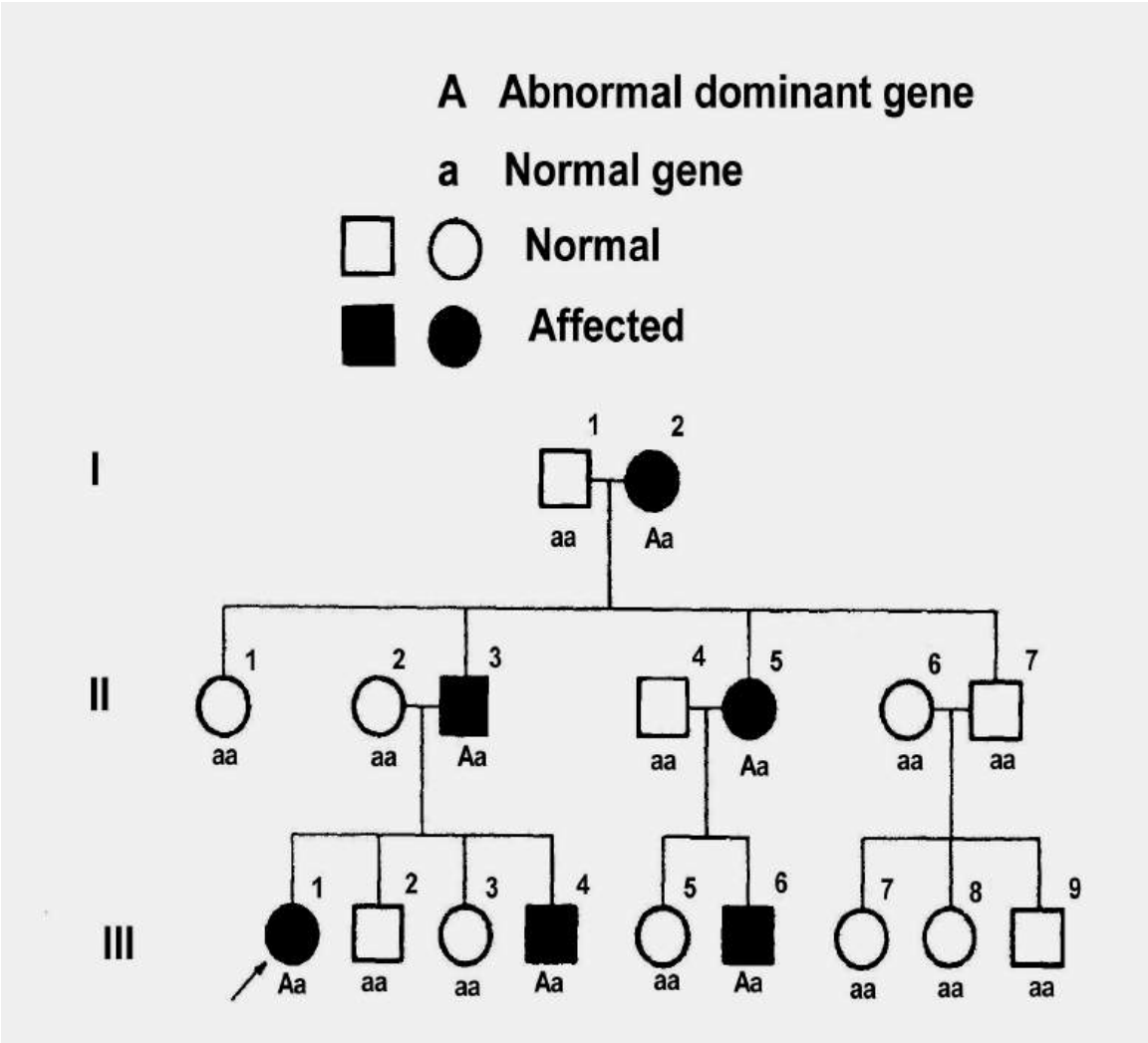
Any change in DNA sequence constitutes a mutation. The change can be in the form of substitution, insertion or deletion. Substitution refers to a change in a single nucleic acid base (point mutation). A substitution in a codon can result in incorporation of the wrong amino acid into a protein, leading to a change or loss in function. These *point mutations* are analogous to spelling mistakes in writing. A clinical example of a single base substitution (point mutation) is the sickle cell mutation, where thymine is substituted for adenine in the beta-globin gene. *Insertion* or *deletion* of amino acids into the final protein product can result from improper RNA splicing. Because of great redundancy in genetic codes (many codons code for the same amino acid), and since there is only 20 essential amino acids, not all substitutions, insertion or deletion result in an effect. Deletions and insertions can involve a range from single bases, up to entire exons, a gene, or several genes. If homologous regions of DNA or chromosomes are misaligned, unequal crossover can occur, resulting in deletions or insertions (additions). Recombination or exchange of genetic material usually occurs in meiosis, but can also occur during early mitotic division of the blastomere. In the latter event, an individual of two cell lines is produced (mosiacism).

Aberration of genetic material can be produced by a multitude of environmental influences including radiation, drugs or viruses. Major changes in the genetic material results in numerical or structural abnormalities in the chromosome (see under Cytogenetics). Limited gene mutation will not be manifest in chromosomal analysis, and can only be detectable by molecular chemical studies.

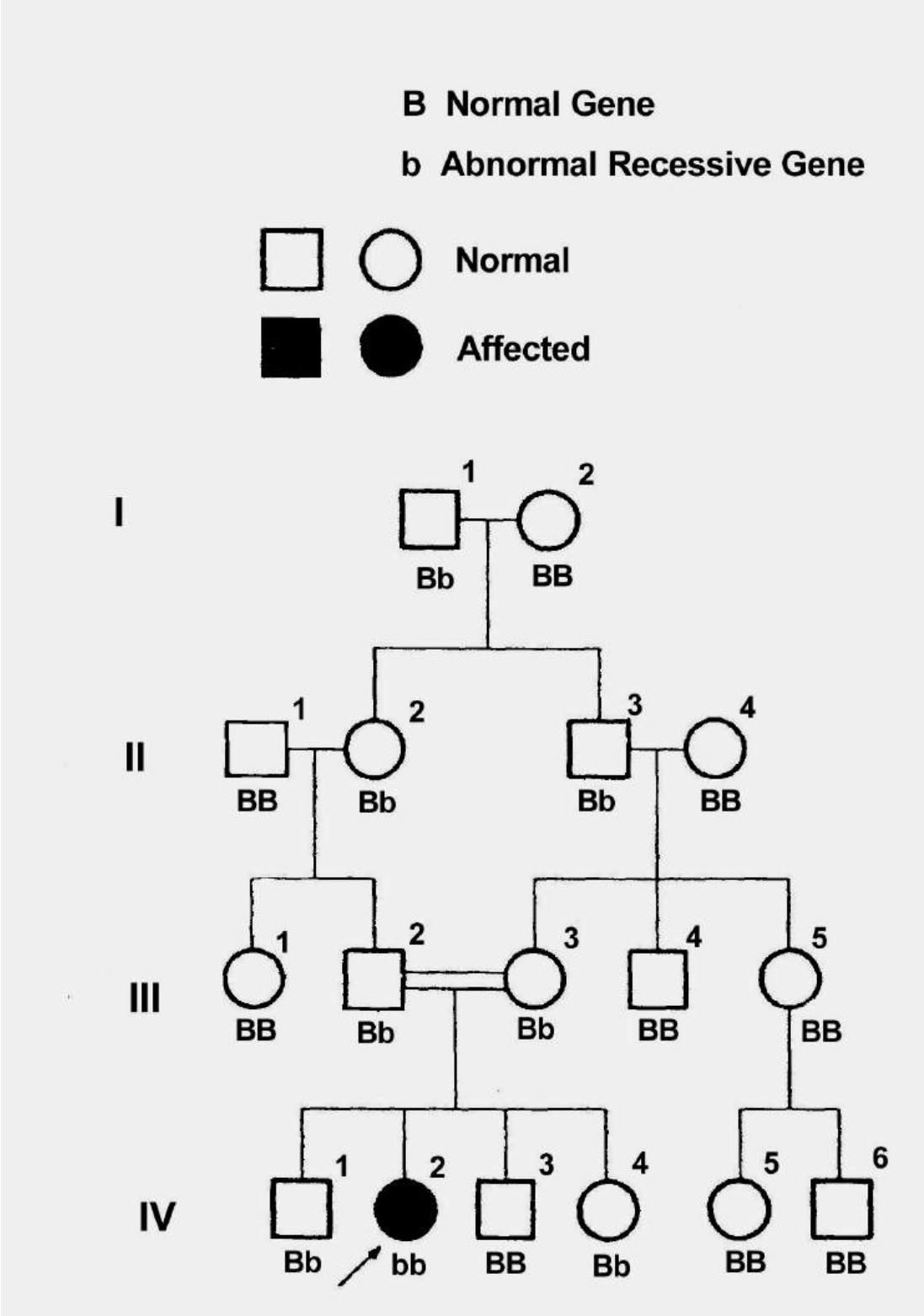
Mutations are transmitted to the siblings according to Mendelian inheritance rules which can be either: autosomal dominant, autosomal recessive, X- linked recessive, and early X-linked dominant.

- ***Autosomal dominance:*** Transmission is not linked to the sex of an individual, and homozygous and heterozygous children are affected (only one allele needs to be abnormal) (Figure 8). With two heterozygous parents, each child has a 75% risk of being affected. With one heterozygous parent, each child has a 50% risk of being affected. The effect is also subject to variable expression depending upon posttranscriphonal influences. Examples of autosomal dominant conditions include Rhesus factor inheritance, Huntington disease, neurofibromatosis, and Marfan syndrome.
- ***Autosomal recessive:*** These conditions are phenotypically expressed only in homozygotes (both alleles must be abnormal). With heterozygote parents, each child has a 25% risk of being affected; and a 50 % chance to be a carrier. Examples of autosomal recessive conditions are cystic fibrosis, sickle cell disease, and adrenal hyperplasia due to deficiency in 21-hydroxylase (Figure 9).

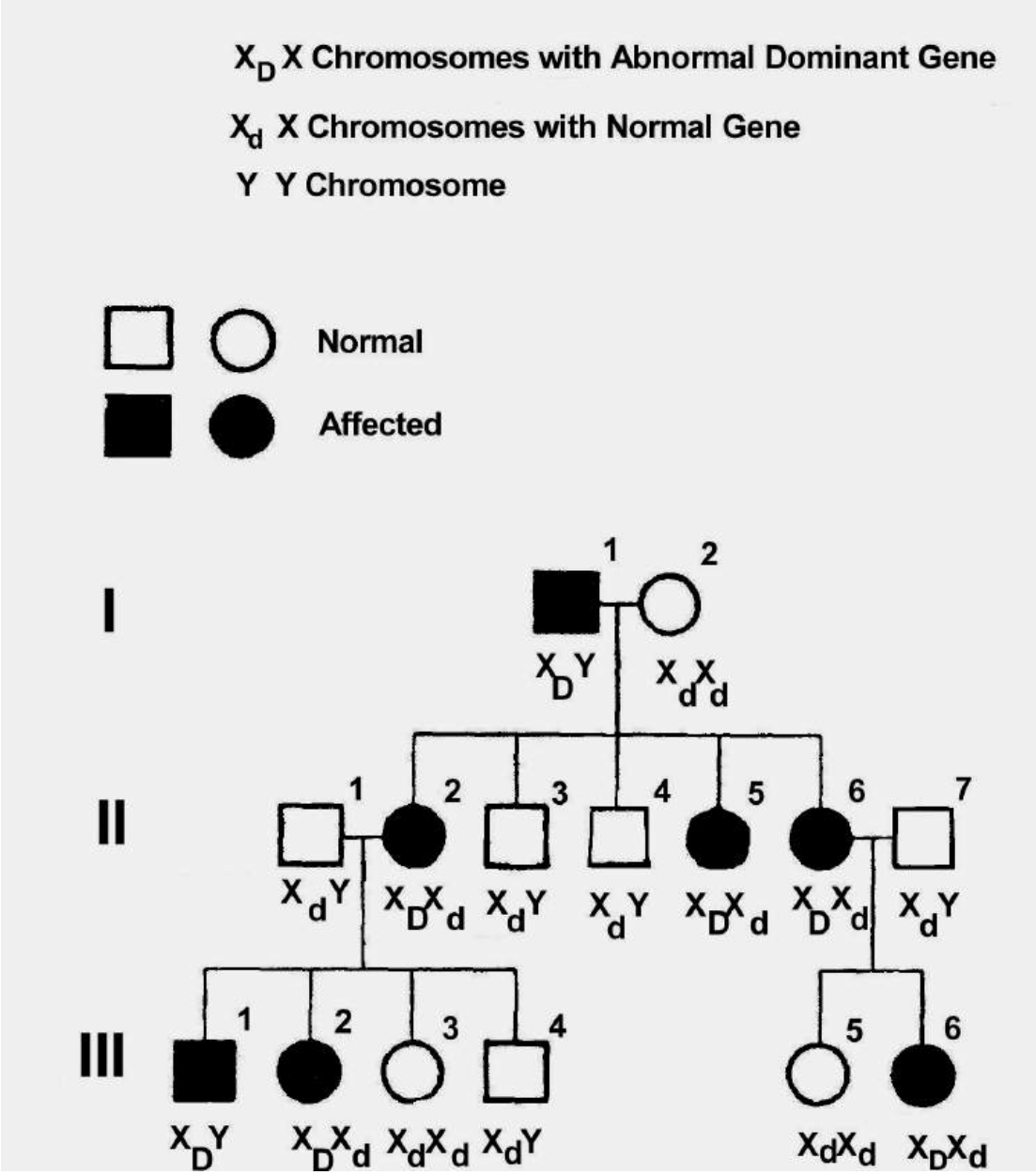
- ***X-linked recessive inheritance:*** An affected father can transmit the condition only to daughters. Only homozygous females are effected (Figure 10) when the condition is recessive. Red-green color blindness and hemophilia A are examples. X-linked dominant traits are most exceptional.
- ***Genomic imprinting:*** Genomic imprinting indicates predominant influences on the genome function of the mother or the father. In general, it seems that maternal contribution to the genome is more important for embryonic development. In certain autosomal recessive conditions, the expression, severity and age onset will be influenced by the gender of the parent providing the mutant gene or chromosome. On the other hand, it seems that placental development is controlled mostly by paternally derived genes. Thus, a complete hydatidiform mole has a normal 46,xx karyotype, but all its chromosomes are derived from the father (paternal).



Cytogenetics and Molecular Genetics; Figure 8: Pedigree illustrating autosomal dominant inheritance.



Cytogenetics and Molecular Genetics; Figure 9: Pedigree illustrating autosomal recessive inheritance.



Cytogenetics and Molecular Genetics; Figure 10: Pedigree illustrating autosomal X-linked recessive inheritance.

Techniques of molecular biology:

These principally comprise;

1. Techniques to analyze segments of DNA and RNA to determine gene structure and location in the organism.
2. Techniques to hybridize fragments of DNA from different organisms. The hybrids can be made to multiply if coupled certain vectors and incorporate in the chromosomal material of other organism mainly bacteria.

Over the last decade, the technology of molecular biology has markedly developed and allowed identification of genetic complement (gene print), diagnosis of many diseases

and predisposition to disease; synthesis of therapeutic agents; and opened the possibility of gene therapy.

Principal tools in molecular biology:

A. Certain enzymes have been separated from a variety of organisms and are used to catalyze certain molecular biology reactions.

1. ***Restriction endonucleases:*** are enzymes that break the phosphodiester bonds at a certain specific nucleic base sequence. Restriction enzymes are available that cut DNA into pieces ranging from many small fragments to a few large pieces, depending upon the number of nucleotides in the recognition sequence.
2. ***DNA polymerase:*** is an enzyme that brings together single nucleotides into a DNA molecule. A DNA polymerase *can form DNA only in the presence of a DNA template.* RNA polymerase can make RNA also only in presence of a DNA template.
3. ***DNA ase:*** can remove nucleotides.

   By combining DNA ase treatment with polymerase action, radio-labeled nucleotides can be introduced into a DNA molecule producing a ***DNA probe***. A DNA probe can be compared to the antibody used in immunoassays. As the antibody is specific and only recognizes the hormone against which it is formed, the DNA probe specifically detects a certain sequence of DNA.
4. ***Reverse transcriptase:*** is a DNA polymerase that is RNA dependent. It is called reverse transcriptase because the flow of information is from RNA to DNA, the reverse of the usual direction of flow. This enzyme permits the copying of an RNA molecule into a single-stranded DNA that is called complementary DNA because it is a mirror image of the RNA.

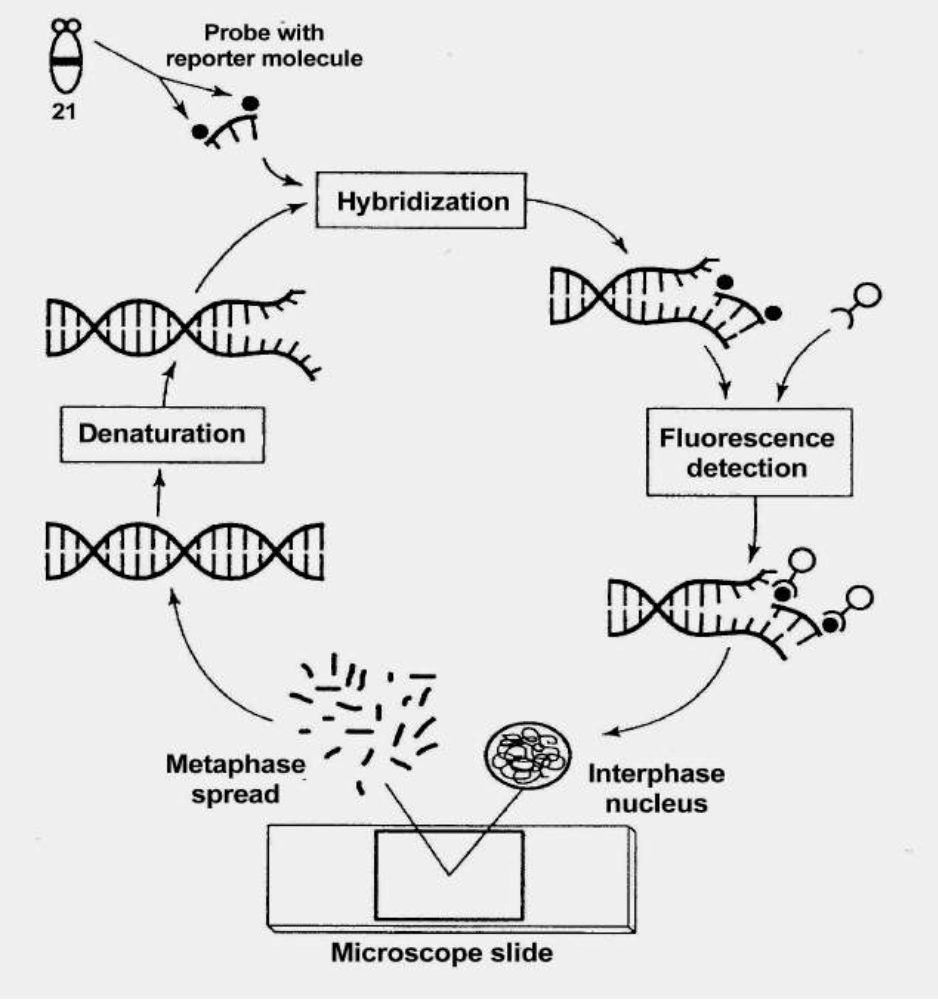
B. Hybridization:

The analysis of DNA for purposes of identifying specific genes depends upon the principle of complementary base pairing. In the double stranded helix of DNA, each strand is complementary to its fellow strand, in a sense, one being positive template and the other negative template, each specifying the other. Each strand therefore serves as a template for its complementary strand. Under certain conditions, the double-helix molecule can be separated (denatured) into constituent strands. When these conditions are reversed the two molecule will anneal back in a double helix i.e. hybridize. Certain nucleotide sequence on DNA first identified by utilizing a fragment of DNA that have the complementary known base sequence. This latter fragment acts as a DNA probe, and is obtained from anther source. The probe is labeled with identifier (usually with a radioactive isotope), and used a probe to identify the presence of a "target" complementary DNA fragment in samples of unknown DNA by

hybridization. In similar fashion, a single strand RNA will hybridize to complementary DNA molecule, thereby forming a DNA/RNA hybrid. This approach can be utilized to identify the structure of the studied DNA molecule.

In situ hybridization is a variation in which DNA probes hybridize to specially prepared whole cells or tissue sections. This technique has found wide application in Cytogenetic analysis (as described above), histopathology, genetic diagnosis and research.

Fluorescence in situ hybridization (FISH) offers another mean of chromosome identification. DNA is denatured in situ in a preparation on a microscopic slide. A complementary DNA labeled with fluorescent tag and derived from a specific site of a known chromosome is added as a probe to hybridize with the corresponding site in the preparation. The annealing of the probe to the specific DNA sequence(s) will leave behind fluorescent site(s) on the preparation. The two processes of DNA denaturing and hybridization occur without disrupting the chromosome (Figure 11).



Cytogenetics and Molecular Genetics; Figure 11:Fluorescence in situ hybridization (FISH). *The technique permits DNA denaturation and hybridization to occur without disruption of the integrity of the microscopic preparation.*

There are several applications of FISH:

1. Identification of trisomies (two fluorescent marker)
2. Identification of structural abnormalities in a chromosome.
3. It has been widely used in preimplantation genetics.
4. and also in examination of fetal cells in the maternal circulation.

The advantage of FISH is its completion in few hours (result in the same day), and its possible use on old paraffin blocks (i.e. it does not require cell viability). Its limitation is the need for availability of specific probes.

C. Electrophoresis:

DNA and RNA are charged molecules, and therefore, the nucleotide fragments, will migrate in an electrical field. Nucleotide fragments can be segregated and analyzed by gel (agarose or polyacrilamide) electrophoresis, the largest fragments migrating the slowest, this results in a characteristic blot of fragments, lines or patches.

1. ***Southern blot analysis:***

   DNA is first denatured to separate the two strands, and then it is digested by certain restriction enzymes to produce fragments of nucleotides of certain specific lengths. The fragments are separated by electrophoresis. Specifically labeled DNA probes are made to hybridize to different parts on the blot depending upon the principle of complementary base pairing. Hybridization means that a specific probe anneals (sticks) to its complementary base sequence. The fragments with this sequence are thus identified and quantitated by autoradiography.

   The Southern blot was named after the scientist who deserved it.

2. ***Northern blot analysis:***

   Refers to a similar RNA processing. It was called Northern (a sort of scientific witticism) because RNA is the opposite image of DNA. Northern blotting is used to assess the extent of gene expression, e.g. to determine whether hormone stimulation of a specific protein in a tissue is mediated by a messenger RNA.

3. ***Western blotting:*** (Again a scientific witticism) is used to *separate* specific *proteins* like viral antibodies or antigens utilizing hybridization to a specific labeled nucleotides probe.

D. Polymerize chain reaction (PCR):

The technique of PCR is used to quickly amplify small fragments or areas of DNA of known nucleotide sequence into quantities large enough to be analyzed with electrophoresis and blotting methods. This technique produces enormous numbers of copies of a specific DNA segment without resorting to cloning. The sequence of the

DNA segment must be known. It should be a short (10-100 bases) oligonucleulotides. For this DNA fragment, two complementary markers are available (synthesized) which are having specific beginning and end points. Each member marker will anneal to and flank the specific sequence on the DNA on the two complementary strands of the double helix that needs to be amplified. These flanking sequences are called primers.

The DNA sample, the primers, and an excess of the four nucleotides are incubated with a certain heat-resistant DNA polymerizes.

The first step involves separating the studied DNA into single strands by denaturation with heat (92ºC), then the temperature is lowered (40ºC) causing the two primers to anneal (stick) to its complementary regions on the DNA strand leaving between the nucleotide sequence which needs to amplified. This acts as a template for a new strand. The temperature is then raised to 62ºC, and DNA polymerize then synthesizes a new strand beginning and ending at the primers, forming a new double strand DNA. Therefore, the cycle comprises denaturation, annealing, and synthesis. Repeating the cycle many times (by alternating the reaction temperature) amplifies the amount of DNA available for study more (than 1 million fold); the increase occurs exponentially. Thus, DNA can be analyzed from a single cell, and genes can be visualized by blotting without labeled probes.

Because the process requires alternate heating and cooling, a DNA polymeraze resistant to heat is required. This property is present in tag polymeraze present in (tag) microorganism (thermus aquaticus) that lives in Hot Springs. This heat resistant polymeraze has allowed automation of the process.

PCR can be used to test for certain mutations like cystic fibrosis or B thalacemia. The DNA mutation of these diseases have been sequenced and specific probes have been prepared. Once amplified by PCR, the DNA sequence can be tested for by hybridization to mutant allele specific probe.

The technique of polymeraze chain reaction has made possible the study of incredibly small amounts of DNA. Most impressive is the amplification of small amounts of degraded DNA from fossils in museums.

E. Cloning DNA and recombinant DNA:

Cloning means isolation of a gene and making copies of it. A DNA library is a collection of DNA molecules derived from cloning methods. A complementary DNA library is the DNA counterpart of all messenger RNA of a cell or tissue; the search for the gene of interest is thus focused. By starting with m RNA, the search is concentrated on those genes, which are expressed. Such library is made using reverse transcripts.

The cloned DNA can be inserted into an appropriate vector in order to replicate it. A vector is an entity in which foreign DNA can be inserted. The vector plus the foreign DNA segment is inserted into a host cell; the host cell reproduces both the vector and the foreign DNA during cellular division. The first vectors were *bacterial plasmids.* These are circular DNA molecules (micro chromosomes) that coexist in the cytoplasm with bacterial chromosomal DNA (bacteria have no true nucleus and the chromosomal DNA molecules are present in the cytoplasm and replicated during bacterial division). The plasmid of a certain bacteria is disrupted (broken) with restriction enzymes, followed by incorporation of foreign (e.g. human) DNA with DNA ligase. This produces plasmid / DNA molecules *(recombinant DNA)* which are replicated during bacterial multiplication. Plasmid vectors can incorporate foreign DNA fragments up to 1046 nucleotide in size. The replication of the host bacterial cells will produce a huge number of copies of the genes / plasmid complex and the coded protein.

Certain cell lines have been used as host cells in place of bacteria for the *in vitro* production of certain protein e.g. the Chinese hamster ovary cell lines. The desired replicated DNA fragments can then be recovered by electrophoresis.

Other vectors exist including:

- *Phase vectors:* These are bacteria phases, which are viruses that infect the bacteria and replicate with them. Phase vectors can incorporate larger DNA inserts up to 20 KB.
- *Cosmic vectors:* These are artificially produced combination of phase vector and plasmid, which can carry DNA fragment.
- *Yeast artificial chromosomes:* Can carry a whole gene.

Recombinant DNA is increasing used in the manufacturing of proteins specific to man, like protein hormones. The first product was human insulin and now recombinant human FSH is being available. This replaces, at least in part, the need for extraction of these proteins from biological materials, which are not always available.

The human genome project:

This is an international effort to elucidate the location and structure of all human genetic material (3 billion base pairs and about 5,000,000 genes). The project entailed an immense effort and is expected to be completed early in the present decade.

Clinical applications of molecular genetics

The following are just *some* of the rapidly expanding uses of molecular genetics. They will be grouped under three headings pertaining to prenatal diagnosis, endocrinology, reproduction and oncology.

1. Molecular biology in prenatal diagnosis

Prenatal screening for congenital abnormalities depends upon a number of tools, which can be used in combination or in sequence. These comprise *chemical tests, ultrasound examination, cytogenetic and molecular biological tests.* Genetic studies are rarely the primary tool for diagnosis.

Sampling of the embryo and fetus for genetic diagnosis

Currently prenatal diagnosis of genetic abnormalities cannot be performed without obtaining fetal cells or DNA by invasive procedures, which place the pregnancy at certain risk. These have included:

1. *Chorionic villus biopsy*;
2. *Amniocentesis;*
3. *Umbilical cord sampling; and*
4. *Transcervical harvesting of fetal cells by transcervical saline flushing:* the lower pole of the gestational sac. The latter procedure can be considered minimally invasive, but is not completely free of risk.
5. It has long been known that fetal derived cells might be found in the *maternal circulation.* Over the last few years, many research groups have developed numerous technologies aiming at using these cells for prenatal diagnosis. Also, there has been a recent interest in separating *fetal DNA from maternal* circulation and utilizing this DNA for prenatal diagnosis. Fetal DNA in the maternal plasma or serum may be used to detect Y- chromosome sequences i.e. for fetal sexing in case of suspected sex-linked disorder. Fetal DNA can also to determine fetal RH-D status in a RH-D negative mother or for the diagnosis of cystic fibrosis and beta-thalassemia.
6. In procedures utilizing *in vitro* fertilization, a single cell biopsy can be obtained from early embryo for cytogenetic and molecular genetic study before embryo transfer.

The predisposition to congenital abnormalities can be assessed by cytogenetic or molecular biology test done on one or the two parents. Special target couples are selectively examined for the trait. Examples include advanced maternal and paternal age, previously

affected child prior affection in the family, repeated abortion or stillbirth and certain known parental affections. The predisposition to certain anomaly can also be assessed by pedigree of the parents.

Pre- implantation genetic diagnosis:

Pre- implantation genetic diagnosis allows selection of genetically normal embryos for transfer to the uterus. A single cell biopsy is obtained by micromanipulation from few-cell embryos during IVF. Following the fertilization, zygotes are grown to day 3, typically to the 6-10 cell blastomere stage. One (or two) cell can be removed for genetic study. Genetic diagnosis for certain DNA abnormalities is carried usually by FISH technique. This has allowed the diagnosis of sex of the embryo when there is risk of sex-linked abnormalities in the offspring. Single gene dependant defects can be detected e.g. sickle cell anemia, β-thatassemia and cystic fibrosis. Embryo biopsy does not appear to affect subsequent viability and, after the diagnosis is achieved, unaffected embryos can be transferred later the same day. Pre-implantation diagnosis avoids the risks and ethical and personal dilemmas of amniocentesis or chorionic villus biopsy, and pregnancy termination.

Inherited genetic abnormalities:

Genetic abnormalities can result in: 1) early embryonal loss or fetal demise or 2) a birth of a defective child. The latter defects can result in recognizable birth defect or may result in a disease, which become recognized in later life.

Abortion:

Fifty percent of spontaneous abortions show evidently pathological (blighted) ova in which the embryo is absent or evidently defective. In sixty percent of spontaneous abortions on which karyotyping is done chromosomal abnormality can be detected. The commonest abnormalities includes mainly in the order of frequency *autosomal trisomy, monsomy X, triploidy, tetraploidy and structural abnormalities.* These abnormalities are usually casual and not repetitive.

Cytogenetic studies of couples with recurrent pregnancy loss (abortion and still birth) show approximately 2 to 3 percent incidence *of balanced Robertsonian or reciprocal translocation* in one of the parents.

Congenital malformations:

At least 20 to 25 percent of congenital malformations are the result of chromosomal abnormalities or single gene defects. However, it has to be remembered that 65 to 75 percent of malformations have unidentifiable causes and are presumed to be the consequence of a

complex interaction between a genetic predisposition and fetal environmental factors which is called multifactorial inheritance.

Chromosomal abnormalities; *These chromosomal abnormalities can be numerical or structural:*

i. Numerical autosomal abnormalities

Trisomy 21 is the most important cytogenetic abnormality resulting in Down's syndrome. The condition is usually recognizable at birth:

The suggestive features include: the head is relatively smaller than normal with flat occiput, nasal bridge is flat, the eyes appear wide-spaced due to presence of epicanthal folds, the palpebral fissure are up-slanting (hence Mongol appearance), the tongue is big and protruding, a loose skin fold at the nape of the neck, poor general tone, short finger, and simian crease in both palms. Major malformation like heart defects and gastrointestinal atresia may be associated. Variable grades of mental retardation will become manifest in later childhood.

Down's syndrome (trisomy 21) is commonly ***a spontaneous event***. Its incidence increases with maternal age, with a likelihood of 1 in 1200 in a 20-year-old mother and 1 in 70 for a $\geq$ 40-year-old mother. Paternal age does not influence the likelihood.

Down's syndrome can less commonly result from translocation of chromosome number 21. The affected individual has a total of 46 chromosomes, but one chromosome (usually chromosome 14) has an extra copy of chromosome 21 attached to it (Roberstonian translocation). This translocation may be spontaneous but it can be inherited from carrier parents who have a balanced translocation; i.e. this carrier parent is having a 45 karyotype, but with an unusually big chromosome carrying the material of the missing chromosome.

Other autosomal trisomies like trisomy 13 and trisomy 18 are less common and are frequently associated with life-threatening birth defects; still- births and neonatal deaths; or result in major mental defect.

Autosomal monsomies are very rare and are generally lethal during the embryonal life.

ii. Structural autosomal abnormalities:

These comprise deletion, translocation, inversion and ring chromosome formation. Translocation is the most clinically significant type. Robertisonian translocation involves the acrocenterio chromosomes. The most important example is the inherited type of Down's syndrome (see above).

Mosaicism can result from non-disjunction during an early mitotic division in the blastomeres. The clinical effect varies between embryonal death and defective infant depending upon the relative proportion of the abnormal cell line.

iii. Sex chromosome abnormalities

The most common abnormalities include the following:

- Gonadal dysgenesis (see under Amenorrhea and Abnormal Sexual Differentiation). These mainly involve monsomy i.e.45 X, but can also show deletions and mosaic pattern.
- Klinefelter syndrome (47,XXY) (see under intersexuality).
- Extra X chromosome: 47,XXX. Females with one extra X chromosome may be indistinguishable from those with a normal 46 XX karyotype, although they commonly have decreased fertility.
- Extra Y-chromosome i.e. 47,XXY: Males with this karyotype may have increased height and severe acne. Decreased learning ability and criminal tendency may be asocial.
- Certain Y-chromosome deletions have been found in some cases of non-obstructive azoospermia.

Single-gene defects:

Single-gene mutations cause disorders that are inherited according to mendelian pattern. These mutations can be present in roughly about 1% of all newborns, but their incidence can be increased in consanguineous marriage. As with any mendelian inheritance the mode of inheritance can be classified into:

1. Autosomal dominant,
2. Autosomal recessive, and
3. X linked (which are usually recessive).Fragile X abnormality is not uncommon

i. Autosomal dominant inheritance:

A mutant gene producing its effect when present in one member of paired chromosome is referred to as a dominant gene. Generally, one parent carrying this abnormal gene has a 50% chance to transmit this gene to his or her offspring-this is called *vertical transmission.* This means that no generation is skipped. Certain such dominant genes can occasionally exhibit low penetrance resulting is skipping of one generation.

The most important autosomal dominant mutations comprise Rh group, achondroplasia, acute porphuria, familial hypercholestrolemia, hereditary spherocytosis, Huntington chorea, myotonic dystrophy, neurofibromatosis, and Von Willebrand disease.

ii. Autosomal recessive inheritance:

An autosomal recessive disorder is expressed when two copies of a mutant gene are inherited, one from each parent i.e. the affected individual is homozygous both parent are carriers for the abnormal gene. Common examples include albinism, congenital adrenal hyperplasia, cystic fibrosis, deafness, familial Mediterranean fever, sickle cell anemia, thalassemia, B- thalassemia, phenylketomuria. Because the disease is present in only one generation, this type of inheritance is often referred to, as *horizontal transmission.* The probability of *a subsequent* child being affected after the birth of one affected child is one in four.

Consanguinity or kinship increases the likelihood that a couple will share the autosomal recessive genes. First cousins share 1/8 of their genes; second cousins share 1/16. If there is family history of an autosomal recessive disorder, it is possible to calculate the mathematical risk that the couple will have an affected offspring. With negative family histories, there is still an increased risk that both members of a consanguineous marriage are carries for a deleterious recessive gene. In consanguine marriage there is an increased risk for genetic disorders, miscarriage and still birth in the offspring, but the relative risk is relatively low, approximately double the risk for non- consanguineous marriage.

iii. Sex-linked inheritance:

Sex-linked disorders are in reality all X-linked. These are classified as dominant, recessive or fragile.

The X-linked dominant disorders tend to be lethal in male off spring. *The majority of sex-linked disorders are recessive*. The best knowns are color blindness, glucose-6-phosphate deficiency, hemophilia or factor VIII deficiency, testicular feminization and Duchenne muscular dystrophy. Only male off springs are effected (oblique transmission). Half of male offspring of a carrier mother will be affected and half of the daughters will be carries.

Fragile-X syndrome: This X-chromosome abnormality is the most common inherited cause of learning disability and mental retardation; about 1 in 4000 males of Caucasian stock are affected. The prevalence in severely mentally retarded, (usually institutionalized) populations may reach 2 to 6 percent. In the females, the condition is much less common and milder. The male with fragile X syndrome typically has before puberty a long or triangular face and prominent ears. Macro orchidism may develop after puberty and other congenital abnormality includes mitral valve, aortic dilatation.

The condition results from a fragile site on the X chromosome, this site fails to condense normally during mitosis. This is caused by repeat trinucleotide CGG sequences. On karyotyping, these areas appear unstained or constricted. All males and 50 % of

females with full mutation (FM) have clinical syndromes. Women with partial mutation can pass it to offspring. Carrier females may fail to demonstrate the fragile site in cultured cells.

Recent molecular biology has allowed direct diagnosis of fragile-X syndrome and of carrier status in a cytogenetically normal woman, as well for prenatal diagnosis in the fetus. Antenatal screening for fragile X syndrome can be directed to high-risk group i.e. women with learning disability, or in presence of family history of mental retardation.

2. Molecular biology in endocrinology/reproduction

1. The gene for gonadotrophin releasing hormone Gn RH has been localized on the short arm of chromosome 8; it has been isolated and cloned. This gene encodes actually for a precursor protein that incorporates many other amino acid sequences. Mutations in the Gn RH gene are expected in hypogonadetrophic amenorrhea in which FSH and IH levels are low or undetectable. These patients should respond to exogenous gomadotrophin or pulsed Gn RH therapy.
2. *KAL gene:* Kallman syndrome is a sex- recessive abnormality that mainly affects males. This syndrome is determined by mutation of the KAL gene on the Xq chromosome (being on the pseudo autosomal portion of the X chromosome and therefore escapes, X inactivation).
3. Molecular biology contributed much to the separation and characterization of amino acid sequence of *inhibins*. There are a number of inhibins. The inhibin gene has been found to be homologous to the gene for the antimullerian hormone produced by the testes.
4. The alpha-subunit common to *FSH*, *LH*, *TSH and HCG* has been traced to a gene which is localized on chromosome 6. This gene has been isolated and sequenced. The beta-subunits for FSH are on chromosome 11p. The beta subunits of both *LH and HCG* have been traced to a family of gene on chromosome 19q. The common gene determination of β- subunits of these two latter hormones explains the great similarity in their effects. The difference between LH and HCG can be attributed to different promoter regions. A different translation stop signal in the HCG gene permits the addition of extra glycosylation sites and thus a longer half-life.

   The synthesis of glycoproteins like LH,FSH and HCG entails a post-expression association of the alpha and beta subunits, and glycosilation. These processes occur in the human Golgi apparatus. Expression of the beta-sub unit of HCG occurs only in the placenta.

FSH deficiencies have been ascribed to specific gene mutations. These mutations have been detected by molecular biology in women with premature ovarian failure who are having a normal karyotype. Such woman can have a high level of immuno reactive FSH coupled to decreased bioactive FSH beta subunits.

5. FSH (and recently LH) has been synthesized through recombinant DNA technology. The production of this recombinant glycoprotein requires a mammalian cell line instead of bacterial replication. This cell line is transfected by the vector/gene complex to provide for the necessary glycosylation, which does not occur in bacterial system. Glycoproteins like FSH present two additional challenges for recombinant DNA technology (over peptide hormones like growth hormone and insulin): The first is that the gonadotrophins are composed of two subunits alpha and beta, which are subscribed from separate genes. The second is the need for proper post-translational modification of the protein backbone by the glycosylation. These features have necessitated the use of a mammalian single cell line grown in cultures. The Chinese hamster ovary (CHO) cells are used for the purpose of expression of FSH, these host cells allows for co-expression of human α and β FSH sub unit genes and the glycosylation required. The human α and β genes are assembled (hybridized) separately and then coupled to a cloning vector that enables transfecting them to the host CHO cells. The culturing of mammalian cell on a production scale is technically much more difficult compared with microbial fermentation and requires the use of certain growth promoting factors. Certain characterization steps are required to ensure purity of the products. The recombinant FSH is being increasingly used in clinical practice.
6. *congenital adrenal hyperplasia:* CAH is an autosomal recessive disorder with a deficiency of an enzyme necessary for adrenal steroidogenesis, most commonly the 21-hydroxylase enzyme. The 21- hydroxylase gene has been localized to the short arm of chromosome 6. Molecular analysis indicated that the genetic defect specifically involves the structural gene for 21- hydroxylase. This is defective in individuals with congenital adrenal hyperplasia.
7. One type of *growth hormone* deficiency has been linked to an autosomal recessive pattern The cloning of growth hormone gene has permitted the localization of growth hormone gene. The growth hormone gene is in a cluster that includes the gene for human placental lactogen. This cluster of gene contains multiple units of DNA that are homologous and is prone to recombination, which leads to deletion of one gene and duplication of another.

8. The short arm of the Y chromosome carries a genetic locus responsible for differentiation of the testes, called the testis-determining factor (TDF). Certain inter sex disorders can result from exchange of X and Y DNA when the short arms of the X and Y-chromosomes pair and crossovers occur during meiosis.

   The exact locus (or loci) of the ovarian determinants on the x chromosomes has not been identified. X chromosome deletion has however been associated with primary amenorrhea or early premature menopause.
9. Because of the importance of X-linked diseases, the X- chromosome is one of the most studied chromosomes. Most of its gene has been now characterized and many of the inherited disease genes had been cloned.
10. Genes encoding for hormone receptor proteins have been identified. A relevant example is the gene encoding steroid binding receptors, which is situated in the X-chromosome. It is a macro gene, which shows certain abnormality in individuals with androgen insensitivity syndrome.

3. Molecular biology of gynecological cancer

Neoplasia can be regarded as a complex failure in cellular homostasis in which uncontrolled epithelial proliferation occurs in a population of cells that do not communicate normally with surrounding tissues. As a result, expansion of the tumor cell population occurs, eventually to local invasion and metastasis.

Cancer is a genetic disease

Evidences:

- Cancer cell populations are occasionally having abnormal karyotypes and genotypes.
- Cancer cell populations frequently show abnormalities in gene expression.
- Division of cancer cell never produces normal cell.
- Agents which cause damage to DNA (chemical mutagens, ionizing radiation, and some viruses) also increase susceptibility to certain cancers.
- Individuals with certain genetic abnormalities are more predisposed to certain cancer.
- It has been shown that the human genome contains genes with the potential of causing cancer (oncogenes), as well as genes that have the ability to block malignant growth (suppressor genes).

Genetic alternations in cancer:

In malignant cells, the normal pattern of gene expression is disturbed. This may occur by a number of mechanisms, and more than one abnormality is frequently present. In most cases, cancer is thought to arise because of a multiple-step process in which various genetic alterations are accumulated over a period of time. The genes involved can be either *oncogenes*, *or suppressor genes, or both types.*

Oncogenes:

The discovery of cellular oncogenes was first described in certain animal tumors associated with viral infection (viral oncogenes). Numerous viral oncogenes were found to have normal cellular homologues known as proto-oncogenes. The oncogenes seem to be mutated proto-oncogenes.

The oncogenes are expressed in the formation of certain proteins that enhance cellular division. *Oncogenes are dominant*, only one of the pair of alleles needs to be mutated for the cell to manifest the new pattern of gene expression. The role played by oncogenes in cancer pathogeneses has not been fully understood. They may encode growth factors or their receptors and may alter gene transcription. Certain genes may suppress or induce apoptosis (active process leading to programmed cell death).

An important example of oncogenes has been demonstrated in chronic myeloid leukemia. The patients with disease have a certain chromosome translocation resulting in what is known as the Philadelphia chromosome, which have been shown to comprise known oncogenes.

Tumor suppressor genes:

These genes exert a growth –inhibiting effect in normal cells and give rise to tumors only when their function is lost or reduced. In contrast to oncogenes, *tumor suppressor genes act recessively* i.e. tumors only arise if both alleles are mutated.

An example of tumor suppressor gene in the field of gynecology in the gene p 53. This gene is located on the chromosome 17 p and encodes a certain nuclear protein called p 53. This protein control the normal cell cycle by maintaining genomic integrity, and inducing apoptosis in response to DNA damage. Cells containing normal p 53 protein (called wild-type protein) undergo specific pauses in cell cycle, especially after DNA damage, to allow the cell to restore the genetic sequence to normal. In the presence of mutation of p 53 gene, these cycle checkpoints are overridden and the cell replicates the abnormal DNA sequences and passes them on to the daughter cells. Mutant p 53 can suppress the normal wild type p 53 gene. The mutant p 53 gene can be demonstrated in immunohistochemical stained preparation in as many as 50% of advanced cancer. This abnormality is common to many solid cancers.

Mechanisms of genetic alteration:

Changes in the structure of an individual gene may occur by means of a number of different mechanisms including *point mutation, deletions, amplifications, or translations.* Alternatively, the structure of the gene may be intact but abnormality is at the level of transcription (see above).

1. ***Point mutations:*** This result in alteration of the synthesis of the sequence(s) of amino acids encoded and the resultant protein. The RAS family of oncogenes*, H-RAS*, K-RAS, and N-RAS, provide the classical example of point mutations leading to activation of dominantly acting oncogenes. In this family, mutations in one of only three amino acids at positions 12,13 and 61 in the protein structure are sufficient to fix the protein in activated conformation. Point mutations are also common in the tumor suppressor gene p 53.
2. ***Deletions*** involve larger-scale loss of the gene, and their importance lies in that they can lead to the loss of normal growth control functions. Loss of the second of a pair of tumor suppressor genes often take this form (suppressors act recessively) with deletion of large portions of chromosomal material or even an entire chromosome.
3. ***Gene amplification*** represents the opposite process to gene deletion in that multiple copies of a gene are present, resulting in enhanced synthesis and activity of the encoded protein. The c-erb B2 oncogene is frequently amplified in breast cancers, and in up to one-third of ovarian cancers.
4. ***Translocation*** describes the process whereby part of one chromosome become detached from its normal position and joined to another chromosome. This process can bring a gene into an environment where it is subject to different control mechanisms, increasing or decreasing its expression, or can lead to the formation of a new gene by the fusion of parts of two separate genes. The Philadelphia chromosome is an example of this occurrence in which two genes are brought together to form a new hybrid gene, which has increased activity.

Moreover, abnormality in the control of *gene transcription* can lead to enhanced synthesis of gene products in the absence of structural abnormality.

Genetic events in gynecological cancers:

Gynecological cancers provide important examples of different mechanisms of carcinogenesis. ***First,*** ovarian and endometrial cancer can occur as components of two important familial cancer syndromes (familial breast/ovarian cancer syndrome and Lynch 2 syndrome. ***Second,*** in cervical cancer, the initial genetic alteration is thought to be directly initiated by an environmental factor-papillomavirus. ***Third,*** in sporadic ovarian cancer the

environmental factors associated with carcinogenesis are thought to operate indirectly by increasing the opportunity for spontaneous mutation in a number of critical genes.

Ovarian cancer:

1. A small proportion (less than 5%) of ovarian cancers are caused by familial syndromes. Pedigree studies of family with a high incidence of cancer have revealed three syndromes associated with ovarian cancers. These include, in the order of frequency:
    1) The familial predisposition to ovarian and breast cancer. The high frequency of these two cancers is also associated with tendency for onset in young age.
    2) Ovarian site-specific ovarian carcinoma; i.e. specific familial repetition of ovarian cancer.
    3) Lynch 2 syndrome is a familial association of nompolypous colonic carcinoma with endometrial and ovarian cancer (lynch I is site- specific familial tendency of this type of colonic cancer).

        There is a much smaller tendency for site-specific familial endometrial cancer.
2. ***The gene responsible for familial breast /ovarian cancer is located on the chromosome*** 17q. Almost all breast/ovarian cancer families and 40% of the families with breast cancer alone have genes named breast cancer 1 and 2 (*BRCA 1 and BRCA 2*) on the 17q locus. There are indications that these genes act as *suppressor genes*. This is suggested by tendency for loss of heterozygosity in tumors from familial breast/ovarian cancer (suppressors are recessive). These genes influence the process of mismatch repair resulting in propagation of abnormal DNA sequences. The predisposition to these familial cancer can therefore, be considered as a defect in ability of DNA repair.
3. There is a good deal of evidence to implicate a number of oncogenes in the development of ovarian cancer. These act by activating growth factors and their receptors of tumor tissue. These proteins act in an autocrine fashion. Two oncogenes have been implicated in ovarian cancer: 1) the macrophage colony-stimulating factor M-CSF encoded by the c-FMS oncogene; and 2) the epidermal growth factors (EGF).
4. The genetic nature of ovarian cancer is also evidenced by “gross” cytogenetic alterations frequently seen in ovarian cancer including polyploidies and aneuploidies. There is however, no consistent pattern of chromosomal alteration. The frequency of these abnormal chromosomal, pattern (ploidy patterns) can helps in assessing the prognosis in borderline and invasive ovarian cancer. In addition, the percentage of the cell population in the S phase of the cell cycle can also help to differentiate benign from malignant ovarian tumors.

Endometrial carcinoma:

1. Cytogenetic abnormalities are not common in endometrial cancers and their presence indicates aggressive disease.
2. Mutation of certain oncogenes (e.g. K-RAS) and amplification of other oncogenes have also been associated with poor prognosis.
3. Expression of mutant suppressor gene p 53 occurs most commonly in late stage of the disease.

Cervical cancer:

1. It is now known that human papilloma virus (HPV), particularly the subtypes HPV 16 and 18 is the primary causal agent for development of pre-invasive and invasive cervical cancer. In cervical cancer, HPV DNA is frequently integrated into the host genome but this is often associated with loss or block of expression of most of the viral genome. Some viral genes are sometimes retained in the host cell genome transforming them to a replicating cell line. This mutation leads to loss of tumour suppressor gene function, particularly p 53 and Rb. Infection of cell lines with HPV 16 and 18 have been shown to lead to alteration in growth pattern of immortalized cells (cells able to survive in culture after repeated passage) leading to aberrant growth (see also under Carcinoma of the Cervix).
2. Cytogenetic abnormalities have been detected in small percentage of cervical cancer; aberration of chromosome 1, less frequently in chromosome 3,11 and 17 have been seen relatively. Their presence indicates poor prognosis.
3. Loss of hetrozygosity is more marked in cases of cancer cervix specimen, particularly in chromosome 3,5 and 11.

Gestational trophablastic disease (GTD):

It has been be known for some time that complete hydatidiform moles are diploid (46, XX) but with the origin of the genetic material being totally paternal. This results from fertilization of an ovum by either two X carrying sperm or by a duplicated set of 23X chromosome of a single sperm (see under Trophoblastic Neoplasia). The mechanism of loss of the maternal DNA is not known. Partial hydatidiform moles usually show triploidy (69 XXY being the most common).

Glossary of common molecular biology terms

Allele	Alternative forms of a gene at a given chromosomal site (Locus).
Amplification	Increase in the number of copies of a gene.
Apoptosis	Active process leading programmed cell gene.
Autocrine effect	Growth stimulation induced by the binding of a growth factor secreted by a cell to a receptor in its own cell membrane.
Base	Adenine, cytosine, guanine, and thymidine-the components of DNA.
Chromosome	Theses carry the genetic code made of DNA chains composed of nucleotides arranged in a sequence specific to each individual.
Chromosome mapping	The assigning of a gene or other DNA sequence to a particular position on a specific chromosome.
Cloning	Isolation of a genetic material and making copies of it.
Cytokine	Proteins which act as intercellular signals to co-ordinate the immune response.
Dexoyribonucleic acid 'DNA'	The molecule in the chromosome responsible for coding the genetic message. It consists of repeated groups of nucleotides. It has a double helix configuration.
Deletion	Loss of a portion of a chromosome.
Exon	The base sequence of a gene that carries the information required for protein synthesis.

"FISH"	Fluorescence in situ hybridization. A technique of detection of certain chromosomal segments by hybridization with fluorescent probes.
Gene	A region of DNA sequence specifying the coding and regulatory sequences for the expression of a protein.
Gene expression	The process by which the information encoded by a gene is converted into a functional protein. In clinical genetics, a gene is usually expressed in an individual protein.
Genome	The complete set of genes of an organism and the intervening DNA sequences.
Genotype	The genetic constitution of an individual, usually at a particular site.
Growth factor	Proteins that bind to receptors on the surface of cells and modify their growth.
Growth factor receptor	Proteins embedded in the cell membrane with an extracellular receptor region and an intracellular signalling region. The receptor can be activated by the growth factor.
Heterozygote	An individual with two different alleles at the same locus on each of a pair of chromosome. A heterozygote who has a dominant disease gene and one normal gene will be affected by the disease; one who has a recessive disease gene and a normal gene will be a carrier.
Homozygote	An individual who has two identical alleles at the same locus on a pair of chromosomes.
Intron	Transcribed portions of the DNA sequence that do not contain coding information for protein synthesis.
Karyotype	The complete set of chromosomes of an organism.

Linkage The tendency for genes lying close together on the same chromosome to be inherited together.

Locus Site on a chromosome.

Loss of heterozygosity Loss of one allele at a chromosomal locus, followed by deletion on the remaining locus leading to homozygosity.

Mendel In the 1860s Mendel laid down laws for hereditary transmission which are still holding up till now.

mRNA Messenger RNA formed by the transcription of DNA.

Microsatellites Repeated DNA sequences in tandem. They are short segment repeats of 2 – 4 nucleotides common within introns and show pronounced polymorphism useful for: i) gene mapping and linkage analysis; ii) markers of loss of heterozygosity; and iii) as a diagnostic tool for detecting tumor cells in histologically unremarkable specimens.

Mutation A change in DNA sequence. This can range from an alteration in a single base (e.g. sickle-cell haemoglobin) to loss or gain of chromosomal material (e.g. the Philadelphia chromosome in chronic myeloid leukaemia).

Northern blotting Laboratory technique for locating RNA sequences.

Nucleotide A subunit of nucleic acid (DNA, RNA) consisting of a base, a sugar, and a phosphate.

Oncogene A gene whose product can cause cancer by stimulating abnormal cell growth and excessive proliferation.

Open reading frames DNA segments which are transcriptional units capable of encoding for proteins.

Phenotype	The physical characteristics of an individual resulting from the interaction of its genotype with environmental factors.
Polymerase chain reaction	This is a way of " amplifying " or making multiple copies of any piece of nucleic acid. It allows amplification of any gene sequence.
Polymorphism	The existence, in a population, of two or more relatively common alleles at a genetic locus. It is a variation in the sequence of the gene that tracks with the gene and is not a mutation.
Promoter/enhancer	DNA sequences that act as control points for DNA transcription.
Proto-oncogene	A gene that normally regulates cell growth and proliferation but which can cause cancer when mutated.
Reverse transcription	DNA synthesis from RNA templates. It occurs naturally in retroviruses and is used to synthesize DNA in the laboratory.
Ribonucleic acid	A single strand of nucleoide sequence which copies the DNA during the process of gene expression.
Southern blotting	Laboratory technique for detecting DNA sequences.
Splicing	Process by which intronic sequences are removed from initial RNA transcript to form messenger RNA.
Transcription	The synthesis of RNA from its corresponding DNA sequence.
Transcription factor	Specific regulatory proteins that control gene expression by switching genes in and off.
Translation	Production of a protein from mRNA code.
Translocation	Exchange of DNA material between chromosomes.
Tumor suppressor genes	(TSG) A gene which normally slows growth and proliferation. Abnormalities of TSGs can lead to uncontrolled cell replication and so to malignancies.
Watson and Crick	In 1950s these two scientists proposed the structure of DNA.
Western blotting	A laboratory technique for detecting proteins by nucleotide probes.

Chapter 26

SEXUAL DYSFUNCTIONS IN WOMEN

Contents

Introduction

The gynecologist is frequently consulted about sexual matters, normal and abnormal. He is one of the important resource persons about this function.

Sexual dysfunctions are quite common, more so in the female than in the male. However, the couple is frequently both responsible for the problems. Women may be shy to complain about sexual problems, and may endure them silently. However such problems can result in a great deal of personal unhappiness and intense suffering.

Sexual dysfunctions and sexual insatisfaction can be the basis of many psychosomatic complaints like pelvic pain and heaviness, lower back pain, premenstrual tension syndrome, dysmenorrhea, vaginal discharge, bleeding, headache, fatigue etc… Failure to appreciate and

try to correct the sexual problems results in persistence of such complaints, which undermine the health, related quality of life (HRQL).

Normal Sexual Function in Women

Sex is one of the basic human instincts and is strongly developed in normal women. This instinct is subject to many controlling social regulations. These regulations are contributed to be religions and other social norms. Marriage is, by for the main outlet for the sexual instinct. Premarital and extramarital sexual relations are socially unacceptable. Homosexual relations are totally unacceptable in our community.

In human being, sex is an emotional as well as "physical" experience; the mind strongly influences all the stages of sexual contact. The constituents of sexual relation comprise the (1) physical attraction and (2) sexual intercourse.

1- ***Sexual attraction***:

This is called ***libido*** or sexual drive. The object of heterosexual attraction in the adult is to bring the male and female into pleasurable physical contact, which leads ultimately to sexual intercourse (coitus). Coitus is required for itself and not only as a means of reproduction. Sexual attraction is a compelling drive that gives physical and mental relaxation.

A woman attracts by facial appearance, curved figure, particularly at the breasts and hips, behavior, stance, walk, voice, adornment and by mental qualities. The male's attraction is mainly behavioral manliness, symmetrical looks, strong body, and intelligence and may be social status. The contribution of the different attributes in the female or male may vary in different societies and with different persons. This component of sex is strongly influenced by the mind mainly by centers in the temporal lobe, which relay its impulses via the hypothalamus. The brain opiates like Beta-endorphines are involved in determining libido.

Hormones play a less defined role in determining libido. Testosterone plays a significant role in the male libido. There are evidence that testosterone is also involved in determining the female's libido, but to a much lesser extent than in male. In the female testosterone is produced by the adrenals and ovaries. After menopause, blood testosterone markedly drops and this may contribute to diminished interest in sex after the age of 60 year. Some maintain, albeit at a diminished level, an interest in sex through old age.

Estrogens play a limited role in determining libido. However, the postmenopausal estrogen deficiency can cause atrophy and loss of lubrication of the vaginal epithelium in some women, which result in dyspareunia. Dyspareunia and the resulting inability to reach orgasm can result in decline in libido.

2. ***Sexual intercourse***:

Sexual intercourse or coitus is the peak response to sexual desire. The male penis gets erect and hard due to sexual excitement. The erect penis is introduced in the vagina and after repeated thrusts a climax of excitement is reached; orgasm is reached followed by a sense of satisfaction.

Sexual intercourse is mostly for the pleasure of it but is the means for reproductions.

Stages:

The human sexual response is divided into four stages as described by Masters and Johnson.

Stage 1: Excitement:

Excitement can be determined by a wide variety of stimuli. These include fantasies, and visual, tactile, olfactory and/or sound stimuli. There is a great personal variability in the effect of such and other stimuli upon sexual arousal of either the male or the female. Tactile stimuli are usually the most prominent. Many areas of the body are erogenous, that is, capable of giving rise to a pleasurable erotic sensation when stimulated, under appropriate circumstances. This stimulation is achieved by touch, fondling, massaging or kissing. In the woman these areas include the lips, tongue, back of the neck, shoulders, breasts, buttock and thighs, but specially the vulva particularly the clitoris and the lower anterior vaginal wall. In the man the map is not usually that wide and concentrate on the external genitalia particularly the penis.

In the woman, sexual feelings may be dormant as compared to those in man and develop by experience and learning. The process of improvement in sexual arousability may continue for several years of experience and is usually helped by active, loving and considerate partner.

Usually the male takes the initiative in sexual contacts but this is not necessarily so. In conservative societies women may be shy to take the initiatives or even to be actively participating in the act. This is depends upon rearing and the premarital mother's instructions. After sometime of successfully consummated marriage a woman can become more easily aroused and sometimes take the initiative and actively participate in the act to ensure her pleasure and the pleasure of her husband.

The stage of sexual excitement that is frequently called the foreplay may last a few minutes but can be willfully prolonged to a few hours.

In males the signs of excitement are:

- Erection and hardening of the penis.
- Drawing up and swelling of the testes.
- Secretion of few drops prostatic secretion. This only happens if this stage is prolonged. These secretions are not the ejaculate but usually contain sperm (i.e. can result in pregnancy).

In the females, the signs of excitement:

- Enlargement of the breasts and erection of the nipple.
- Lubrication in the vaginal passage.
- Increase in length and diameter of the clitoris.

The erect penis is ready to be inserted into the vagina. The lubricated vagina gets ready to help the penile introduction and thrusts.

Stage 2: Plateau:

This results from repeated penile thrusts in the vagina. The following changes occur :

- *In males there is*
  - Further increase in diameter and hardening of the penis and glans.
  - Further enlargement of the testes.
  - Lubrication of the urethral passage by secretions from the bulbourethral glands.
- *In females there is*
  - Further enlargement of the breasts.
  - Lubrication of the labia by secretion from the Bartholine glands.
  - Blood congestion of the cavernous blood spaces in the lower one third of the vaginal wall, particularly rich in the anterior wall. Engorgement of this part produces a platform called the orgasmic platform (occasionally referred to as G spot = Grafenberg spot), (Figure. 1).

    This plateau of sexual pleasure lasts, in the usual intercourse for, few minutes before ending in orgasm. Some misinformed couples are under the impression that the intercourse should last (after the penile introduction) for a prolonged time; and many of the complaints of premature ejaculation are unfounded. Some couples may cooperate to prolong this part of the act for quite longer time, but this is not the rule.

Stage 3: Orgasm

Orgasm is the all-possessing physical pleasure, which represent the climax of sexual intercourse. Both the male and the female have rapid muscular contractions of pelvic muscles. These release the body tension that was built up in the earlier two stages. The orgasm lasts for approximately 0.8 seconds. The ejaculation does not need be forceful ejection, as sometimes thought by some couples.

- *In male*s, orgasm comprises contraction of the full length of the shaft of the penis producing ejaculation of the semen.
- *In females,* there is contraction of the orgasmal platform. The muscles of the uterus may also contract. The cervix does not open, as it is sometimes believed.

The male and female do not necessarily reach the orgasm at the same time; at the beginning of marriage the wife is sometimes delayed or may fail to achieve orgasm in some of the acts. With increasing experience a couple quickly adapt themselves to each other so that orgasm is achieved simultaneously. Simultaneous orgasm in the male and female is not

required for achieving conception and even, is doubtful that it increases the chance of conception.

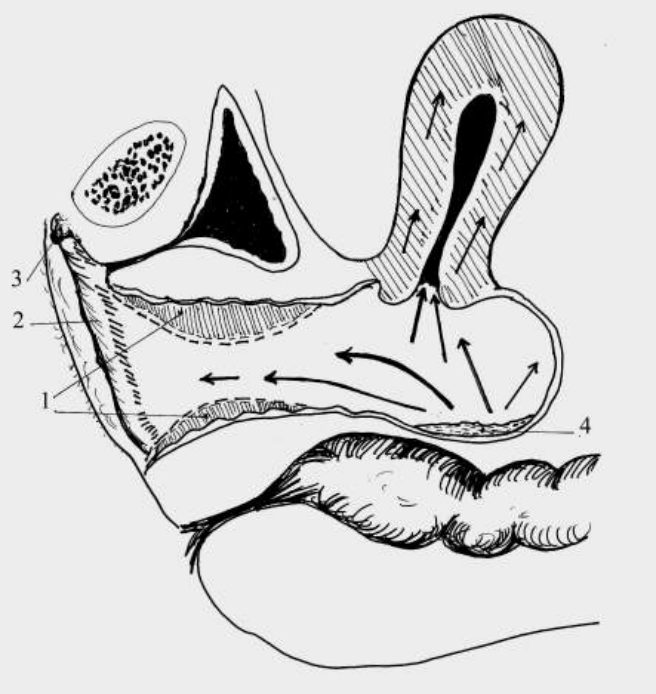


Figure 1: The female genital tract at the time of sexual orgasm*. 1. Orgasmic platform; 2. Labium minus; 3. Erected clitoris; 4. Seminal pool: a small part goes to the cervix, and a good part comes out. The penis is not represented.*

Stage 4: Resolution

In this stage the body returns to the state before excitement.

- *In male* there is
  - Loss of erection.
  - Decrease in size of the testes.
  - Lowering of the testes.
- *In females* there is
  - Loss of nipple erection.
  - Loss of engorgement orgasmic platform.
  - Presence of seminal fluid (the seminal pool) around the cervix. When the woman moves some of this seminal fluid come out of the vagina and this mixed with discharge of the vaginal fluid. This phenomenon does not diminish the chances of conception. Keeping the wife on her back in attempt to keep the semen inside her is a practice that does not increase the chance of conception.

After orgasm and ejaculation the penile erection subsides and sexual arousal diminishes. The males need to rest before resuming sexual activity. This involuntary rest is called the *refractory period*. This refractory period varies from 10-30 minutes in young men and from an hour to a day or more in older men in there fifties or sixties.

The refractory period in women is not distinct. They can have one arousal after another if sexual stimulation is continued. Most of the women have the physical capability to experience more than one orgasm in one act; some cannot achieve this. Finally, the satisfaction derived from sexual intercourse varies in degree between individuals. A good deal of the satisfaction is sometimes drawn from the ability to satisfy the partner.

Effect of female circumcision (cutting) on sexual practice

This is an unfortunate Egyptian custom in which the clitoris (or part of it) together with the anterior part of the labia minora are removed (see under traumatic lesions of the genital tract). Sometimes more parts of the vulva are excised. This deprives women of important erogenous structures. Some circumcised women may have as a, result frigidity, diminished arousability and/or inability to reach orgasm. Circumcision can diminish their ability to achieve clitoridial orgasm i.e. orgasm achieved by clitoridial manipulation. The majority however, can achieve a normal vaginal orgasm (achieved after penile introduction). Most women derives more intense pleasure from the vaginal component of sexual intercourse, clitoridial stimulation is to them just a prelude to the real thing. Therefore, the majority of circumcised women are not sexually incapacitated; a minority is.

However, a list of sexual dysfunctions can result from this traditional practice of female circumcision as described under traumatic lesions.

Coital positions

There are a number of coital positions. The couple can use any one of them. None of them is wrong so long as they are satisfactory with both partners. None of them has been proven by evidence to be consistent with increased (or diminished) conception rates.

Oral sex (kissing or sucking the sex organ of the partner) is common and has not been proven to cause harm. On the other hand, anal sex is unclean, painful, injurious and increase transmission of certain sexually transmitted diseases notably HIV infection. It is religiously unacceptable.

Frequency of intercourse

There is no set limit for the frequency of intercourse in married couples. During the early stage of marriage the frequency can be high, more than once daily. After the first year the frequency can be two to three times weekly. The sexual intercourse can continue throughout life of the body is healthy and the mind is willing. In these matters the couple should follow their natural inclinations.

Ordinarily, sexual desire in the female shows no special seasonal variation or relationship to the menstrual cycle. Sexual intercourse is religiously (in Moslems and Jews) prohibited during menstruation or puerperium. In Moslems sexual intercourse can however, occurs during another episode of bleeding, if it is medically acceptable.

MARRIAGE

Marriage is the socially acceptable pattern of fulfillment of the sexual instinct. This system is deteriorating in some culture. Law does not permit marriage for a girl under 16 years or a boy less than 18 years. In rural areas families go around this law, particularly for girls.

Marriage carries many social advantages over other forms of male and female relationship. One of them is the affection between the couple and stability of the relationship, both allows for progressive improvement of sexual performance and the sexual satisfaction strengthen the marriage bond.

The "first night" in marriage is a significant night in the life of the Egyptian woman. Premarital sex is not allowable and there is great emphasis on the virginity of the wife; an intact hymen is taken as testimony for this. The "first night" is therefore called the "night of penetration" or "entrance".

Five common types of problems may arise in the "night of penetration" and the early days of marriage, which can bring the bride to medical attention:

1- Failure of, or difficult penetration or non-consummation of marriage.
2- Honeymoon cystitis.
3- Excessive defloration bleeding: defloration injury.
4- Failure of occurrence of bleeding creating doubt about premarital chastity of the bride, a matter of great concern in our culture.
5- Transmission of sexually transmitted disease.

1- Non consummation of marriage

A marriage is not consummated until sexual intercourse has taken place and penetration has occurred. Sometimes, the first night may prove a great disappointment. After the excitement and tension of the wedding ceremony, the bride and bridegroom are emotionally, if not physically exhausted. Add to this are shyness and embarrassment of the bride, and nervousness and inexperience of the groom, and a common result is failure of intercourse to take place in this night. Sometimes this may result from temporary impotence of the man or occurrence of -premature ejaculations. The vaginal introitus may prove narrower than expected or the hymen is tough, or nervousness causes vaginismus so penetration fails to occur. This is sometimes very embarrassing because the events of the night need be reported to inquiring mothers during the "morning after" visit of relatives, El-Sabaheyya. If the bridegroom is considerate and unwilling to cause his bride a dreaded pain and avoid having the job accomplished in the first night (as some books advise), the bride may be offended to think that he could resist her attraction. Impotence in the first night can

shatters the bridegrooms' self-confidence, and he approaches subsequent attempts with fear of another failure. This can perpetuate itself-culminating in "early-marriage" impotence.

The normal couple surmounts these difficulties quickly, especially if they are prepared for then. Within a few days they find that coitus is possible. The act can remain painful for 2 to 3 weeks. Frequently the early attempts fail to bring the bride to orgasm. A mutually satisfactory sexual intercourse may require some months until achieved. The performance can continue to improve, may be, for some years.

2- Honeymoon cystitis

Symptoms of urethеritis and cystitis, including frequency and burning micturition are common in the early days of marriage. They result from traumatization of the urethra by attempts at intercourse. It is rarely a manifestation of transmission of gonorrheal, trichmonal or chlamydeal infection. In the latter situations there are other symptoms like excessive discharge and pruritus vulvae. These cases require full investigations of the couple and treatment of infection(s). However the simple honeymoon cystitis subside of its own accord within few days.

3- Defloration injury:

This can result from brute penetration by inconsiderate, drunken or drugged bridegroom. The introduction is sometimes attempted in a wrong direction. Injury can result from resistance of an incooperating young bride. It can result from disparity in size of parts (most exceptional) or toughness of the hymen. The intercourse may injure a congenital incomplete transverse or longitudinal vaginal septum, or fused labia resulting after circumcision.

Excessive blood loss in the "first night" is a frequent daily case in the RR of many hospitals. The blood loss can be severe, and the injury may range from cutting the fourchette to perineal or vaginal tear or even a vaginovesical or rectovaginal fistula (see under injuries in the Female Genital Tract). Careful examination, better under anesthesia, evaluates the type of injury. Blood transfusion is sometimes needed.

4- No bleeding at "penetration"

In our culture, a girl is expected to bleed as a result of defloration of the hymen in the first sexual intercourse. The expectation of significant bleeding had its origin in the traditional (or Balady) defloration, which is still practiced in some rural areas. There, the bride is deflorated by the Daya (a traditional birth attendant). This Daya accomplishes this job with her finger or a sharp object (a stick or key) carrying on it a handkerchief. The blood on the latter is a testimony of the bride's virginity. The process is done in presence of the mother-in- law and the mother. The experienced Daya, in order to ensure a safe and rewardable job makes sure to produce an injury that readily bleeds. The blood on the handkerchief is shown to relatives waiting outside the door and this is received by a rupture of

joyful cries of women (Zaghroota's). Now the Egyptian male has been mostly moved to "modern" defloration done by his penis in the without the witnesses, but he still expects to produce some bleeding in the first night. Failure to do so raises serious doubts in his mind about the premarital chastity of the bride; he expects to be the first and the only man in the life of his wife. Such a disappointed bridegroom nearly always relates the story to his mother who may insist to have the girl examined to know whether they have taken a "girl" or a "woman". This is most embarrassing for both families and is disgrace to the bride's family, they need to remove.

The story is frequently brought to the attention of a gynecologist. He is in a difficult situation. The job is distasteful and embarrassing given the many relatives of both sides of family waiting outside the consultation room (occasionally with the guns ready). The examination is difficult, needs be done with good light. It is needed to have the cooperation of the bride, which is sometimes not available. A PR examination by the index finger is done, and the finger is bent forward to stretch the fourchette and the hymen. It is sometimes difficult to see the small recent wound or two wounds in the hymnal ring. The hymen is sometimes corrugated to simulate an old tear. Frequently the hymen is found intact.

Amongst alternative explanations the "poor" gynecologist can produce, the best is an "elastic hymen". This is more appreciated by audience than alternatives. Tearing of the hymen without bleeding is not satisfactorily received. The explanation by the possibility of having the hymen lacerated through other forms of physical activity or trauma should better be avoided. In deed it is most doubtful for the hymen to tear as result of any traumas other than sexual intercourse or deep masturbation. The hymen is "deeply" situated and is not injured by any physical activity including riding or cycling. It can be injured by impalement trauma. The hymen may be absent in rare occasions.

Sometimes it is an ethical dilemma. Equally difficult is how to respond to a girl's request to have her hymen repaired, hymenorrhaphy; sometimes she has been a victim of rape. In fact, it is most difficult to accomplish repair of this too thin membrane, which cannot carry sutures. What can be done is fusing the posterior halves of the labia minora. This leaves a tiny opening in front that can deceive the "unknowing" young bridegroom.

- ***Sexual intercourse during menstruation***

The Moslem couple cannot have sexual intercourse during menstruation. This is an absolute religious rule. However, they can have intercourse during any non-menstrual spotting or bleeding including menorrhiagia and bleedings resulting from use of contraceptive. However, there no medical harm if an inadvertent intercourse has happened before the end of menstruation.

- ***Sexual intercourse during pregnancy***

This is possible but excessiveness and undue exertion are better avoided. Sexual intercourse is to be avoided in women with bleeding during pregnancy or placenta previa. Habitual aborter should avoid sexual intercourse. Intercourse is better avoided during the last 4 weeks of pregnancy in attempt to diminish the bacterial load of the upper vagina.

Interest in sex may diminish during pregnancy in some women. This may result from a feeling that the aim has been achieved or from fear about the pregnancy.

Intercourse is to be avoided (on religious basis) until clearance of puerperal lochia or until the 6th week postpartum whichever earlier. Some women may have a low interest in sex during some postpartum months, or during lactation. The husband may have loss of interest or the wife may be overwhelmed by her nursing duties.

- ***Continence***

Continence or singleness has no immediate or remote harmful medical effect. Nocturnal emission can occur and are normal.

- ***Masturbation***

Masturbation is self stimulation for sexual pleasure. It may or may not result in an orgasm and ejaculation of semen. Most adolescent boys engage in masturbation. However, it is not stigma of normality, some men have never practiced masturbation. Females also masturbates although may be to lesser extent, in comparison to males. Females masturbate by stimulating their clitoris and vulval region.

Adults who are married may continue to masturbate. There is a general misconception about harmful effects of masturbation. It however, may result in anxiety and sinful guilty feelings in these young people. These feelings can lead loss of concentration in study or work. It may increase isolation tendencies. However, physically, the practice of masturbation is not harmful. It has no relationship to postmarital sexual activity and does not result in weakness of libido or potency in subsequent marriage.

Sexual Dysfunctions

There are three sexual dysfunctions in women which are closely related, may be associated with one another, and one of them may lead to the other. These include ***Dyspareunia***, ***diminished libido***, and ***failure to achieve orgasm***. Healthy women might occasionally experience one of these symptoms. The condition *rises to the level of dysfunction only when the complaints are persistent or recurring, and-most importantly-when they cause personal distress.*

Statistics are difficult to obtain on the incidence of these dysfunctions, particularly in conservative societies. In the United States the following incidence have been reported.

Women:

Low sexual desire: lack of libido	22%
Arousal difficulty: lack of orgasm	14%
Dyspareunic on apareunia	7%

Men:

Premature ejaculation	21%
Erectile dysfunction - impotence	5%
Low sexual desire - lack of libido	5%

More than one dysfunction may be present in one person and in the couple. Arousal problems usually lead to loss of interest and vice versa. Dyspareunia leads to arousal difficulty. A problem in one partner can be blamed, correctly or incorrectly, on the other.

The corresponding figures in our society are most deficient.

The reader is referred to textbooks on Andrology for the male problems.

A. Lack of sexual desire - lack of libido

This is sometimes called true frigidity. Frigid means cold. This word is applied in case of the female to imply either lack of sexual desire or difficulty in sexual arousal and achieving orgasm. There are, however, indication pointing to difference between the two conditions, hence they are dealt with separately.

Causes of lack of sexual desire lack of libido

Understanding the cause of lack of libido in women depends upon recognizing the following points:

1. The mind is the seat of libido. Specific pathways or neurotransmitters have not been finally identified. The temporal lobe is involved relaying impulses to the hypothalamus. The dopamine agonists' apoendorphines may be involved in the deciding libido and the process of sexual arousal.
2. The ovarian estrogens play some part in the libido in women but are not essential in the sex urge in human being. Testosterone and dehydroepiandersterone DHEA may be more important than estrogens. Female libido continues after menopause. But, it is diminished after the age of 60 years.
3. Sexual desire is often not as strong in women as in men and some women may always need to be aroused by their husbands. In these women, the subsequent components of sexual intercourse can proceed normally up to satisfactory orgasm.

   Women's libido improves by practice during their twenties thirties and may be early forties, to decline thereafter. Women as old as 70 year can continue to have an occasional intercourse under the appropriate circumstances. However, the development of drugs (e.g. Viagra) that improve potency of an aging husband may

cause embarrassment and disharmony, for a wife who is not prepared. Intense research will culminate soon in producing counter-parting drugs for the female.

4. Lack of sexual desire has rarely a *"pelvic"* cause except when resulting from dyspareunia.
5. Mental and psychological stresses, depression and some psychotropic drugs including antidepressants can depress sexual desire.
6. Certain *progestogens* containing contraceptives may diminish libido in some especially sensitive women. However, the majority of contraceptives have no adverse effect on libido. On the other hand, contraceptive use may improve libido through removal of fear from conception.
7. *During pregnancy* libido may be diminished in some women.
8. *After pregnancy*: For a variable period after childbirth most women lose sexual desire. This is partly because they have be physically and psychologically harassed by childbirth, and partly because they are psychologically preoccupied by the care of the newly born. Some women have aversion to sex during the early postpartum and the husband should not press them into it. The return of libido may take some months.
9. *General diseases* like diabetes mellitus and renal insufficiency or cancer can diminish interest in sex.
10. Lack of deep affection for husband can diminish libido.
11. Psychological problems.
12. Early impressions during childhood or adolescence may inhibit the libido of an adult woman. They may amount to psychosis.

    Example include:

    (a) Bad memory of the procedure of circumcision: In this procedure the girl is exposed to strangers and experiences severe pain and bleeding. Fear of approaching the genital part can result in frigidity and/or vaginismus.

    (b) Child abuse by the father (or witnessing the abuse of her mother) may result in unconscious hatered to all members of the male sex.

    (c) Frigidity can reflect a puritanical upbringing, which may inculate ideas that sex is sinful, and that coitus is an animalcal practice, or it is just a duty of the wife to husband to give him children.

    (d) An only child may develop fixation of her affection to her mother and has difficulty in transferee of her emotion to the husband.

    (e) Narcissism of a beautiful girl is the feeling that one's own body is a greater source of self-satisfaction than the body of another person. This woman though may be beautiful, is poor in lovemaking. She dreads any change produced in her body by pregnancy, childbirth contraception, and lactation (Narcissus was a

young Greek god who fell in love with his own reflection in the pool). Such girl finds it difficult to offer all what she possesses to another person.

(f) There may be more obvious reasons for loss of sex urge- love for another man, husband's poor behavior, clumsy approaches or his unfaithfulness.

13. Fear

A common cause of frigidity is fear of pregnancy and childbirth. A young girl may be allowed to see the horrifying suffering of her mother or sister during childbirth. This is common in a poor community where home delivery occurs in a limited household. Fear of contracting STD or above all is fear of being hurt by coitus can depress libido.

14. Dyspareunia

Pain during intercourse results in loss or diminished desire for sexual intercourse.

15. Hysterectomy

Unless otherwise carefully counseled before the operation, hysterectomy may occasionally mean the end of her sexual life. Dyspareunia due to painful scar can be the initiating point of loss of libido.

16. Sterility

Long-term sterility can result in a woman losing interest in sex.

17. Prolonged separation

This is frequently met with, with many husbands traveling for several years to work in other countries unaccompanied by their families. On their return they may find the wife lacking interest in sex, having been used to inhibiting her desire for a long-time. This is particularly so when the desired family size has been completed. The increase in the couple ages may contribute to this diminished interest in sex.

18. Ill health, physical fatigue and other interests

This may result from overwhelming responsibilities to the household or to the woman career or study.

19. Endocrine disease

Although cessation of ovarian function at menopause does not ordinarily cause lack of libido, it can in some women do so. Deficiency of androgen may be the underlying cause of diminished libido. Adrenal failure, primary or secondary to pituitary dysfunction, like in Sheehan's syndrome can cause lack of libido. Thyroid dysfunctions, diabetes mellitus, and indeed, any gross endocrine disorder can inhibit libido.

Treatment

This is difficult. This is a defect in modern-time gynecology. Interest and cooperation of both partners is required. Consideration, patience and cooperation of the husband are important. Elucidation of the cause and its explanation to the couple is only sufficient in mild

cases. Correction of long established faulty old impressions and psychosis may take a long time and require psychotherapy.

- If there is evidence of an endocrine disease, its treatment can be helpful.
- If there is any cause for dyspareunia, it should be corrected.
- *Drugs*: So far, no confirmed remedy is available. The possibilities include:
    a) *Aphrodisiacs*: These are substances thought to increase the sexual desire. They are mostly part of folk medicine and comprise extracts of trees, roots (gynsing), flowers insects' animal part (horn of Rhino), Spanish fly (cantharide beetle), Strychnine, Yohimbene (made from park of a tree). All these preparations are not of proven value based on qualified evidence.
    b) Testosterone skin patches. These are still under trial they can improve libido but can result in virilism (acne, and hirsutism) in sensitive women.
    c) DHEA is a precurser of androgens. It can be combined to estrogen in a depot monthly injection given to postmenopausal women.

B. Arousal difficulty and lack of orgasm:

Definition:

It is difficult to estimate what is normal, for there is a considerable variation from time to time and from person to person. In most women, there is a progressive improvement of arousability after surmounting the initial difficulty in early marriage. Given the right mate, the woman may continue to improve for several years, but after the age of 50 years there is a fall of sensitivity over years. Some women always fail to achieve full sexual satisfaction or perhaps they do not achieve what they personally expect.

Etiology:

All the cause of lack of libido. Added to these are:

- *Female sexual cutting (circumcision or mutilation).*

It is difficult to estimate how much the vaginal arousal and orgasm can compensate for clitoridial stimulation. There are no reliable studies, but the impression is that this is mostly achieved in the Egyptian females who are by far - mostly circumcised. [This is not to be taken to weaken the author's opposing stance to the practice of female circumcision]. However, the public media (or medical profession) handling of the story of female circumcision may be unnecessarily exaggerating and initiating a feeling deficiency or inadequacy in some women who have been beforehand, leading a satisfactory sexual life.

- Relaxed vaginal walls

An overstretched vagina with lax pelvic muscle interferes with the close sexual contact and sometimes makes it difficult for the woman to achieve orgasm. This is frequently a complaint of the husband. Colpoperineorrhaphy in these cases can make coitus more satisfactory. Excessive tightening of the vagina should be avoided because this can result in dyspareunia and/or create difficulty to an elderly husband with failing potency.

- *Premature ejaculation*

Failure on the part of the husband to offer a required foreplay and to control the coital act and defer his orgasm until his partner reaches hers can be at the root of the problem.

Treatment:

- This is essentially similar to that described for lack of libido. Trial to identify the problem and give the advice about its correction is the main line of treatment. There is no way out without the help of a cooperative husband.

- The couples should be advised to experiment with different coital technique.

- The success achieved with viagra in treatment of erection defects in the male has encouraged its trial in women with a broad-spectrum of sexual dysfunctions. However, initial trial has not demonstrated viagra to be better than placebo. New trials are underway, targeting specific groups, e.g., postmenopausal women or women with lack of orgasm. The aim is to achieve a better engorgement of the clitoris and the orgasmal platform in the lower vagina.

- Prostaglandin E-1 cream is being tried as a local vasodilator to improve vaginal arousal.
- A clitoral device has been approved in the United States. This prescription device creates a gentle suction over the clitoris in order to increase blood flow and sensation.
- The use of pornagraphy material is unadvisable. It may have negative effects by showing exaggeration, which are not "usual" or natural.
- The gynecologist sometimes, at the end, advise his patient to silently bear with the problem and use the physical contacts as a way of rendering affection to the husband.

C. Dyspareunia and Apareunia

Definition

Dyspareunia means that sexual intercourse is difficult and painful or that penetration is incomplete. Apareunia is the inability to practice intercourse. The difference is usually a matter of degree. The difficulty and pain usually leads to or is associated with lack of arousal or lack of achieving orgasm. It may also lead to loss of interest in sex and diminished libido. However, the libido can be normal in spite of repeated frustrations.

Both partners are concerned in dyspareunia and, although the complainant is usually the wife, it can be the problem of the husband. Occasionally the trouble is a weak potency of the husband and the plame is put on the wife who is accused of having a narrow or obstructed introitus, or weak response.

There are two distinct types of dyspareunia; the superficial and deep. Superficial dyspareunia means pain and/or difficulty in penetration into the vagina. Deep dyspareunia mean that penile thrusts cause deep pelvic pain. These may occur in special coital positions or may occur at specific time like premenstrually or in mid-cycle.

Etiology

I. Introitus (superficial) dyspareunia

A. Male causes:

1. Impotence

This is failure to obtain or maintain erection of the penis. This is particularly met with in early marriage. An overconsiderate or weakly virile husband can experience difficulty. This unexpected occurrence is frequently blamed, in rural culture on what is called "tying" which ascribed to evil spirits. The condition is also expected in aging husbands.

2. Inorganic

Ignorance, inexperience, lack of consideration, or clumsiness on the part of the bridegroom may cause dyspareunia that can amount to vaginismus.

3. Extreme obesity

Obesity has to be very gross to prevent penetration.

4. Disparity in size

Large phallus is exceptionally a cause of dyspareunia in a diminutive wife.

5. Too frequent intercourse: when the wife is not ready.

B. Female causes:

1. *Physiological*: Some pain is expected at first penetration. Repeated intercourses are usually painful during the first week of marriage.
2. *Congenital or inherent abnormalities*
   - *Thick rigid hymen:* the hymen is rarely too rigid to prevent penetration.
   - *Vaginal aplasia*, or *congenital septa* or membrane: Longitudinally divided vagina is rarely a cause of difficulty; intercourse takes place to either side of the membrane. Transverse septum or partial or complete vaginal aplasia cause real difficulty. In rare instances the urethra is dilated by the perseverance of the husband, until he practices intravesical intercourse.
   - Inherent narrowness and inelasticity of the vaginal orifice: This is more likely in women marrying late near menopause with sclerosed vulva.

- Shortness of the vagina
- Normally the vagina is distensible. In elderly women it can be rigidity short.
- *Extreme obesity*
- *Inaccessibility of the vulva*
- This may result from severe adduction deformities associated with diseases or hips or legs. Variation in coital position may overcome this difficulty.

3. *Traumatic*
   - Scarring of introitus or fusion of labia minora or majora resulting from *female circumcision*. In the Nubian/Sudanese circumcision, the whole of the vulval structures are removed and the wound is stitched around a stick for just the allowance of escape of urine and menstrual blood.
   - *Badly repaired episiotomy or vaginal and perineal lacerations.* This can be a distressing complaint after the first delivery.
   - Excessive removal of vaginal skin and tightening the pelvic floor muscles *during repair of genital prolapse*. This is a common mistake, which is unfortunately difficult to correct. The operation is frequently done for middle-aged women; their husband may be having a declining potency and cannot achieve any postoperative dilatation of the vagina.
   - Tender scar, neuromas and inclusion dermoids may result from the above-mentioned wounds. These lesions can be extremely painful and require care for their identification.
   - *Shortness of the vagina* may result from total hysterectomy.
4. *Infections*
   - *Vulvovaginitis* can cause dyspareunia: Recurrent candidiasis, trichomoniasis, or herpetic infection can cause severe dyspareunia. The husband can be also affected. He have lesions on his phallus particularly on the remnant of the frenum under the glans; this site may repeatedly breakdown causing him severe pain. The couple may be ping-ponging the infection and both partners require treatment.
   - *Bartholinitis* acute or chronic, or a bartholin abscess.
5. *Hormonal*

Dryness of the introitus and vagina may occur after menopause and causes coital difficulty. Lack of lubrication can be caused by failure of Bartholin gland to lubricate the vulva as a part of lack of libido or lack of sexual arousability.

6. *Dystrophies*

Lichen sclerosus or squamous cell hyperplasia can diminish the elasticity and the width of the vulval introitus.

7. *Large tumors of the vulva and vagina.* The commonest is a Bartholin cyst.
8. *Functional:*

   Vaginismus: This is an important, difficult type of dyspareunia. It is a condition of spasm affecting the sphincter vaginae and levator ani muscles, especially the latter. The spasm may be so great that the lower vaginal gets closed and both the wife and husband may presume presence of an organic obstruction. In severe cases there is hysterical adduction of the thighs making approach to the vulva impossible. Repeated disappointments may rock the confidence of the husband in his virility, and he starts to have weaker erection. The condition frequently enters in a vicious circle and become difficult to treat. It can continue for several months or years, particularly of the husband resign to interfemoral or interlabial external intercourse.

   The condition is commoner in young highly-strung, spoilt women, with an overconsiderate husband. The bride may be too shy to accept her husband approaches. It is less common in women of rural background. It may be associated with weak libido and/or weak arousability. However, sometimes these other aspects of sex are quite normal. The condition may not be cured, as expected, by pregnancy and vaginal delivery. Vaginismus may have a background of faulty sex education, bad memories or impressions about sexual intercourse, the other sex or childbirth. It can be resulting from a tender lesion in the genital tract or neighboring organs. However, a cause cannot occasionally be found.
9. *Extragenital causes:*

   These include anal fissure and infected piles. Dyspareunia can result from urethral caruncle, urethritis or urethral prolapse.

II. Deep-seated dyspareunia:

Except in its lower most part, where its innervation is somatic, the vagina is insensitive. Upper vaginitis or ulceration or wound causes no pain. Deep-seated dyspareunia invariably results from diseases in surrounding structures like:

1. Cervicitis associated with deep tender tear.
2. Chronic pelvic cellulites, parametritis.
3. Salpingo-oophoritis.
4. Endometriosis.
5. Fixed retroversion flexion. The pain is not caused by the uterine position itself but by the disease that has fixed the uterus in retroversion. Constitutional retroversion flexion should not cause dyspareunia.
6. Prolapsed ovaries fixed in the Douglas pouch.

7. Tender lesion in the bowel, especially infected fissure or hemorhoid or spastic colon.

Diagnosis of a cause:

- *Ascertain whether the pain and difficulty are felt superficially at the introitus or deep in the vagina and pelvis.*
- Ascertain whether the pain or difficulty is experienced in every act or it is occasionally experienced. In the latter case the associations should be ascertained.
- Ascertain whether the problem is a matter of difference in libido between the couple and/or reflecting lack of arousability.
- Exclude the male contributions to the problem.
- Ask if the pain is momentary or sustained and whether it experienced at the time of coitus or later. If it persists after, or occurs, several hours later, its basic cause is psychogenic. It may be away to escape the attention of the husband. Backache occurring late after coitus may be related to exertion of certain pelvic joints during the act or due to the coital position.
- Determine whether the dyspareunia is primary or secondary.
- Determine whether it resulted after a delivery or an operation.
- Absence of any local tenderness during vaginal and bimanual examination raises doubt about presence of an organic cause. A complaint of dyspareunia may be a way of escaping disliked approaches of the husband.
- Try to evaluate an emotional background.
- The associated symptoms and physical sign will point to an organic cause. all necessary investigations are done to elucidate the cause including laparoscopy. This is needed in deep dyspareunia and can show chronic PID, tumor or endometriosis.

Treatment :

- *Any organic cause for superficial or deep dyspareunia should receive treatment*. Tender scars should be excised and dilated. Estrogen administration is needed for elderly patients with vaginal dryness. This can be topical (cream or pessaries e.g. primarine vaginal cream or pessaries) or systemic. Any infection should be eradicated.

Tratment of Vaginismus

Vaginismus deserves special handling and this is frequently difficult.

1. Instruction (better with help of diagrams) about the normal anatomy and the direction of the vaginal canal should be given to the couple.
2. Firm advises about ways of overcoming the difficulty. The necessity of overcoming shyness and fear should be emphasized on bride, and the need of the husband for being persuasive, patient but also firm in his trials. All these are required at the same time.

3. *If one-finger vaginal examination is possible*, the prognosis should be good. The couple is assured that they're no organic obstruction. The woman is advised to introduce her finger with the help of a water-soluble jelly (k-y gel) into the vagina. If this succeeds she is advised to repeat twice daily for some days before introducing two fingers. She can then allow her husband to pass his finger into the vagina. This drill gives her confidence that the penis can be accommodated without pain. If she is still virginal, the first penetration (which can be the vaginal examination) will cause some bleeding and pain. In this case the couple should better abstain for a week or so before joining in another drill with finger manipulation.
4. *If one finger-vaginal examination is not allowable*, further pressure on the part of the gynecologist to have the examination completed is usually futile. He should exercise kindness to the patient who is told that she has a narrow vagina that needs dilatation. This is done in the hospital under anesthesia the vaginal introitus is manually dilated until it readily admits three fingers. This is usually initially better than widening the introitus by a perineotomy, which leaves a wound that, can remain tender for some time and may initiate the hysterical spasms once touched. After few days from the dilatation under anesthesia, a follow up drill of dilatation using plastic or metal dilator is initiated. This is repeated daily and can be accomplished either at home by the patient or better initiated at hospital by an experienced nurse or an assistant. Small dilators should be used first and gradually moving to bigger ones until the patient can herself insert number is dilator and leaves it inplace for 10 minutes.
5. This regimen usually works in mild to moderate cases. Severe cases require a *middle-line deep episiotomy*, which is sutured transversely. No attempt at intercourse or dilatation is made until the wound has completely healed.
6. Severe cases require psychiatric consultation, and can prove most difficult to treat.

Sexually Transmitted Diseases

[See under reproductive tract infection]

Abnormal Sexual Practices

The peno-vaginal intercourse is by-far-the commonest sexual practice. It is the one allowed by religions and the one consistent with reproduction. The prevalence of other forms of sexual practices in our community is impossible to assess. From the gynecologist seat one may judge that masturbation is a quite common practice. Some form of oral sex is also prevalent. Anal sex in married couples should be rare. Homosexuality is socially unacceptable. It comprises sexual relation between two females (lisbians) or two males

(Gay); an individual is described as bisexual when he is both heterosexual and hemosexual. The designation of such practices as abnormal is not acceptable in some societies who give the personal freedom precedence to established societal norms.

Transverstism and trans-sexuality

Transvistism is a condition in which the individual has an urgent desire to dress in clothes worn by the other sex. Trans-sexuality is a compelling urge to change sex, and cross-dressing is part of this urge. This usually reflects a psychological problem, but the individual may otherwise be normal. This latter condition is quite rare. The individual can demand medical help to be changed to the other sex. This is not acceptable in Islam.

Nymphomania

This is a woman who has an incessant and overpowering desire for sexual intercourse. This is a rare problem requiring psychiatric care.

Sadism, Masochism, and Pedophilia:

The sadist is unable to gain sexual satisfaction unless he or she inflicts cruelty on the sexual partner. The masochist derives sexual pleasure from being beaten or whipped.

Pedophiles are adults who seek their sexual pleasure from children. This may include homosexual, heterosexual and lesbian relations. Such practices are both emotionally traumatic and physically harmful to the involved child.

Sexual Abuse

Rape

Rape refers to forced sexual relations (on a woman) often with actual or threatened violence. This means that the carnal relation has occurred without her conset. Moreover the consent is no defense when the woman is under 16 years of age (age of consent). Rape is a serious crime punishable by capital sentence under the present Egyptian penal law. However, the crime is increasingly reported

Some victims of rape may prefer not to report the incident and suffer its consequences silently. However, the best place for the victim to go to is a hospital reception room without washing her private parts. A doctor consulted by a woman alleging rape should examine her as soon as possible recording all her or his observations and findings:

- The woman's detailed account of the happening.
- Her emotional state.
- Whether her clothes are torn, stained (the clothes are material evidence).

- The presence of bruises and wounds and their description.
- The state of her fingers and nails, and the presence of skin debris or blood.
- Wounds, bruises in the vulva, hymen and vagina.
- Presence of semen on her vulva, vaginal or pubic hair. a microscopic examination of part of the material proves presence of sperm. These specimens are material evidence that should be kept for identify verification including DNA matching with the semen of the accused man.

If the accused man consent to be examined, the evidence to look for, is the presence or absence of injuries, bruises or scratch marks in any site, semen on his phallus, the state of his clothes, loose hair around genital which can be those of the victim.

All measure should be taken to diagnose transmission of venereal disease particularly gonorrhea, chlamydia syphilis and HIV in the victim. The appropriate prophylactic treatments should be given.

Psychiatric help may be needed

Sexual Molestation

Molestation covers a large range of behaviors from kissing, hugging, petting, stroking or squeezing part of the woman's both that makes her very uncomfortable. It also includes uncovering her by pulling off, or tearing her clothes.

Sexual Harassment

Sexual harassment is any unwanted sexual attention, which a woman experience. Examples include leering, passing offensive remarks, touching, leaning over, brushing past, and relating sexual explicit jokes, obsence phones. Sexual harassment is increasing made allegation of working women against their seniors and colleagues at work.

Chapter 27

HYSTERECTOMY

- ❖ Surgery is the branch of medicine that covers diseases and infirmities correctable by surgical interventions.
- ❖ Surgery should not ignore or belittle the alternatives of nonsurgical managements.
- ❖ Surgery couples to technical dexterity attention to details.
- ❖ The obligation of the surgeon to his or her patient does not end in the operation theatre. It should extend to ensuring the best health-related quality of life.

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- Preparations of patients
- Technical details of abdominal total hysterectomy
    - Possible difficulties
- Technical details of subtotal hysterectomy
- Complications of hysterectomy
- Technical details of vaginal hysterectomy
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    - and laparoscopic Hysterectomy
- Changing trends in hysterectomy
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    - Total versus subtotal hysterectomy
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    - Removal of the normal ovaries
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Evolution of Hysterectomy

- Vaginal hysterectomy was performed many years before abdominal hysterectomy.
- The first abdominal hysterectomies were performed on both sides of the Atlantic by the middle of 19th century.
- Nowadays, hysterectomy has become the second most commonly done major operation after cesarean section in many parts of the industrialized countries. This trend is spreading to developing countries. Although not eliminated, the morbidity and mortality associated with the procedure have been greatly diminished. This has encouraged widening the indications for hysterectomy to include more benign diseases and symptoms related to the genital system.

Indications of Hysterectomy

I. Benign Diseases or Symptoms of Uterine Origin

▪ *Uterine Myomas*

Uterine myomas are the most common indication for hysterectomy. Myomas are common tumors occurring in roughly 30% of women above the age of 30 years. They are frequently asymptomatic and commonly managed conservatively because of the very low rate of malignant transformation (0.1- 0.3 %). Myomas causing abnormal uterine bleeding or pressing on surrounding structures are usually treated surgically. Of the two surgical alternatives, myomectomy and hysterectomy, the latter is chosen when there is (1) no need or (2) there is a real difficulty or (3) risk of conserving the uterus (see under Myomas). Recently, other alternatives to these two surgical approaches have been developed including the use of Gn RH agonists and hysteroscopic myomectomy, and myolyses.

The indications of hysterectomy (or myomectomy) in asymptomatic myomas include the following:

1. Subserous pedunculated myoma, for fear of torsion.
2. Cervical or broad-ligament myoma, for fear of pressing upon surrounding structures in the future.
3. Rapidly growing tumors, for fear of being malignant.
4. Growth of myoma after menopause for fear of being malignant.
5. Large-sized myomas equivalent to a 12 - 14 week gestation in a perimenopausal patient for the following reasoning:
   - Future need of hysterectomy will mean a more difficult surgery.
   - Improving quality of life by cessation of menstruation.
   - Avoiding silent pressure on urinary tract.
   - Sterilization.

These reasoning are not always valid and should be weighed against the desire of the patient to preserve her uterus; the patient should not be pressed to remove her uterus for asymptomatic myomas.

▪ *Uterine Prolapse*

Vaginal hysterectomy is frequently done as part of the treatment of uterine prolapse. Removal of the uterus may help in allowing better correction of pelvic relaxation by eliminating the weight of the elongated and enlarged organ. However, it needs to be combined with: 1) correction of the associated vaginal prolapse; 2) proper correction of hernia of Douglas Pouch; 3) suspension of the vaginal vault by the uterine pedicles and 4) good pelvic floor repair. Failing to do so will leave a weakly supported vaginal vault, which will be

everted out; a displacement, which is difficult to correct. Vaginal hysterectomy with the aforementioned additions is the preferred treatment of uterine prolapse when:

- The patient is post or perimenopausal.
- The prolapse is marked.
- The uterus is small.
- There are other reasons for removing the uterus like uterine bleeding or a small sized myoma (a big myoma may be difficult to remove vaginally).

A second degree uterine descent with marked elongation of the supravaginal elongation and no other uterine pathology *may be* better treated, in a postmenopausal woman, by Fothergill's operation. The body of the uterus is may be well supported in the pelvis, and the hysterectomy will be a more difficult alternative.

- ***Dysfunctional uterine bleeding***

The treatment of dysfunctional uterine bleeding is essentially medical. However, hysterectomy is nowadays increasingly used for treatment of intractable and severe dysfunctional bleeding; about 20 to 30% of hysterectomies done in USA have this indication. Hysterectomy is only justified if dysfunctional bleeding is:

1. Recurrent and flooding causing soiling of external clothes or the bed and interfering with the patient's daily life.
2. Causing anemia or low ferritin level.
3. Nonresponsive to *"appropriate"* medical treatment. Unfortunately, patients are frequently put to hysterectomy after "nonspecialized", inadequate trial of medical management.
4. The bleeding has required several emergency D & Cs to stop bleeding episodes.
5. Associated with symmetrical enlargement of the uterus. The enlarged surface area of the uterine cavity will continue to cause heavy periods. This enlargement of the uterus may sometimes be caused by high parity.
6. Dysfunctional uterine bleeding associated with atypical endometrial hyperplasia. This complex hyperplasia carries a chance of progression to endometrial cancer amounting to approximately 20%. On the other hand, simple hyperplasia of the endometrium will progress to cancer in less than 1% of the cases. In young patients, both disorders, particularly the simple one, can be treated with cyclical or continuous progestional agents. In the case of atypical endometrial, a 3-month course of therapy should be followed by repeated endometrial biopsy to document reversion to normal endometrial pattern. Not infrequently, even after such reversion to normal, the hyperplasia may recur, necessitating further treatment and follow-up. The patient may be counseled, however, to have

hysterectomy if she is perimenopausal and having atypical glandular hyperplasia, or when she is not expected to remain under surveillance.

7. Consideration of hysterectomy option in cases of dysfunctional uterine bleeding is only valid for women above the age of 35 or 40 years and with completed family.

   Vaginal hysterectomy is a more acceptable and feasible approach in this indication. In such types of recurrent severe types of dysfunctional uterine bleeding, a number of alternatives for complete or partial ablation of endometrium have been recently introduced including diathermic (by the resectoscope or the rolling ball), cryo - or thermal ablation. These approaches should diminish the need for hysterectomy in cases of dysfunctional uterine bleeding. (See under Abnormal Uterine Bleeding).

▪ *Adenomyosis*

This represents the growth of endometrium into the depth of myometrium promoting hyperplasia and fibrosis of the latter. The condition presents with dysmenorrhea, menorrhagia and uterine enlargement, which is usually symmetrical, but more prominent in the anteroposterior dimension. The condition is difficult to diagnose; may be suspected by sonography or MRI. It should be a rare indication for hysterectomy, which is resorted to after failure of other measures of treatment like hormonal treatment and curettage and only in perimenopausal patients with completed family.

▪ *Chronic inversion of the uterus:*

Hysterectomy is sometimes required for chronic inversion particularly when associated with presence of myoma.

▪ *Nonneoplastic Diseases of tubes and ovaries*

Chronic Salpingo-oophoritis

The treatment of chronic pelvic inflammatory conditions is essentially medical. Ablative surgery in the form of abdominal hysterectomy plus bilateral slapingo-oophorectomy (AH + BSO) is considered for *intractable* disease, *not responding to conservative treatment,* with *disabling pelvic pain* or *excessive bleeding.* It is also considered for persistent big adnexal masses like *tubo-ovarian abscesses.* As an emergency, such surgery can be done for *rupture tubo-ovarian abscess.*

The distorted anatomy and extensive pelvic adhesions caused by chronic infection makes this hysterectomy sometimes really difficult. Radical removal of all infected structures is needed; you cannot leave behind the infected adnexa.

Pelvic endometriosis

Extensive pelvic endometriosis in a patient *above the age of 35 years* may be an indication for AH + BSO *when nonsurgical treatment fails* to relieve distressing symptoms or *after failure of conservative surgery.* For this indication, ablative surgery can also be difficult due to adhesions. The difficulty can be diminished by prior 3 to 4 month treatment with GnRH agonists, which may diminish the size of endometriotic lesions (see under Endometriosis)

Ectopic pregnancy

Certain rare types of ectopic pregnancies may require hysterectomy:

- Interstitial pregnancy.
- Cervical pregnancy.
- Abdominal pregnancy when the placenta is inserted upon the uterus.
- Repeated tubal pregnancies when both tubes have been badly damaged. However, the patient in the latter case needs to give her specific informed consent on removal of the uterus, since she can still benefit from IVF/ET after removal of both tubes.

▪ *Benign or borderline ovarian tumors*

TAH + BSO is the treatment of choice of these cases if the patient is above the age of 40 and has completed the desired family size.

II. Premalignant and Malignant Tumors of the genital system

▪ *Cervical Intraepithelial Neoplasia (CIN)*

Hysterectomy is recommended for patients with severe CIN or carcinoma in situ who are not keen on having more children. Otherwise, more conservative procedures like cervical cautarization, cryosurgery, laser surgery, large loop excision, or cervical conization are done.

Vaginal hysterectomy is preferred unless, contraindicated by adnexal disease or pelvic adhesion. A vaginal cuff should be removed with the uterus when the dysplasia extends to one of the fornices (as determined by colposcopy or Schiller's test). Otherwise, removal of a vaginal cuff is not required. Follow-up cytological screening is required at 6-month intervals for two years before the patient is returned back to the regular screening policy. (see under Carcinoma of the Cervix)

▪ *Early Invasive Cervical Cancer*

- ***Stage I-A*** cervical cancer can be treated by a simple total hysterectomy and removal of a vaginal cuff. This diagnosis requires prior adequate cervical conization which has been thoroughly examined and shown minimal, superficial, microscopic stromal invasion limited to a depth of invasion not more than 3 mm below the surface epithelium, with no confluence of invasions and no tumor tissue in vascular spaces. Otherwise, failing these criteria the case is considered as Stage I-B.
- ***Stages I-B and* II-*A*** carcinoma of the cervix is treated by Wertheim's - Meig's radical hysterectomy (see under Carcinoma of the Cervix).

▪ *Endometrial carcinoma and uterine sarcoma*

As indicated above, atypical adenomatous hyperplasia has a 20% chance of conversion to endometrial cancer and is better considered an *in situ* stage of endometrial cancer. It is generally treated by hysterectomy unless the patient is keen to keep her uterus for childbearing and the lesion reverts to normal after progestogen treatment as demonstrated by repeated curettage. Less severe hyperplasia usually are reversible and do not require hysterectomy.

Endometrial carcinoma and sarcoma of the uterus are treated by total hysterectomy and bilateral salpingo-oophorectomy. Radical abdominal hysterectomy (with partial vaginoctomy and pelvic and paraortic lymphedenectomy) may be done in the more advanced disease of Stage II or more if the general condition of the patient can allow. However, since the majority of the patients with endometrial carcinoma are old and frail, it is usually sufficient to do TAH + BSO with the adjuvant treatment with pelvic irradiation (see under Endometrial Carcinoma).

▪ *Ovarian and Fallopian Tube Tumors*

Malignant ovarian (and tubal) tumors are treated by abdominal hysterectomy + bilateral salpingo-oophorectomy which is followed by multiple-agent chemotherapy.

In special circumstances in young patients and in case of limited disease, or not definitely malignant tumor, conservation of the function of the uterus and the other ovary is chosen through performing oophorectomy of the involved ovary.

On the other hand, apparently benign tumors of the ovaries in patients above the age of 40 - 45 are better treated by AH + BSO if the desired family size has been achieved. The argument with this approach is that one is not sure of benign nature of many ovarian tumors until after careful histopathology, or ovarian tumors are occasionally multifocal, and the apparently normal other ovary may be harboring a yet microscopic malignant tumor.

- ***Trophoblastic neoplasia***

Total abdominal hysterectomy is the safest treatment of hydatidiform mole in a patient who has completed the desired family size and who is elderly. This avoids the risk of bleeding associated with vaginal evacuation of the mole, and the relatively increased risk of choriocarcinoma in elderly patients.

Trophoblastic neoplasia is, nowadays, essentially managed by chemotherapy either with a single agent or multiple agent protocols. Hysterectomy is rarely necessary. It is indicated in patients with evidence of progression or persistence of trophoblastic disease in spite of chemotherapy; like persistently high hCG titer, or persistence of bleeding and/or uterine enlargement.

- ***Malignant Diseases of other adjacent pelvic organs***

When malignant diseases of the bladder, rectum and sigmoid colon are treated surgically, the uterus usually needs to be removed to allow for adequate removal of the disease.

III. Obstetric indications of hysterectomy

- ***Uncontrollable postpartum hemorrhage***

This is one of the worst situations that may face an obstetrician. The decision to remove the uterus in this emergency should not be delayed long, particularly in a patient with a reasonable number of children. Blood transfusion facilities are occasionally inadequate in our service. The consent of the husband needs be taken after adequate explanation. However, measures like bilateral uterine artery ligation or ligation of the anterior division of the internal iliac arteries should be attempted first before resorting to hysterectomy. This is one of the situations in which a second opinion is required before removing the uterus. The condition must be clearly documented in the records of the patient.

- ***Rupture Uterus***

This can be a rupture of a previous cesarean section scar or other scars, rupture occurring because of obstructed labor; or resulting from vaginal obstetric operation. Suturing the wound may be possible. However, hysterectomy is the better alternative if the desired family size has been completed or the uterus is badly damaged. A second opinion is also required in this case.

- ***Acute inversion, which*** has failed to be corrected and is associated with severe postpartum hemorrhage.
- ***Certain types of ectopic pregnancy (see above)***
- ***Septic abortion with septic shock***

This condition is usually treated medically with parenteral antibiotics, corticostroids and evacuation of uterine contents. If these fail to correct the general condition that continues to deteriorate, abdominal hysterectomy may be required and better not be delayed long.

- ***Gynecological tumors complicating pregnancy***

Myomas complicating pregnancy are better not be touched during pregnancy. This is unless the patient is undergoing cesarean section for another indication and she is not interested in further pregnancy, when the uterus can be removed at the time of section. A subtotal hysterectomy is the better choice in this case to avoid excessive bleeding.

On the contrary, the presence of pregnancy should not delay the proper surgical management of ovarian tumor, unless the delivery (or reasonable fetal viability) is expected within weeks.

Radical hysterectomy for cervical cancer is possible during early pregnancy and should not be delayed. The pelvic vessels are congested which may increase intraoperative bleeding, but the fascial planes are easier to dissect.

IV. Unusual and Questionable Indications of Hysterectomy

▪ *Estrogen replacement therapy*

Uterine bleeding resulting from postmenopausal hormonal therapy (PHT) is usually unacceptable for many women and is the commonest cause of discontinuation of such treatment. Even with continuous combined regimen, intermittent irregular bleeding occurs in approximately 30% of users (even after allowing for 4 - 6 months of adjustment to this therapy). However, This occurrence or argument *should not,* promote performing an otherwise unnecessary hysterectomy. Removal of the uterus avoids this nuisance bleeding and risk of endometrial cancer. However, the risks and the financial implications of hysterectomy are not warranted. Alternative postmenopausal treatments are now increasingly available, other than giving estrogens (e.g. SERMs) for those women not tolerant to the bleeding. The slightly but significantly increased risk of development of breast cancer also needs to be weighed and added to the risks of hysterectomy in the risk and benefit ratio of continuing PHT. The use of one of the SERMs is associated with diminished chance of bleeding, endometrial hyperplasia and breast cancer. This should obviate the need for hysterectomy.

- ***Cancer Prevention***

The risk of development of epithelial ovarian cancer in a woman with two or more first-degree relatives afflicted with this disease is high -- 50%. This can be an indication of bilateral oophorectomy. Hysterectomy is better done for this patient as well in order to avoid uterine bleeding with hormone replacement therapy.

- ***Chronic Pelvic pain***

There are many causes for chronic pelvic pain, a symptom usually treated with the management of the cause. The management of this common complaint depends on a thorough diagnostic workup including, at the end, laparoscopy. In the absence of specific pelvic pathology, the gynecologist *should be reluctant* to resort to hysterectomy, even when the patient requests this. A psychological element may be present and the condition may reflect chronic anxiety. The condition may be related to dyspareunia or a sexual problem. It can be associated with spastic colitis or urinary urgency. The diagnosis should address these possibilities with a number of symptomatic treatments including the use of antispasmodics, analgesics, and non-steroidal antiinflammatory drugs. More conservative surgical interventions like diathermic laparoscopic uterosacral neural ablation (LUNA), to ablate nerve supply of the uterus may be tried before resorting to hysterectomy.

Two related syndromes have been described and may cause chronic pelvic pain: *the pelvic congestion syndrome* and the *Allen-Master universal-joint syndrome.* The first is ascribed to vascular congestion and hyperemia of the pelvis which cause pelvic heaviness and pain, dyspareunia, lower backache, excessive tiredness and/or headaches which are all worst premenstrually. The syndrome is most difficult to ascertain by diagnostic method as a separate entity from other cases of chronic pelvic pain. The Allen-Master syndrome shares the same presenting symptoms with two additional manifestations: (1) The first is that the uterus is found in severe third-degree retroversion flexion and the cervix can be moved independently in all directions in the pelvis as if having a universal joint. (2) The second feature is the particular postpartum association; the patient is giving a history of difficult or precipitate labor with evidence of lacerations of the fascial tissue layers in the broad and cardinal ligaments.

In the opinion of the author is that hysterectomy may be of benefit in some of the resistant cases of chronic pelvic pain or pelvic congestion syndrome. Big series of hysterectomies done for chronic pelvic pain report substantial improvement in some variable rates ranging from 50% and 95%; some patients have incomplete relief of symptoms and some have other complaints, a sort of “system substitution”. The surgeon can be most unfortunate when the substitutive complaints are related to his surgery.

- ***Sterilization***

Hysterectomy is a major surgery, which should never be done for sterilization. The alternative of tubal sterilization is much less risky. However, the need for permanent contraception may be supportive to another indication for removing the uterus. For example, a 35 year-old patient with symptomatic vagino-uterine prolapse requesting sterilization may have vaginal hysterectomy and repair rather than Fothergill's operation plus tubal sterilization. Another situation is a 35 year-old patient with 10 week-sized myomatous uterus and menorrhagia requesting sterilization may be advised to have hysterectomy rather than myomectomy plus tubal sterilization.

- ***The concept of elective hysterectomy*** (arguments and counter arguments)

This concept is present in some Western countries; a woman requesting removal of her normal uterus (and ovaries) after completing the desired family size and a gynecologist may encourage his patients to have such procedure. This concept may be the background of widening the "indications" of hysterectomy. The arguments in favor of removing the normal uterus are the following:

1. ***The uterus has but one function: reproduction.*** After the last planned pregnancy, the uterus becomes a useless, bleeding and symptom-producing, potentially cancer-bearing organ and therefore should be removed. The counterarguments are the decision to terminate fertility may be regretted in the future due to a change in circumstances e.g. loss of a child or another marriage. The uterus to many women is important to gender identity, sexuality, marital relation, and self esteem, much more than a potentially problem-bearing foreign body after reproduction has been completed, or even if the husband is azoospermic. Hysterectomy may upset the fine "balance of forces or potentialities" in a certain marriage, the woman becoming on the weak side after removing her uterus. The husband may change his mind about having more children and may seek that in another marriage.
2. ***Malignancy prophylaxis:*** Total hysterectomy and bilateral salpingo-oophorectomy will eliminate most of the risk of cervical, endometrial and ovarian cancer. However, these risks can be greatly diminished by screening of the women population and organization of medical care of aging women; a definite progress has been achieved as regards carcinoma of the cervix. The operation of TH + BSO is a major surgery which in good settings has a mortality of about 20 per 10,000 and morbidities several times this figure. Much more importantly TH + BSO may impair the health-related quality of life (HRQL) particularly when the ovaries are removed at a young age. The

implication of the need for HRT for long years and the resultant slight, but statistically valid, increased risk of breast cancer after prolongation of such therapy.

3. ***Permanent contraception:*** Permanent contraception is achieved by hysterectomy. This aim can be achieved by tubal sterilization (or vasectomy of the husband) without exposure to hazards of hysterectomy. The possibility of occurrence of *post-tubal-ligation syndrome* characterized by pelvic pain and dysfunctional uterine bleeding, which may ultimately necessitate hysterectomy has been taken as an argument in favor of hysterectomy option. However, the existence of such syndrome has been challenged by some reports, which denied the increased occurrence of such symptoms after tubal sterilization, [particularly when the procedure of sterilization is done by techniques entailing minimal damage to the tubes like the clip sterilization]. The gynecologists may be more readily resorting to hysterectomy when symptoms develop after tubal sterilization as a part of elective hysterectomy strategy; again an unjustifiable trend.
4. ***Hysterectomy will allow more liberal use of postmenopausal estrogen replacement therapy.*** This point has been discussed above. The advantage of hysterectomy may be the absence of the need to add progestogens which might lessen some of the cardioprotective effects of estrogens.

Types of hysterectomy: Terminology

Abdominal Hysterectomy:

- ***Subtotal hysterectomy*** = supravaginal hysterectomy.
- ***Total abdominal hysterectomy +/- bilateral salpingo-oophorectomy*** (TAH +/- BSO). The removal of the uterus including the cervix with a minimum of the surrounding parametrium and the paracervical tissue. This is the type of operation done for benign diseases. It is called ***intrafascial hysterectomy*** since nothing of the pelvic fascia is removed; the paracervical clamps are applied beneath the pubovesicocervical fascia (bladder pillars) immediately lateral to the cervix. No vaginal cuff is removed.
- ***Extended hysterectomy*** This refers to the complete removal of the uterus including a cuff of the vaginal tissue. The ureters are identified on the front of the cardinal ligament and dissected down. Then the upper medial part of the cardinal ligament is clamped and cut. This operation is described as the ***extrafascial hysterectomy*** and corresponds to class 1 of the classification suggested in Rutledge for hysterectomy done for carcinoma of the cervix. It is the type of operation done for endometrial carcinoma and Stage I A carcinoma of the cervix.]

- ***Modified radial hysterectomy*** removing the medial half of the cardinal and uterosacral ligaments. The uterine vessels are divided medial to the ureters. This procedure corresponds to class 2 in Rutledge classification. It can be done in Stage I B of cervical cancer if the tumor is small <4 cm and well differentiated. Otherwise, the classical radical hysterectomy is done.
- ***The classical Wertheim-Meig's operation*** It corresponds to class 3 in Rutledge classification. Both ureters are dissected down to the bladder. The upper third of the vagina and paravaginal tissue are removed. The uterosacral ligaments are divided at their origin and the cardinal ligament at the pelvic wall. It also comprises a bilateral pelvic lymphadenectomy. It is done for Stages I B and II A cervical cancer. More extensive surgery belonging to Rutledge class 4 and 5 are rarely used. In these, most of the vagina is removed together with all pelvic cellular tissue down to pelvic floor. On the whole, the author advises remaining with the classification of total hysterectomy, extended hysterectomy, modified radical and radical hysterectomy.

Vaginal hysterectomy (VH)

Laparoscopically assisted vaginal hysterectomy (LAVH)

The laparoscopic assistance includes exploration and severing of adhesions and the transection of the upper border of the broad ligament including the tubes and ovarian vessels (or severing the infundibulopelvic ligament in case the ovaries are removed). The laparoscopic assistance usually stops at this, but may also include incising the uterovesical peritoneum and downward mobilization of the bladder from the front of the cervix and securing and cutting the uterine vessels with the upper part of the cardinal ligament. This latter procedure carries increased risk of ureteric injury.

Laparoscopic Hysterectomy

Laparoscopic hysterectomy is essentially a subtotal hysterectomy as described under LAVH; the uterus is morcellated and sucked out by an automatic morcellator. The cervix is diathermically conized from below removing the transformation zone (Semm's Operation). This operation needs a special expertise and instrumentation.

Radical vaginal hysterectomy (Schauta's operation)

The transvaginal radial removal of the uterus with an appropriate margin of normal tissue. A muscle cutting vaginoperineal (Schuhardt) incision can be used to improve access. It is not possible to remove the pelvic lymph nodes via the vaginal route, and this can be done either transperitoneally using a laparoscopic technique or via the retropertonially using two suprainguinal incisions.

Total versus subtotal hysterectomy for benign conditions

Abdominal hysterectomy done for benign disease of the uterus during the second half of the 19th century and first half of the twentieth century were mostly subtotal. Progress of surgical techniques, blood transfusion, anesthesia and antibiotics has allowed increased resort to total hysterectomy. It was first reported by an advocate, Richardson (1929) of USA. The use of total hysterectomy sharply increased after 1950. The removal of the cervix aimed essentially at removal of the risk of cervical cancer in the left behind stump. By the 1980s total hysterectomy has become the standard care. Subtotal hysterectomy was considered stigmata of unfulfilled job and lack of competence on the part of the surgeon. The balance is now moving back in favor of subtotal operation. This recent trend has been based mainly on the ability to effectively protect women against cervical cancer through screening programmes, and the appreciation of increased morbidities of the total operation. This has become more felt after expanding the indication of removing the uterus for many benign conditions. In our setting, it needs to be kept in mind that we are not yet having a screening programme for cervical cancer.

Why to remove the cervix?

1. The retained cervix can become inflamed and cause discharge and can develop nathothian follicles.
2. If excision of the endometrial cavity has been incomplete continued menses could occur.
3. The main argument, however, is obviating the risk of cancer in the cervical stump. However, the effective introduction of mass screening programmes in many developed countries has resulted in a dramatic fall in the incidence of cervical cancer. However, it has to be remembered that coincident with the increasing use of cytological screening since 1960s, there has been the increasing number of hysterectomies performed, which were mostly total. This pervasiveness of hysterectomy in the developed countries might have contributed to part of decline of the incidence of invasive cervical cancer. In our setting there is no organized effort for screening of the population for cervical cancer.

*Why to leave the cervix (*Possible benefits of leaving the cervix)*?*

1. Less operative morbidities

Avoiding the dissection around the cervix will diminish the risk of injury of the ureters, bladder and possibly the rectum. The ureter is injured in roughly 0.5% to 1.0% of total hysterectomies, with the most common site of injury being the lowest 3 cm of the ureter, between its intersection with the overlying uterine artery and its insertion into the bladder. Dissection in this area would be minimized by cervical retention. Removal of the cervix requires clamping and incision to be made on the uterosacral ligament that can endanger the neighboring ureter. Injury of the bladder base and vesicovaginal fistula formation occurs in

roughly 0.5% to 1.0% of total hysterectomies, and is usually the result of inadequate or traumatic mobilization of the bladder off the anterior surface of the cervix and vagina. If inadequately mobilized the bladder has been done, the bladder can be included in the vaginal cuff sutures. These complications can be avoided by retaining the cervix.

Injury of the rectum may result during mobilization of the vagina from the rectum under the Douglas Pouch.

2. ***Less blood loss:*** Blood loss is likely to occur during dissection of the angles of the bladder base from the front of the cervix in total hysterectomy. Moreover, the vaginal edges contain bleeding vessels. The need for and the hazards of blood transfusion should be less with the subtotal operation.
3. Total hysterectomy entails entry into the vagina and ***exposure of the peritoneal cavity to vagina flora*** and infective morbidities including vault cellulites and pelvic abscess formation. Healing of an infected vaginal vault wound may leave granulomas which may cause bleeding, spontaneous or upon contact.
4. The operation time of subtotal hysterectomy is ***shorter*** and the operation is definitely ***easier*** for the novice or general gynecologists to do than the total hysterectomy.
5. Decreased risk of subsequent vaginal vault prolapse.
   Removal of the cervix damages supporting structures of the upper vagina especially the cardinal and uterosacral ligament. This damage may predispose to vault prolapse.
6. Less likelihood of adverse change in sexual function
   Total hysterectomy may leave behind tender points at the vaginal vault and may shorten the vagina; both resulting in dyspareunia. The removal of the nerve supply of the vaginal vault by removal of the Frankenhauser's plexus on the cervix may interfere with occurrence of vaginal orgasm. There are reports of increased sexual dysfunction after total hysterectomy more than after subtotal hysterectomy. The difference was mainly in occurrence of orgasmic dysfunction rather than a change in libido. These studies were small numbered and not final.
7. Decreased risk of subsequent bladder and rectal dysfunctions
   The Frankenhauser's plexus inevitable damage during removal of the cervix contains good parts of the sympathetic and parasympathetic nerve supply of the bladder and rectum. Findings of studies on urethrovesical dysfunction after total versus subtotal hysterectomy are inconsistant. Some suggest relatively increased incidence of urinary frequency and incontinence after total hysterectomy relative to subtotal hysterectomy. However, these were small studies, which were not controlled. Similarly, the data about rectal dysfunction in the form of decreased frequency of bowel movements are conflicting and not certain.
8. Removal of the cervix may accentuate insome women the feeling of organ loss. Women in our culture are of the habit of washing or douching the vagina, during which they are

accustomed to feeling cervix uteri. Its absence may accentuate a feeling of "abnormality" and of "organ loss" in some predisposed women.

Counterpoints

It needs to be noticed that most of the above mentioned arguments in favour of subtotal hysterectomy have not been based on controlled randomized clinical trials. Improving surgical skills and attention to details will markedly diminish the complications of total hysterectomy. Effective screening programmes for cervical cancer are not established in many parts of the world.

In conclusion, the author, an advocate of the "complete" operation of total hysterectomy prefers an attitude of "wait and see" open-mindedly. Meanwhile, the interior of the cervical canal should be electrocautarized during the operation of subtotal hysterectomy to minimize the problems of cervicitis and cancer in the retained cervix. Clearly, all women who undergo subtotal hysterectomy should continue with the scheduled cytological screening. It will be still a possible malpractice case if one of the patients develops stump carcinoma some years after subtotal hysterectomy.

Vaginal versus abdominal hysterectomy

Once proper indication exists for hysterectomy, the surgeon should consider whether this could be accomplished abdominally or vaginally.

Advantages of the vaginal approach

1. The morbidity associated with the abdominal incision (postoperative pain, infection, dehiscence, evisceration, incisional hernia) is avoided.
2. Avoidance of having *a scar on the abdomen* is appealing to some women.
3. Minimal intraperitoneal manipulation (e.g. minimal pertitoneal incision and no packing back of the intestines) diminishes the incidence of ileus. The pedicles in vaginal hysterectomy of the uterus are extraperitoneal; any ooze from them will be outside the peritoneal cavity.
4. *Smoother postoperative:* With vaginal hysterectomy there is an earlier return to bowel function. The incidence of postoperative infection morbidity is less than half that with abdominal hysterectomy. The vaginal hysterectomy patients are generally discharges from the hospital earlier.
5. Vaginal hysterectomy is *better tolerated by elderly patients* and those with complicating medical disease.
6. *Extreme obesity* increases the technical difficulty of abdominal hysterectomy to a greater extent than vaginal hysterectomy.

7. Vaginal hysterectomy gives more opportunity for *correction of genital prolapse* and stress urinary incontinence.

Disadvantages of Vaginal hysterectomy

1. Vaginal hysterectomy gives no opportunity of exploring the pelvis for disease like PID, endometriosis, pelvic pain and adhesions. This disadvantage is avoided by use of laparoscopic assistance.
2. Vaginal hysterectomy is more difficult if the uterus is well supported high in the pelvis as in the case of a nulliparous patient. In this case special experience in vaginal surgery of the surgeon and his assistants is required and the use of special retractors are required. Care should be exercised to avoid slippage of ligatures on the pedicles. The laparoscopically assisted vaginal hysterectomy (LAVH) may facilitate such difficulties through cutting and securing the ovarian vessel, and may be the uterine vessel pedicles through operative laparoscopy. It allows also for abdominal exploration.
3. Vaginal hysterectomy is especially more difficult if there are pelvic adhesions distorting the anatomy holding the uterus above. Again LAVH allows assessing the extent of these adhesions and their severing. Previous repeated cesarean sections might have resulted in fixing the uterus to the back of the anterior abdominal wall or may render identifying and incising the uterovesical pouch difficult in the vaginal approach.
4. A large and/or long uterus may be difficult to remove vaginally. The arbitrary limit is a uterus of 10 - 12 week pregnancy size. This difficulty may be overcome by morecellation of the uterus, or bisecting it. These procedures may result in increased blood loss. A myoma may need to be enucleated through the uterovesical or Douglas pouch. The size of the myomas may be reduced by 4 - 6 month treatment with Gn RH analogue before the surgery.
5. Removal of the ovaries is more difficult with vaginal hysterectomy, particularly when the uterus is not prolapsed. On the whole, removal of normal ovaries is less commonly done alone with the vaginal operation.

   Conclusion: The presences of such difficulties will some time result in vaginal hysterectomy losing their relative advantages. Although vaginal hysterectomy should be considered whenever the uterus is being removed for benign disease, the presence of difficulties should be carefully weighed. The surgeon may desist the vaginal approach and resort to abdominal operation whenever he meets difficulty. Not all hysterectomy started as vaginal surgery will be completed through this route.

   The LAVH will increase the use of the vaginal approach. LAVH combines the advantages of both approaches. However, it requires equipment and special training.

Alternatives to Hysterectomy

1. Medical treatment: see under Abnormal Uterine Bleeding.

2. Endometrial Ablation - an alternative to hysterectomy.

Dysfunctional uterine bleeding is becoming an important indication for hysterectomy (see above). Despite the ability to reduce menstrual flow with a variety of ***medications*** like progestogens and Gn RH, patients dissatisfaction frequently leads to noncompliance, and return of symptoms and ultimately to hysterectomy. Although the latter operation is getting increasingly safe, its implications are not simple. These implications include a mortality of 6 per 10,000; morbidity of several times this mortality, cost, premature onset of ovarian failure, psychosexual dysfunction, and loss of pelvic support.

Recently, several approaches have been introduced for the complete or partial destruction of the endometrium, the first, and most advanced in use is the hysteroscopic diathermy or laser ablation of the endometrium. This and the alternative techniques can be used in the treatment of uterine bleeding once malignancy and other organic lesions of the uterus and cervix have been excluded. The use of such technique of endometrial ablation should diminish resort to hysterectomy.

- ***Patient selection for endometrial ablation:*** the candidate should fulfill the following criteria:
  1. Severe uterine bleeding, a severity justifying hysterectomy.
  2. Nonresponsive to medical treatment.
  3. No organic cause of bleeding. This should be ascertained by a full diagnostic workup that includes diagnostic hysteroscopy and curettage and histopathology.
  4. No intention of future pregnancy. The endometrial ablation is not a sure means of contraception, and should not be offered to a woman as a method of sterilization; some incidences of pregnancies have been reported after endometrial ablation. Tubal sterilization or other means of contraception should be offered.
  5. Endometrial ablation is not offered for relief of chronic pelvic pain of organic or psychofunctional origin.
  6. Endometrial ablation is particularly useful in treatment of patients who are poor candidates for anesthesia and major surgery.
  7. Availability of expertise and apparatus.

Techniques of endometrial ablation

– *Preoperative Preparation*

The endometrium should be preoperatively rendered atrophic to facilitate ablation and decrease bleeding during the operation. This can be achieved by Gn RH agonists, Danazol or a progestogen like norgestrel. The former is the most effective but is more expensive. The effect is monitored by transvaginal sonography. Laminaria tent may be placed in the cervix one day before operation.

– *Instrumentation*

1. *A rigid hysteroscope* having a 12 to 30 viewing angle so that the recesses in uterine cavity can be seen optimally. It should accommodate the energy source and the inflow and outflow of distension medium.
2. The *distension medium* usually used is glycine 1.5% solution. It has the advantages of being clear, slightly hypotonic, nonhemolytic and electrolyte-free (normal saline is conductive and not suitable for electrosurgery).
3. The distending medium is available in 1 liter bags which are suspended one meter above the patient, allowing gravity pressure, augmented by pressure of a sphyogmomantometer bag to ensure effective distension of the uterus. A continuous measurement of the outflow should be observed to avoid fluid overload of the circulation from intravasation. Automatic *hysteromat* records the inflow and outflow.
4. Either electrosurgery and lasers can be used. The major disadvantage of lasers is the cost. It requires a special barrel and needs protection. Laser has the advantage of destruction of the endometrium to a controlled depth (thus less likely to cause uterine perforation), and being malleable, can reach the endometrium in the cornu. The Nd:YAG laser is the type used.

   Monopolar electrosurgery can be delivered by either the urological *resectoscope* or a *roll-barrel shaped electrorode.* By utilization of both the cutting and coagulation waveforms most of the endometrium can be destroyed.

– *Technical aspects*

1. General anesthesia is required.
2. *ND: YAG laser* is used usually with a non-touch technique; the end of the laser fiber is brought to near to the lining of the uterus without touching it. The beam needs be falling as perpendicularly on the endometrium as feasible. The endometrium turns white and swells as it coagulates. A systematic coverage of the uterine cavity is needed in order to minimize skipping areas. Certain areas may need be touched by the laser probe.

3. *Endometrial resection* by electrosurgery removes the whole endometrium with few millimeters of the underlying myometrium. Hemorrhage during or after the procedure is uncommon but may occur. By using the coagulation waveform it is usually possible to control this bleeding.
4. *Roller-ball endometrial resection* uses a 2-mm or 4-mm barrel-shaped electrorode that is rolled over the surface of the endometrium while the flowing electrosurgical energy destroys the endometrium. It is the easiest and safest method but it carries a greater chance of incomplete destruction of the endometrium.

– *Results of hysteroscopic endometrial ablation*

Endometrial ablation has been demonstrated to be cost-effective alternative to hysterectomy. It results in either amenorrhea or a satisfactory reduction of menstrual blood flow in about 70% of cases.

3. Endoscopic management of submucous myomas

Preoperative diagnosis should be established by sonography, hysterpsalpingography and outpatient hysteroscopy. The following classification enables better choice of the suitable cases:

Type I: Submucous myomas whose greater circumference is inside the uterine cavity.

Type II: Submucous myomas whose largest circumference is located inside the myometrium.

Type III: Multiple (more than two) of the submucous and interstitial myomas.

The type I myoma is the most suitable for hysteroscopic surgery which can be done as a one step procedure. With type II myoma a two-step procedure is usually required. After 3-month preparation by Gn RH analogue, partial myomectomy is carried out hysteroscopically. Gn Rh treatment is continued for 2 more months followed by the second step hysteroscopic operation. At this, the remaining part of the myoma is usually found to have protruded inside the uterine cavity, and is usually easily resected. Type III myoma should be treated by conventional surgery.

4. Transcervical Endometrial Cryoablation

This technique destroys the endometrium by suddenly cooling it to -45 ºC i.e. cryoablation. The device is modelled on a Hegar dilator with an external diameter of 8 mm that has a slight angle that allows better central fitting in the uterine cavity. A volume of 3 - 5 mm of saline is injected into the uterine cavity through a separate channel. Rapid expansion of nitrous oxide or carbon dioxide gas channeled through the probe will cool the saline on the

tip to approximately -45 ºC resulting in formation of a very cool ice ball within the uterine cavity, which has contact with the endometrium at all points. This ensures destruction of the entire endometrial surface by a sort of frostbite or cold necrosis. The procedure is done under general anesthesia and the probe is inserted after dilatation of the cervix to no 8 and activated for a total 10 minutes in two freeze-thaw cycles each being oriented towards a different uterine horn.

After a single procedure about 40% of patients are expected to experience a substantial diminution of menstrual blood flow or amenorrhea. It can be repeated. It carries little complications.

5. Thermal Balloon Endometrial Ablation

The balloon thermal ablation system comprises a catheter attached to a latex balloon that is inserted into the uterine cavity. The balloon is filled with a solution of 5% dextrose in water that is heated up to a temperature of about 85 ˚C. The treatment time is 6 - 9 minutes. This destroys the endometrium.

The method is being evaluated in different parts of the world. It results in substantial reduction of the amount of menstrual blood loss in about 60% of patients. Complications were minimal.

6. Microwave Endometrial Ablation

Microwave energy is a form of electromagnetic energy in the GHZ ranges, which are used for home cooking. High frequency short wave has a limited tissue penetration of a depth of 6 mm. A microwave applicator probe (diameter 8 mm) is introduced in the uterine cavity where the microwaves are emitted from its tip in a spherical field. This produces vigorous heat up to 100 ºC limited to the inner 6 mm of the endometrium. This layer is heat destroyed.

Early trials of the system show satisfactory reduction of menstrual blood loss in 70% of subjects and amenorrhea in about 30%. The complication rates are low.

7. Radiofrequency-induced thermal ablation

This is being tried. The safety has not yet been confirmed.

Management of Normal Ovaries at Hysterectomy

The rationale of removing ovaries at the time of hysterectomy is prophylaxis against ovarian cancer, a deadly cancer that is usually diagnosed at a late stage. The rationale of keeping the ovaries is avoiding the loss of their endocrine functions. The decision whether to

remove or not remove the ovaries depends upon the balance between what is gained and what is lost. This balance greatly depends upon the age of the patient at the time of hysterectomy. Given the increasing hysterectomy rates the decision will be increasingly facing gynecologists.

What is gained?

A. Protection from ovarian cancer

- One in 70 women in the United States (1.4%) will develop ovarian cancer. The incidence seems to be rising.
- There is no reliable method for screening women population.
- The diagnosis is usually made late.
- In spite of improvement of treatment modality, the case mortality remains high.
- Conservation of one ovary does not markedly reduce the risk of ovarian cancer.
- However, the gain is limited; it does not look that incidence and mortality from ovarian cancer have declined by oophorectomy during hysterectomy. This conclusion is based on the following reasoning:
    1. In spite of high hysterectomy rates in many developed countries, women with past hysterectomy still form a proportion of ovarian cancer patients, amounting in different studies to only 4% to 8%.
    2. Many of the hysterectomies are done at an age less than 45 years, a time at which ovarian ablation is not acceptable.
    3. A good proportion of hysterectomies are done vaginally where oophorectomy is more difficult and less commonly done.
    4. Statistics have shown that ovarian cancer among hysterectomy patients with retained ovaries is uncommon occurring in approximately 0.1% of cases.
    5. Hysterectomy may diminish the chance of the patient developing subsequent cancer in the retained normal ovaries. The reasons for this observation is unknown but they can be:
        a) Opportunity to examine the ovaries at hysterectomy with conservation of only those, which look grossly normal.
        b) Reduction of blood supply of retained ovaries as a result of hysterectomy may diminish the chance of subsequent neoplasia.
        c) Higher frequency of prior oral contraceptive use among women who undergo hysterectomy diminishing the predisposition; a confounding factor.
        d) Protection of the ovaries from possible carcinogen which spills on their surface from a vaginal or environmental origin

B. Protection from nonneoplastic problems in preserved ovaries

About 1% to 2% of patients who have one or both ovaries conserved at the time of hysterectomy will subsequently require operation for nonneoplastic problems with an ovary or tube. The pathology in the few residual adnexa is usually nothing more than physiologic cyst, a hydrosalpinx, or a fluid collection between residual adhesions. Some of these patients are operated upon unnecessarily.

What is lost?

A. Loss of Endocrine Functions of the Ovaries

The ovary continues to function as an endocrine organ until some years after the menopause. The physiologic importance of these functions seems to diminish with the age.

The *estrogens* mainly estradiol and to a lesser extent estrone are produced in the perimenopausal ovaries. Their sudden withdrawal through bilateral oophorectomy before the menopause results in climacteric symptoms. These include vasomotor symptoms as hot flushes and sweats, and atrophic manifestation like atrophic vaginitis and urinary irritation. The younger the patient at the time of ovarian removal, the severer the symptoms. Removal of the ovaries some years after the menopause does not result in such manifestations.

Estrogen withdrawal also predisposes to metabolic changes that predispose to coronary heart disease, cerebrovascular stroke, and osteoporosis and diminishes brain functions particularly cognitive faculties. It is established that the earlier the age at menopause, whether natural or surgically induced, the higher is the incidence of such health hazards.

The ovaries are also producing androsteindione and dehydroepiandrosterone, which are proandrogens, together with a small amount of testosterone. The physiologic importance of these proandrogens and androgen in women is not established. However, they seem to be influencing sexual performance. Cassation of ovarian function may result in sexual dysfunction like diminution of arousability, libido or chance of achieving orgasm.

Do the ovaries continue to function Normally after hysterectomy?

The mean age at natural menopause is around 51 years. There is a suspicion that hysterectomy may enhance the menopausal changes in the ovaries. Interference with the blood supply of the ovaries is suggested as the cause. The weight of evidence suggests, however, that they do continue to function normally, *or occasionally at a slightly reduced level.* It is suggested that if care is exercised not to traumatize the blood supply of the ovaries at the time of hysterectomy, this may help to preserve their function up till their destined time of menopause. Two measures can help in this direction: clamping and severing tubes as near to the uterus as possible and avoiding drawning done and fixing the tuboovarian pedicles to the vaginal angles.

Can ovarian function be replaced after oophorectomy?

The use of hormone replacement therapy can effectively relieve the vasomotor symptoms and diminish the incidence and severity of postmenopausal health hazards as osteoporosis and coronary heart disease. Women with removed uterus can use estrogen alone to achieve the above benefits. However, the addition of an androgen or proanderogen like DHEA (e.g. Gynodian-depot; Schering , A.G.)can help to improve sexual performance.

Postmenopause hormone therapy is more frequently required after ovarian removal than after naturally occurring menopause, particularly if this is done at young age:

There are three problems with postmenopausal hormone therapy:

1. Cost particularly if not provided through an insurance system.
2. Compliance for long time, at least five years, is needed to achieve the long term benefits, but this is difficult to achieve in the majority of women.
3. The resultant slight but statistically significant increase in the incidence of breast cancer.

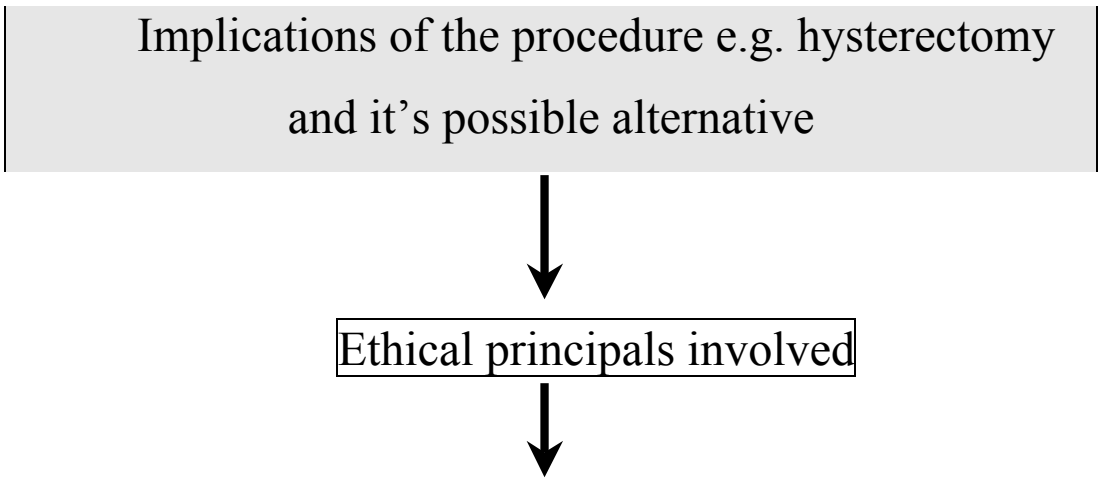
Conclusions

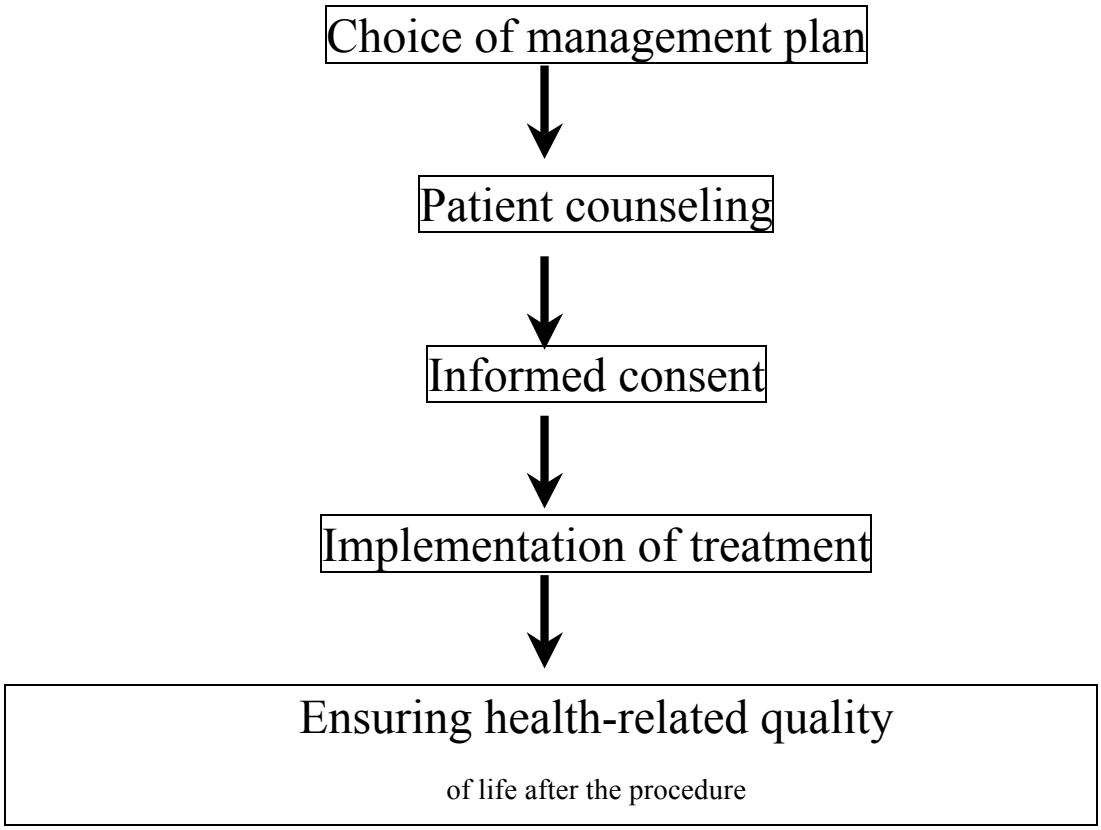
The weight of evidence suggests the following practice:

- Normal ovaries usually should be removed when abdominal hysterectomy is done in postmenopausal women. They are also removed when they can be delivered without much traction during vaginal hysterectomy done for postmenopausal women.
- The grossly normal ovaries of perimenopausal women aged less than 48 years should be conserved when hysterectomy is done. Losing the function of normal ovaries in young women carries more harms than benefits.
- Bilateral oophorectomy should be done when hysterectomy is done for patients with a personal history of breast, colon or rectal cancer; or with a family history of ovarian cancer.

Ethical Aspects in Hysterectomy

Scheme for covering the ethical aspects





Implications of Hysterectomy

There are few decisions in gynecological practice that are associated with more patient anxiety and concern than a woman's acceptance or choice of undergoing hysterectomy. Consequently, the ethical aspects in this operation are gaining special emphasis. The reasons for this special position of this operation are:

1. Hysterectomy is being more commonly done than in the past, and hysterectomy rate in the population is rising. It is estimated that the present rate can result in one third of the American female population having hysterectomy by the age of 60. A trend of rise of hysterectomy is observed in the practice in Egypt, but is fortunately far from this level.
2. The majority of hysterectomies, more than three fourths, are done for elective, uncomplicated conditions, which frequently have alternative management. These alternatives can be in the form of other surgical interventions e.g. hysteroscopic myomectomy or endometrial ablation or alternatives of medical treatment.
3. Hysterectomy will influence certain important aspects of the quality of life of the woman:
    a. It is an end of her reproduction.
    b. It is also an end of the potentiality of reproducing, even when this is not required by virtue of having the required family size. This ability may be important for the woman's self-esteem or the societal esteem (in rural areas) . This is influenced by cultural and social values. The opinion of the relatives particularly of the husband and

the in-laws can influence the attitude of the patient towards hysterectomy. Removal of the uterus may disturb the fine wife versus husband balance of forces. Hysterectomy may be generating a feeling of inferiority. This is particularly so in a community where another marriage is possible for the husband. The experiences of child loss, and even of husband death are not low in our community. It is apparent that the reaction of women greatly varies towards these aspects.

   c. Hysterectomy means an early end of the function of menstruation, which, for the woman and her husband, is a monthly reminder of her femininity. Some women believe that menstruation is a way for the body for getting rid of noxious substances.
   d. Hysterectomy may have deleterious effects on sexual life. These can be based on psychological suggestions, but can be caused by physical changes like short or tight vagina or dyspareunia. Hysterectomy may be a reason (or an excuse) for the husband to have less interest in sexual approach to his wife.

4. In spite of great improvement of the safety of the operation, hysterectomy is not free from risk. A mortality of 1.6 per 1000 is the figure given to the patients in the States, and which is bound to be higher in Egypt. Morbidity of 25 - 35% is expected. These are rarely serious as ureteral injury 0.5 per 10,000 and bladder injury 0.5 per 10,000. However, minor complications like urinary tract infection and wound sepsis are common.
5. The operation is a costly one. The cost of removing the uterus for some one third of the female population may be too much for the community to carry.
6. Removal of the ovaries when bilateral salpingo-oophorectomy is needed along with hysterectomy has its implications (see above); this need be taken in consideration. The removal of the ovaries may be part of the treatment, e.g. for neoplastic diseases, pelvic inflammatory condition or endometriosis. Frequently also, bilateral oophorectomy can be done for prophylaxis; the ethical aspects and the consequent patient counseling is different in the two situations.

Ethical principles involved

1. Beneficence: The operation should be done for definite benefits.
2. Nonmaleficence (perimum no nocere = first do no harm): The operation should not carry harm, or the benefit should exceed the harm.
3. Fidelity: Truth telling and promise keeping.
4. Respect for autonomy: The individual exercises her will on the treatment plan. She has the full choice to make the final decision on her treatment after receiving the proper counseling. The proper counseling should be:
   a. Giving the right facts.

b. Given in a language or a way that can be understood by the patient.
c. Taking in consideration the personal aspects of the patient and the social norms and tradition.
d. Interactive, encouraging the woman to take part in the decision-making process.
e. Ready to answer all queries of the patient.
f. And not paternalistic

Choice of treatment plan

The physician should make the best choice, which she or he sees in the interest of the patient. The treating gynecologist is required not only to make the best choice but also to convince the patient of this choice without exercising pressure on her. He should be ready to accept alternatives needed by the patient if they are reasonable. *Helping patients reach reasonable decisions is an important part of the art of medicine.* The big social gap between the health care providers and receivers sometimes needs be crossed in the medical practice in poor countries.

Patient Counseling

There is usually ample time for counseling patients about hysterectomy. The operation is rarely done as an emergency. The following is a suggested plan for structured counseling; the ***PREPARED*** Protocol:

PREPARED protocol

Procedure	: the course of action to be considered.
Reason	: indication for procedure.
Explanation	: beneficial outcome of procedure.
Preferences	: patient-centered utility (personal and social aspects).
Alternatives	: other procedures and options.
Risks	: potential harmful outcomes of procedure.
Expenses	: all direct and indirect costs.
Decision	: fully informed patient choice.

After Gambone IC and Reiter RC Quality improvement in women's health care. In Moore TR, Reiter RC, Rebar RW, Baker VV, eds. Gynecology and obstetrics: A Longitudinal Approach. New York: Churchill Livingstone, 1997 3: 27 - 36.

The patient may be given a pamphlet describing the procedure to consider at her leisure, and with her relatives and friends mainly with her husband. All the time and effort should be given to the process of helping the patient to make the right decision. This effort

and time is more wasted and will diminish the incidence of patient dissatisfaction about the procedure after it has been done.

Informed consent form

A written consent needs be obtained on hysterectomy. If bilateral salpingo-oophorectomy are included, a separate section should be included on this part of the procedure. The consent form should include the information the patient should have known about the procedure, its possible risks and consequences. It should contain a clear mention that the alternative options have been explained to her.

Obtaining this written consent should never be neglected, verbal consent is not enough. It may be negated in a lawsuit. The signature of the husband needs be obtained as well. This is not mandatory, but is safer to document his agreement with the procedure.

Implementation of treatment

A full description of the procedure should be documented and given to the patient. Frequently we see patients for whom hysterectomy has been done and who do not know whether the ovaries have been removed. Any complication should be clearly documented. The postoperative care should be described.

Health-Related quality of Life after Hysterectomy

Health-related quality of life (HRQL) is a multidimensional concept referring to an individual's total health well being. A consensus has been developed that the fundamental dimensions essential to any HRQL assessment are physical, social, emotional, and functional, as well as the perceptions of overall acceptable quality of life or general life satisfaction. The gynecologist should not lose interest in her or his patient once the technical aspect of the operation has been successfully attained. He should help her by advice and medications or rehabilitation procedures to resume her role in the society as a useful person and to enjoy all that as before or in a better way through the end of her disease and symptoms.

Hysterectomy frequently leaves the patient with many problems ranging from lower abdominal discomfort, addition of weight, dyspareunia, sexual dissatisfaction and even involving depression. The job of a caring physician should extend the care for such possible problems.

Preparation for Hysterectomy

1. *Counseling* (see above).

2. ***Preoperative cervical cytology*** examination is necessary before hysterectomy, even if plan is to do a total operation.
3. ***Correction of anemia:*** Usually there is enough time for this through iron therapy. Occasionally transfusion of packed RBCs is required if the operation is urgent or the blood loss is severe. In spite of the usual recommendation of securing blood reservation of two units of blood is advisable, it is rarely used in total hysterectomy for non-malignant conditions; blood loss should be least expected in this type of surgery.
4. ***Gn RH:*** Under certain circumstances Gn RH treatment is used for 3 - 4 months. This will cause amenorrhea and give time for correction of anemia. Meanwhile, the size of the lesion e.g. myomas or endometriomas will decrease.
5. ***Medical preoperative evaluation:*** A general medical history and physical examination will determine the necessity for preoperative evaluation of the cardiac or pulmonary functions by specialists and may point to special testing of e.g. coagulation profile, cystoscopy in selected cases.

   Intravenous pyologram is required if there is a pelvic mass disturbing the anatomy of the pelvic organs. Pressure upon or displacement of the ureters will be diagnosed that will be necessitating special care in dissecting the mass without injuring the ureters.
6. Patients are asked to avoid solid foods and start a liquid feeding 24 hours before the scheduled time of the operation. Nothing is taken by mouth for 8 hours before the operation. It is better to evacuate the rectum by enema the night before the operation, not immediately before the operation.
7. *Prophylactic antibiotic:* Infection is a frequent complication of hysterectomy whether vaginal or abdominal. This infective morbidity includes cuff cellulitis, pelvic abscess; wound infection or urinary tract infection. The source of infection can be autonomous from the vaginal flora or skin flora. In spite of sterilization of the skin and vagina, infection can still occur at the time of operation particularly when tissues are devitalized by trauma or blood is left in the operation area. *Good surgery is followed by less infective morbidity.* The causative organisms of posthysterectomy infection include aerobic streptococci, anaerobic streptococci, E. choli, Bacteroides species, hemophilus influenza, Klebseila species.
8. Routine antibiotic administration is better given. This usually includes two injections of 1 gram each of one of the second or third generation cephalosporins, the first is given 30 to 60 minutes before operation and the second 8 hours later.
9. The lower abdominal and pubic and vulval hair should be removed some days before the operation by depilating agents. Failing this, these hairs should not be shaved on the night of the operation or on the table. This increases infective morbidity. The hair should be just trimmed low by a scissors in such instances.

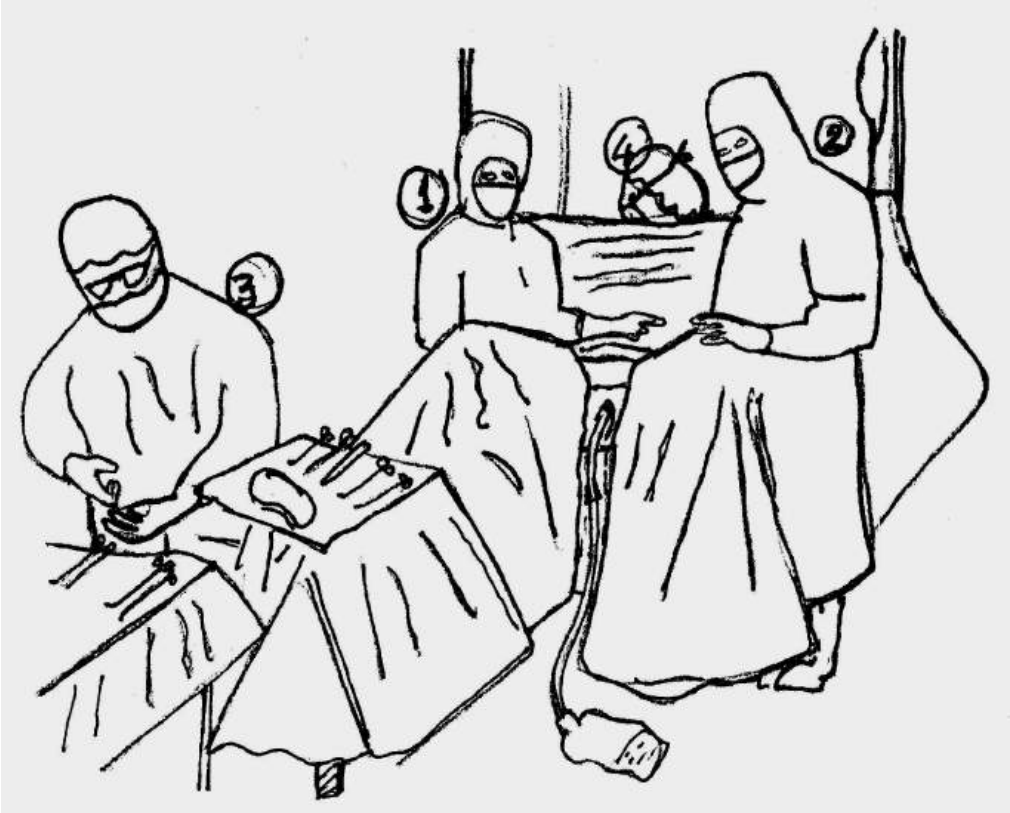
Technique of Total Hysterectomy for benign conditions

Principal features *(Good surgery means attention to details)*

The operation commonly used for this purpose is an intrafascial hysterectomy. It is so described since nothing of the pelvic fascia (pelvic cellular tissue) is removed with the uterus. The uterine arteries are cut just lateral to supravaginal cervix. The lateral vaginal angles are cut just underneath the bladder pillars (the lateral part of the puba-vesico cervical fascia or ligament).

- The posterior vaginal fornix is opened before the anterior fornix. This approach has the following merits:
    1. The posterior fornix is higher than the anterior one, and hence more accessible directly under the peritoneum.
    2. Completion of the dissection of the urinary bladder off the anterior surface of the upper vagina is achieved while stretching, thus defining the anterior fornix by two fingers inserted through the posterior wound. The plane between the vagina and bladder is thus readily identifiable without risking the bladder or ureter during any blind sharp or blunt dissection.
- The vaginal vault is closed.
- The pelvic peritoneum is usually repaired.
- The uterine pedicles are fixed to the vaginal angles using slowly absorbable synthetic sutures in an attempt to minimize the chance of vault prolapse.
- Drains are rarely left in the pelvis; any bleeding should be meticulously and carefully controlled before closure of the wounds.

Patient positioning



Hysterectomy: Figure 1: Positioning of the patient's and surgical team: (1) Surgeon, (2) Assistant, (3) Scrub Nurse, (4) Anesthesiologist.

It is a good practice that gives the patient comfort if she sees her surgeon on the theater before she is given anesthesia.

The patient is usually positioned on the Allen universal stirrups (Fig. 1). With the patient on her back the buttocks are brought down to the edge of the table. The legs are carried on padded stirrups resulting in flexation of the thighs $\pm$ 15 degrees with the horizontal while separating them by an angle of about 85 degrees. This positioning has the following advantages over the dorsal position:

1. With the legs slightly flexed, less strain is put on the patient's lumbar spine than there is from lying flat on the table. The latter can result in straining ligaments. However, care should be exercised during undoing the position at the end of the operation; the two lower limbs are gradually extended at the same time. If one of them is separately extended while the other is on the stirrup, this can excessively stretch and injure the muscle and ligaments of the back at a time when they are relaxed by anesthesia.
2. This positioning allows examination under anesthesia be done immediately before the operation. This allows verifying the extent of pathology and planning the operation to be done. It allows having an idea about the firmness or laxity of uterine support.

3. Catheterization can be done after the anesthesia has been given; the procedure can hurt a patient if it is done before. The availability of the urethra in the operative field can allow cystoscopy or ureteric catheterization when need arises without changing position and draping. A towel clip fixes the draping to the perineum in front of the anus to exclude the latter from the field.
4. If there is a second assistant, she or he can stand between the thighs of the patient where she or he can enjoy a good view of the operation field and can help in downward retraction. If there is no second assistant the scrub nurse can occupy this advantageous position.
5. This positioning allows cleaning the depth of the vagina by bovidone-iodine (Betadine) under anesthesia. This is done three times to diminish the microflora in the vaginal vault.
6. Occasionally a swab carried on a sponge forceps can be inserted in the vagina to put the posterior or anterior fornix to stretch that helps identification in case of difficulty.

Positioning of the operating team

The surgeon stand on the right-hand side of the patient, the assistant on her left side and the scrub nurse between the thighs of the patient or next to the surgeon. It is always helpful to have a high instrument tray on the right hand side of the surgeon. On this she or he will always find the instruments immediately needed.

Draping

The operation field should be washed with a soft brush and antiseptic solution and dried down. The skin and the vagina are sterilized by Betadine extending from the lower thorax down to the upper half of the thighs and the buttocks and down to the operation table. Two points need special attention: the umbilicus and the vagina. The umbilicus is cleaned with four sponges on long sponge forceps. The vagina receives cleaning/ sterilization ending at the anal region.

Mackintosh is applied on the upper and lower limits of the operation field. Towels are placed around the operative field that includes the subumbilical abdomen, vulva. Two thicknesses of drapes cover the abdomen and legs.

A double-gloved assistant inserts the Folley's catheter that is connected to a bag on the floor.

Abdominal Incision

If the uterus is not markedly enlarged a *Pfannenstiel's incision* is adequate. If the uterus is enlarged $\geq$ 12 week gestational size or when adhesions are anticipated a lower mid-

line skin incision is done with a right Paramedian entry through the rectus sheath. *Pfannenstiel's incision* is the most cosmetic way of entering the abdomen. It has an excellent wound security since there is minimal muscle cutting and since the muscle wall and peritoneum are entered in lines perpendicular on one another. The skin can be closed by a cosmetic subcuticular running suture. However, Pfannenstiel incision allows a limited operation field and is not suitable when exploration of the abdomen is required, when the uterus is enlarged, or when adhesions from endometriosis or pelvic inflammatory disease are anticipated.

The skin is transversely incised with a slight upward concavity usually making use of the suprapubic skin crease. It can sometimes be done above or below the crease if this is judged to give better access to the abdominal structures. The length of the incision can vary from 10 to 15 cm. The incision is carried in the subcutaneous fat down to the anterior rectus sheath and external oblique aponeurosis. The superficial branches of the inferior epigastric artery and vein may be identified or cut in the lateral part of the wound and need be secured. The aponeurosis of the external oblique and the anterior rectus sheath are incised transversely on both sides of the middle line. The incisions are joined medially across the linea alba and extended lateral where it may cut in the internal oblique muscle fibers above their origin from inguinal ligament. The inferior epigastric vessels in the lateral part of the rectus sheath can usually be avoided but if cut should be carefully secured. The anterior rectus sheathes, and the aponeurosis of the external oblique muscle are lifted upwards and downwards as far as desired. Perforating vessels are identified and cauterized before tearing off. The recti are slightly separated in the middle line. The posterior rectus sheath and the peritoneum are entered in the middle line in the upper part of the incision. The opening is extended down exercising care not to open the apex of the bladder, which might be lifted high by a pelvic tumor. The transmission of light across the lower peritoneum will indicate the lower limit of the possible extension of the incision.

At the end of the operation, the peritoneal and the rectus sheath incisions are each sutured by running (punctuated by frequent lockings) suture using delayed absorbable synthetic suture material of polyglycolic acid or polyglactin suture (Dixon or Vicryl). It is advisable to add 3 interrupted sutures to the anterior rectus sheath suture line. Subcutaneous sutures are only required in fatty women. The skin is sutured by running subcuticular suture of 2 - 0 Dixon. Waterproof adhesive dressing should cover the wound.

Middle-line Incision

A subumbilical incision reaching down to the public symphysis is usually enough. Rarely this needs be extended upward through the umbilicus. The subcutaneous tissue is

divided on the right side until the right anterior rectus sheath is exposed and divided longitudinally. The right rectum muscle is retracted laterally and the posterior rectus sheath and partial peritoneum is entered slightly to the right side of the middle line.

This wound is a trap-door incision, which is more secure than when the incisions of all the layers are opposed in the middle line. It is repaired in layers using delayed-absorbable suture material.

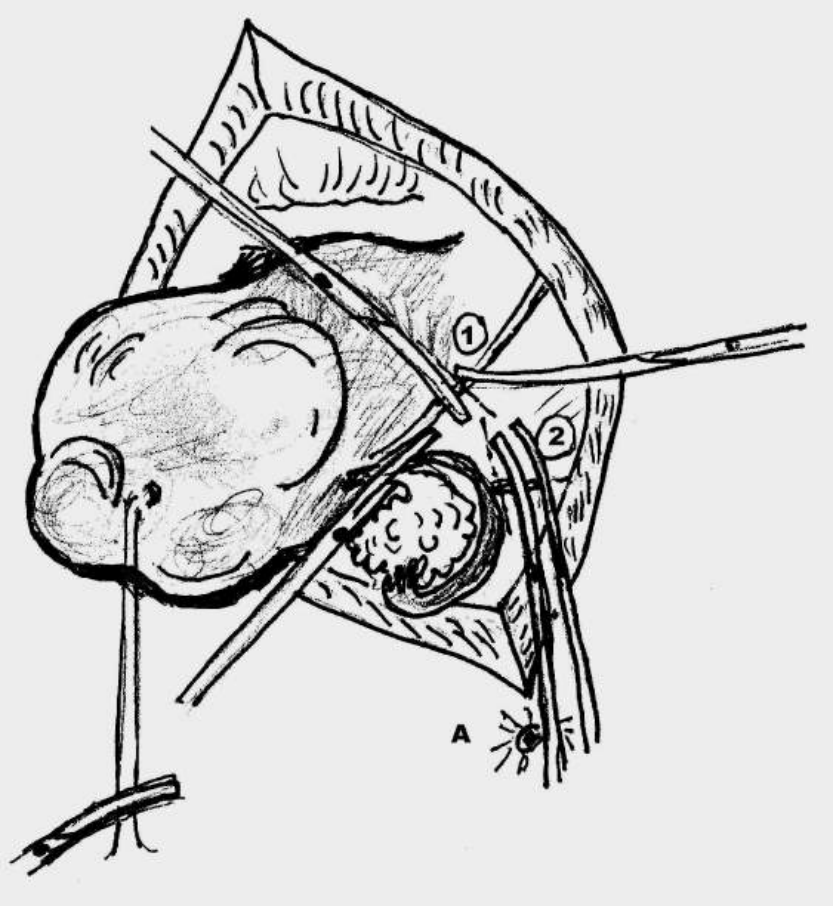
Delivery of the uterus in the wound

The pelvic and abdominal cavities are explored, including feeling the liver, kidney and para-aortic lymph nodes. The patient is put to a Trendelenberg till. Using two taped wet abdominal packs the intestines are packed to upper abdomen. Adhesion, if present, must be released (and secured in stitches) before the intestines are packed up. Breaking the adhesions can be the most difficult and demanding part of the adhesion (see later).

A three-way self-retaining retractor is usually inserted. At this point the extent of pelvic pathology is assessed. The position of the tumor(s) in the uterus is assessed by reference to the structures attached to the uterine cornu. The degree of encroachment of the pathology on the bladder, rectum and ureter is assessed. The latter can be palpated while crossing upon the point of bifurcation of the common iliac artery at the pelvic brim.

The uterus can usually be easily delivered in the wound. It may need to be lifted out by one or two silk transverse-mattress sutures passed in the fundus. Sometimes the biggest myoma may need be enucleated before the uterus can be delivered in the wound.

Clamping and cutting of pedicles in the broad ligaments (Figure. 2)



Hysterectomy: Figure: 2 *Transection of (1) the round and (2) infundibulopelvic ligaments (double clamped); A: the umbilicus(as viewed by the surgeon standing of the right of the patient).*

The uterus is pulled by the assistant to the right side. Two long curved Kocher clamps are put on the left round ligament, which is cut in between. The opening in the round ligament is enlarged by separating the blades of a blunt scissors.

If it is decided to leave behind the ovaries, two long curved Kocher clamps are placed on the left tube and ovarian ligament as near to the uterus as possible and the structure in between is cut by a Mayo's scissors or a scalpel.

If the tubes and ovaries are to be removed the infundibulo-pelvic ligament (the part of the upper edge of the broad ligament lateral to the tubal infundibulum) is stretched on the index finger pressing from behind to carry the posterior leaf of the broad ligament below the ovarian vessels into the anterior window. This serves to skeletonized and lift the ovarian vessels away from the ureter, which is an immediate lateral relation. The posterior leaf is entered by the finger or snipped under vision before the pedicle is clamped. This is done by two curved Kocher clamps on the pelvic side and a straight clamp on the specimen side. The tip of each clamp is passed through the posterior-leaf window. The pedicle is cut by a scissors

or scalpel just lateral to the specimen-side clamp. This leaves a longer pedicle to the lateral side held in two clamps which is not likely to slip free or tear during transfixation-suture. The double clamping of this pedicle is sometimes not done when things are easy.

When there is extensive adhesion on the lateral pelvic wall or when the anatomy is distorted by a big broad ligament tumor, the ureter needs be identified, the peritoneum lateral to it is incised upon and it is retracted away before clamps are applied on the infundibulopelvic ligament.

Transfixation sutures now replace the clamps on the broad ligament. The transfixation of the round ligament is passed through the ligament to avoid its retraction from underneath the suture. The transfixation of the infundibulo-pelvic ligament should be passed in the point below the blood vessel and securely tied to include the tube and ovarian vessels. The infundibulopelvic clamp is usually doubly ligated. The first replaces the most lateral clamp and is a free tie without transfixation. This is to avoid puncturing the ovarian vessels and forming a retroperitoneal hematoma. The second suture is a transfixation suture and replaces the remaining curved clamp; knotting the ligature around the tip and heel of the clamp before the latter is gradually released. The ends of the suture on the two broad ligament pedicles are left long to be included in the suspension of the vagina.

Of the various suture materials the chromic catgut number 1 is the best for the purpose of suturing all uterine pedicles. It is least likely to slip and it is strong enough to allow secure tying. Dixon material is liable to slip off.

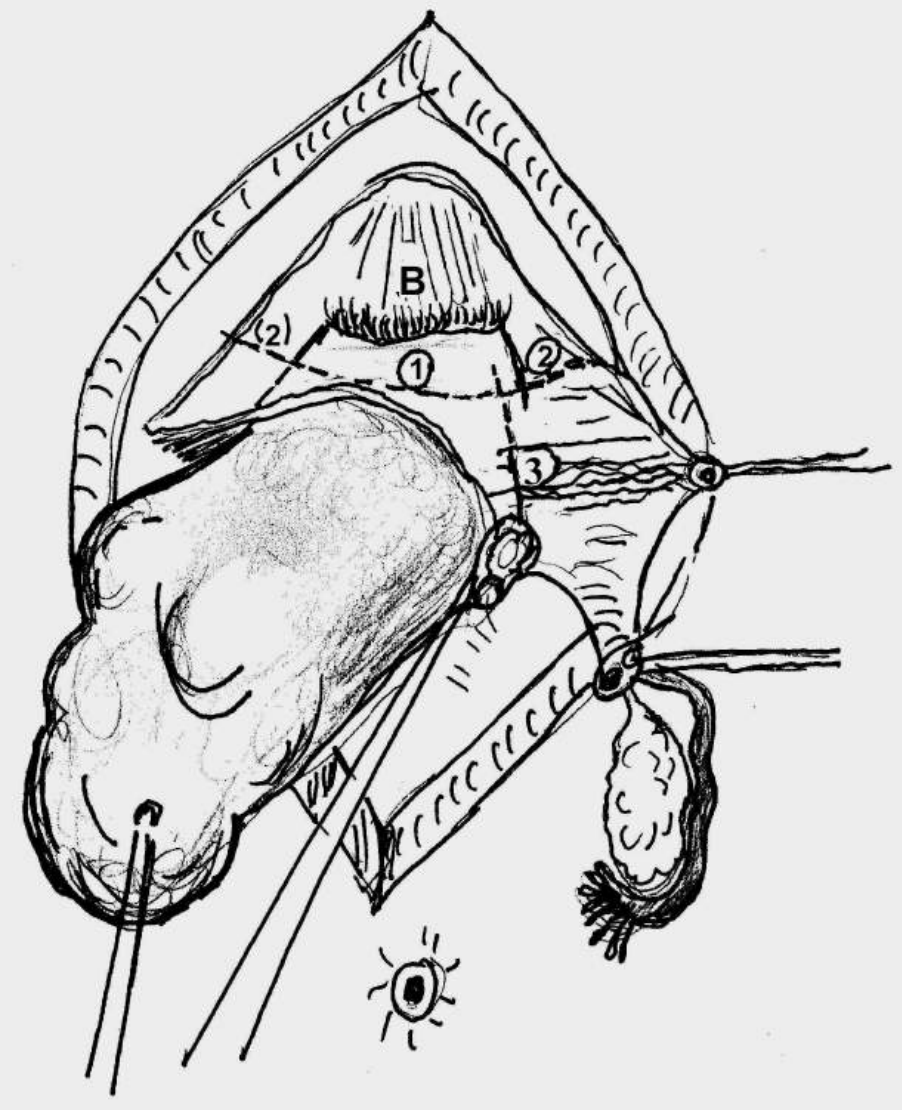
The specimen-side pedicle of the round ligament and the tube are collectively included in the transfixing suture; the end of which is left long for traction upon the uterine specimen.

The same procedure is then carried on the other side.

Entering the uterovesical space

The loose peritoneum between the two cut round ligaments is picked by a toothed forceps and incised across the uterovesical pouch. This is facilitated by passing the tip of a long curved scissors under the peritoneal reflection and opening the blades to develop the space. The peritoneum should be incised just behind the point at which it becomes inseparably attached to the myometrium. The line of the incision is just below an important landmark which is a triangular depression in the visceral peritoneum opening downward. The uterus is then pulled up; this makes apparent a thin fascial sheath stretching between the bladder and the cervix in the middle line; the cervico-vesical fascia. This is incised in the middle line by a long curved scissors. This allows entering the vesicocervical space; the bladder can then be pushed down by a wet sponge on a forceps. The lateral parts of this

fascial layer, which are attached to the bladder angle, are denser and may contain some small blood vessels. They are called the bladder pillars (Figure. 3). These are released by small scissors snips bleeding points are secured and touched by diathermy. The complete reflection of the bladder from the vaginal angle is better deferred to a later stage.

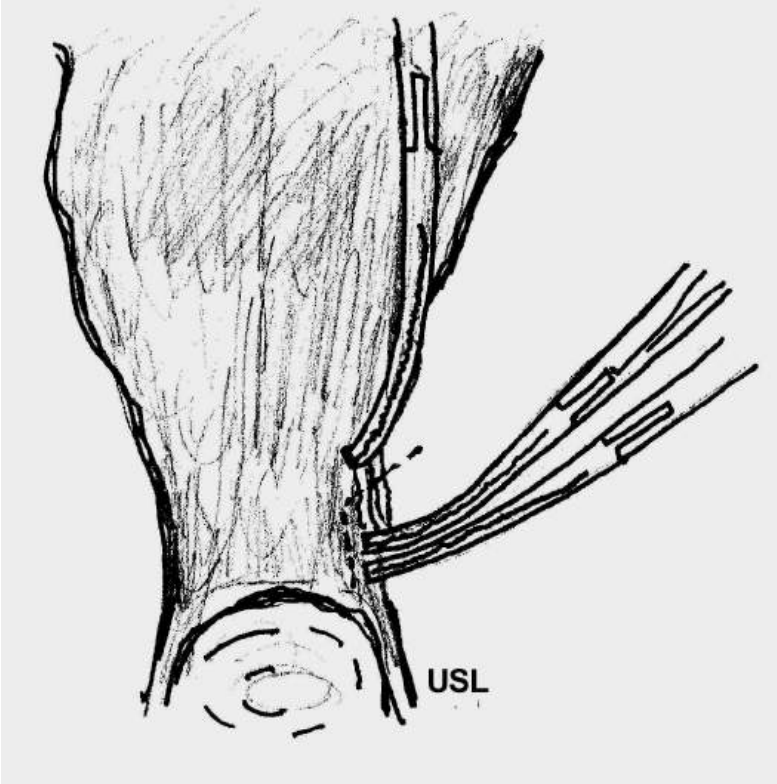


Hysterectomy: Figure. 3: Dissection of important fascial planes: *(1) the vesico cervical fascia, (2) the bladder pillars, and (3) the mesentery of round ligament. B = bladder.*

Clamping the uterine vessels

The posterior leaf of the broad ligament is incised just lateral to the uterus down to the to the uterosacral ligament. The uterus is pulled over to the right side. When the pediele of the left round ligament is pulled laterally, a thin sheet of endopelvic fascia stands up and is seen passing downward from the round ligament towards the lateral border of the uterus. This sheet of fascia, though thin, is always present and leads down to the uterine vessels. It is called the mesentery of the round ligament (in spite of containing no blood vessels). This

fascial layer is cut in downward and medial direction by a scissors and leads to exposing the uterine vessels on the side of the supravaginal cervix.



Hysterectomy; Figure: 4: A posterior view demonstrating double clamping of the uterine vessels. USL = uterosacral ligament.

The ureter is displaced from underneath the uterine vessels by applying traction on the uterus over to the opposite side while a wet swab carried on a swab holder applies counter traction by pushing the parametrial tissue laterally and downward. This allows the uterine vessels to be skeletonized (freed from surrounding fascia) and clamped by a curved long Kocher clamps under vision at the level where is reaches the side of the uterus. The clamp is placed at a right angle to the uterine vessels. Another curved clamp is applied above (medial) and parallel the first, and a third is also applied on the vessel at a small distance from the second clamp. The vessels are cut just under the third clamp extending the incision around the tip of the middle and lower clamps (Fig. 4). This separates the vessels from the uterus and allows direct ligation of the vascular pedicle. Care should be exercised to avoid incising the tissue beyond the tip of the lowest clamp, because doing so results in bleeding from the vaginal branches of the uterine vessels.

The uterine vessels are doubly ligated with no:1 chromic catgut. The first ligature is a free tie placed around the lowest clamp and the second is a transfixation suture replacing the

middle clamp and is tied around the tip and heel of this clamp. The suture ends are cut and no retraction is made on them to avoid slippage. The procedure is repeated on the other side.

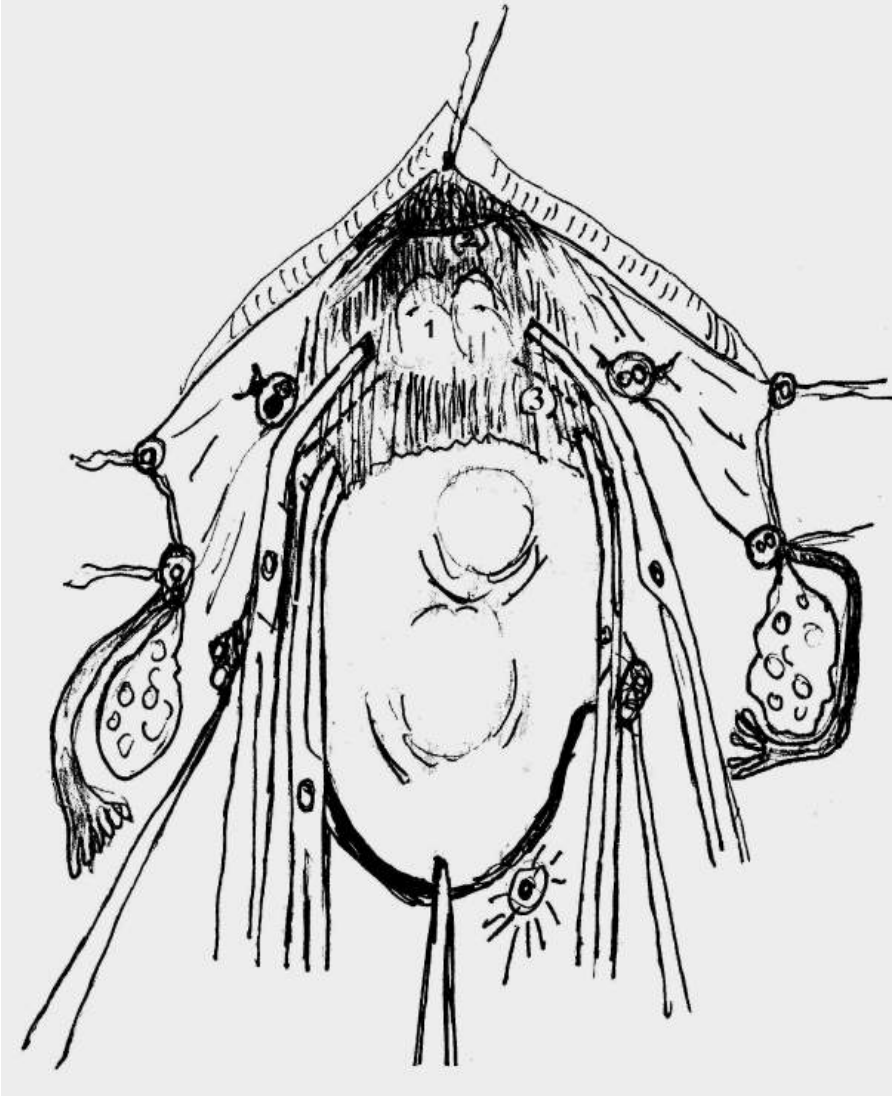
Opening the posterior fornix

The uterus is then pulled upwards and forwards. This stretches the uterosacral ligaments. Each is clamped and cut by a curved long Kocher just behind its uterine attachment. Care should be exercised not to injure the ureter which courses forward just lateral to the uterosacral ligament. Inserting a blunt curved scissors underneath the peritoneal reflection on the vagina raises the peritoneum of the Douglas pouch, and the peritoneum is incised between the cut ends of the uterosacral ligaments. Using blunt dissection by the index finger or a swab upon the vaginal side, the peritoneum is separated from the back of the supravaginal cervix and the rectovaginal space is easily entered. If one is in the correct plane, bleeding is minimal. Care should be exercised not to injure the rectum by excessive blunt dissection in a poorly developed plane.

The posterior fornix is picked by an Allis forceps and the vaginal wall is incised just behind the cervix. This is done by the long curved blunt scissors with its tip directed forward. If difficulty is encountered in identifying the vagina, it can be opened by carrying deeply the incision on one of the uterosacral ligaments. The incision is enlarged laterally towards, but not including, the lateral fornices. The vaginal edges may contain spurters that need to be caught and cauterized.

Opening the anterior fornix

The index and middle finger of the left hand are inserted in the posterior vaginal wound below the cervix and bent upwards in order to stretch the anterior vaginal fornix (Fig. 5). The uterus is now turned to an upward and backward pull. The bladder muscle wall will stand out as a separate fold in front of the stretched anterior vaginal wall. Using blunt dissection, the bladder is further dissected down first in the middle line and then laterally. The fascia of the bladder pillars may need be snipped by a scissors. The fingers inside the anterior fornix are very helpful landmark for this dissection. Fine blood vessels may ooze at this point; they are secured by fine long arteries and cauterized.



Hysterectomy: Figure 5: Transection of vaginal angles. *(1) Stretching the anterior vaginal wall upon fingers introduced through the opened posterior fornix, (2) proper dissection of the bladder and ureter from anterior vaginal wall. (3) Clamping the vaginal angles.*

Now, while pulling the uterus laterally and upwards and pressing the paracolpos on the side of the vaginal angle downwards, the medial attachment of the cardinal ligament is clamped by a long curved Kocher and cut above the clamp. This clamp should be inner to the ligated uterine vessels and must be reaching to the vaginal wall. This clamp contains the vaginal branches of the uterine vessels.

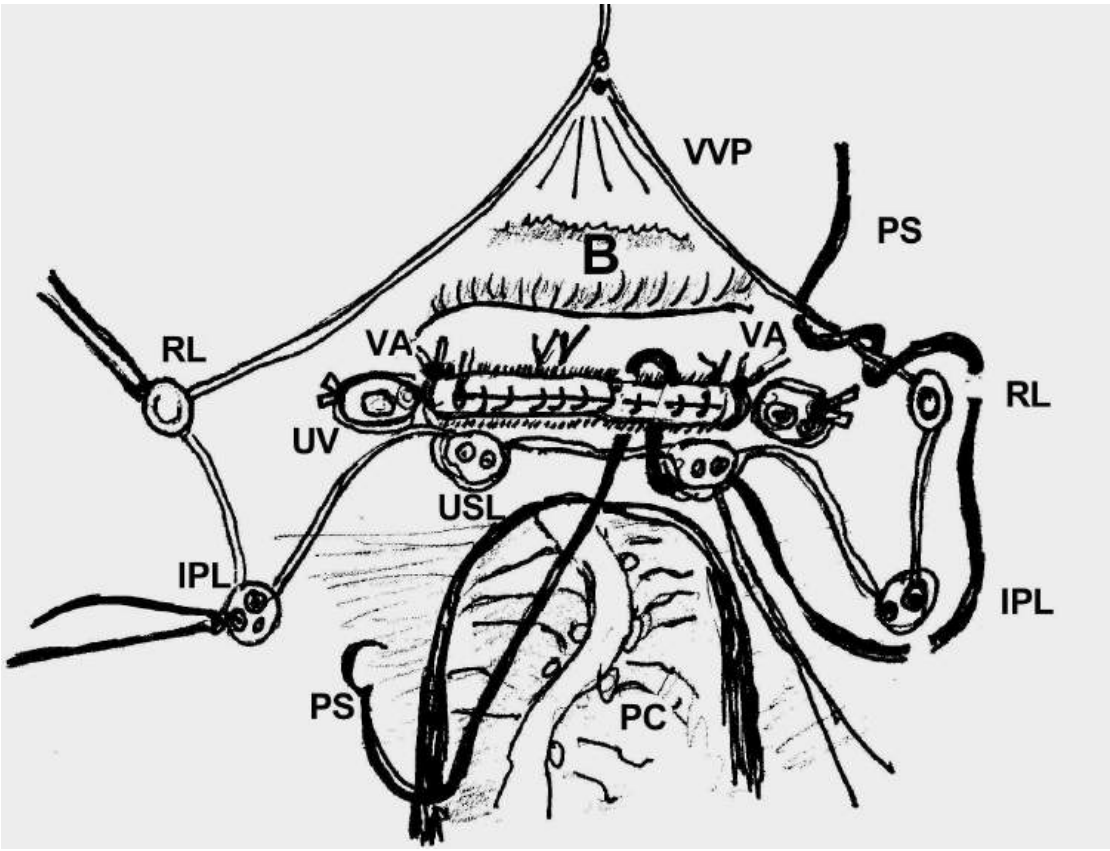
The anterior fornix is picked in an Allis forceps and cut just in front of the cervix. The incision is enlarged laterally until it joins to the incision the vaginal angle inner to the clamps on the cardinal ligament.

At this point suction should be working to help identify spurters from the vaginal edges, if any, which need be secured and cauterized.

The clamps on the cardinal ligament are replaced by transfixation ligature, which is made to include the vaginal angle and needs be tied only around the heel of the clamp. This

ligature is cut and not pulled upon (it may slip); raising the vaginal edges should depend on the already applied Allis forceps.

Closure of the vaginal wound (Figure. 6)



Hysterectomy: Figure 6: *Suspension of vaginal vault (VV) by a purse-string (PS) passing through the vesicovaginal peritoneum (VVP), round ligament (RL), the infundibulopelvic ligament (IPL), the uterosacral ligament (USL) and the vaginal vault. B = bladder; and PC = pelvic colon(Note: the purse-string is depicated thick for the sake of clarity).*

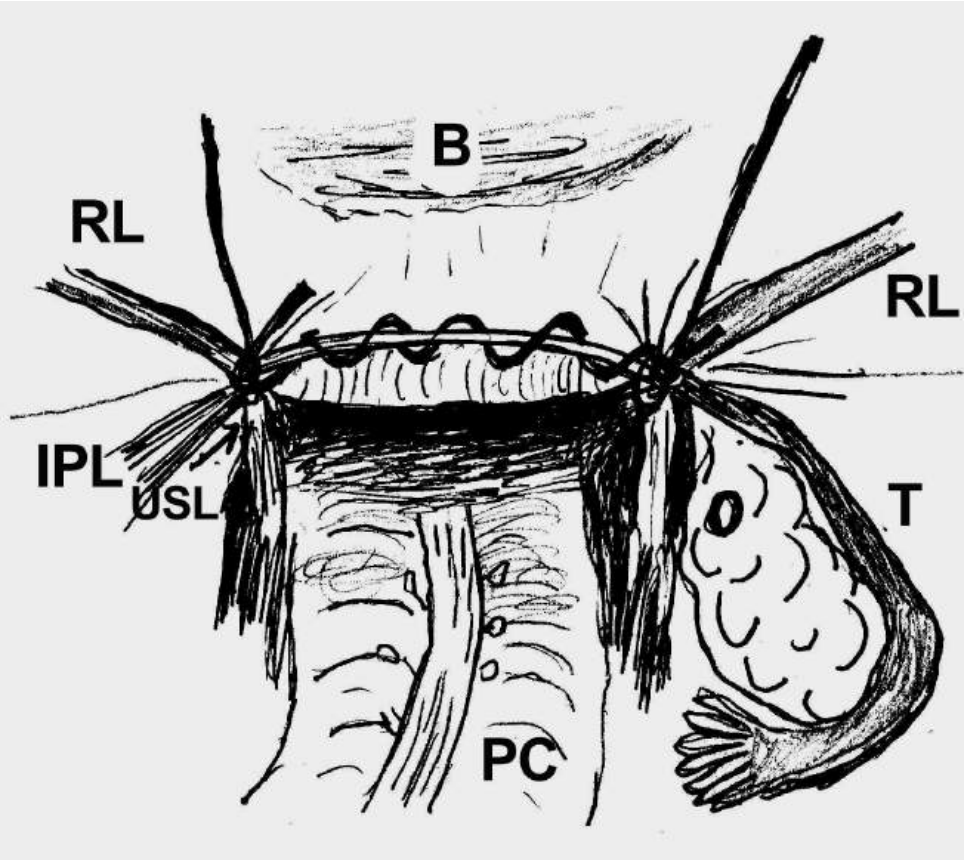
Some surgeons do not close the vagina completely; because they take the view that any blood accumulated in the pelvis after the operation can drain away into the vagina so that there is no possibility of the development of a hematoma. If the vagina is left open, a continuous interlocking suture must encircle the cut edge.

The author is of opinion that if there is bleeding from anywhere in the operation, it is better carefully and meticulously secured before closure of the wound. Healing is better and wound infective morbidity is better when the wound edges are approximated. The vaginal edges are therefore better sutured together. This is done by using delayed -absorption synthetic suture (1 – 0 Dixon), the edges are approximated by inverting-lamberts suture missing the vaginal edge. By the use of this technique of suturing, a minimal foreign body

reaction occurs the vaginal vault. This minimizes the chance of formation of granulations in the vaginal scar, a common postoperative complication that can cause discharge and contact bleeding for some time.

There should also be a rare need for leaving suction drain. If however this is mandatory the drain pathway should be all extraperitoneal and should come out a separate stab in one iliac region.

Closure of pelvic peritoneum (Figure 7)



Hysterectomy: Figure 7: Peritonization of the pelvis*: RL = round ligament, T = tube, O = ovary, USL = uterosacral ligament, IPL = infundibulopelvic ligament, B = bladder; PC = pelvic colon. Left ovary conserved.*

This should always be attempted and is usually possible unless a big gap has been created. There are three pedicles on each side; the round, infundibulopelvic and uterosacral ligaments. These are included in an inverting purse string on one side that exteriorize the pedicles. The suture is then continuously run across the pelvis with repeated interlocking. It is made by a delayed-absorption synthetic 0-2-suture material. When it reaches the angle of the vagina, the suture is made to pick upon and include this angle. The other end of the running

suture will be made in a purse string, which similarly includes and inverts out the three pedicles on the other side. This technique ensures suspension of the vaginal angles to the uterine pedicles, a measure that can diminish the chance of vault prolapse. There is no raw area or pedicle left bare for adhesion to build upon.

When the ovaries are left behind, they should not be included in the peritonization of the pelvis and are left hanging to the side of the pelvic brim. This is to avoid occurrence of postoperative dyspareunia.

Another measure to diminish vault descent is not to leave behind a deep Douglas pouch. If this is found deep, the cul-de-sac is obliterated by a series of purse-string sutures at levels starting from the blind pouch and repeated up to the mouth of the pouch. Delayed-absorption synthetic material is used for this purpose. They are done by Dixon or vieryl sutures. Great care should be exercised not to include the ureters, which are in the lateral wall of this peritoneal pouch. Also, no narrow recess should be left lateral to purse string; this can result in internal strangulation of an intestinal loop.

Closure of the abdomen

The pelvis is inspected, the packs are removed and the abdominal wound is closed. The skin closure of Pfannenstiel incision is done by subcuticular sutures.

Examination of the removed specimen

This part of the operation, notes about the finding should be included in the records. Most specimens are better sent for pathological appraisal.

Postoperative care

- Leaving an indwelling urinary catheter is *unnecessary.* It increases postoperative morbidity.
- Early ambulation is encouraged.
- Oral feeding is usually started by next morning.
- Discharge from the hospital is possible 3 days after the operation or occasionally earlier.

Difficulties and Complications in TAH

1. Difficult exposure

This can result from choice of wrong type of abdominal incision, obesity and nature of the pathology. A large myomatous uterus may be difficult to deliver in the wound. Complete or partial enucleation of the biggest accessible myoma may be required before the uterus can be delivered in the wound.

When difficulty is anticipated, a longitudinal incision is needed; it can be extended according to the need. If Pfannenstiel's incision is not adequate, it can be enlarged by cutting on the insertion of the recti in the pubic bone. Fixation of the uterus by strong ligamentary supports deep in the pelvis is just a bad luck, which is dealt with by patience and good assistant(s).

3. Adhesions

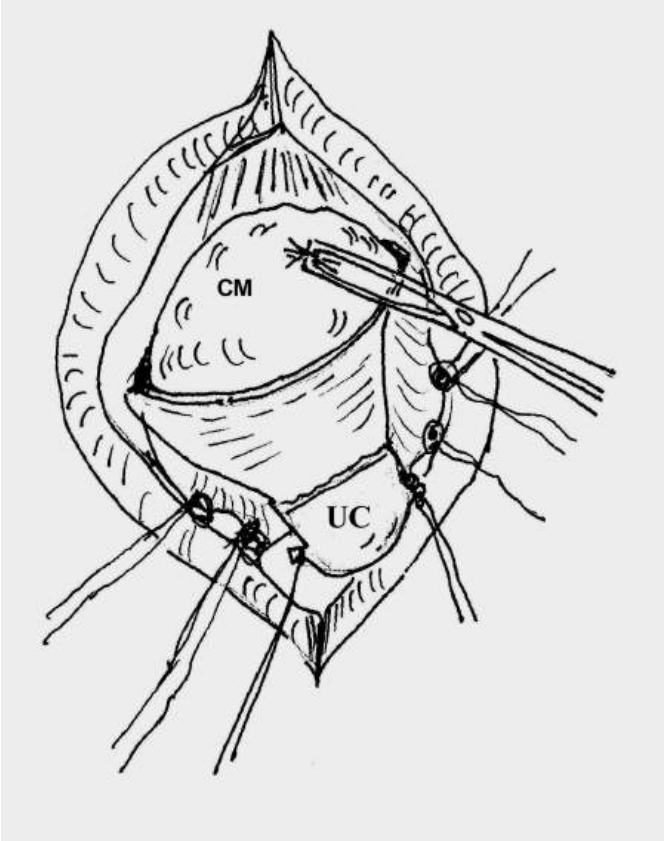
Adhesions can sometimes be dense particularly in case of pelvic inflammatory conditions and endometriosis. Patience, care and experience are required until anatomical landmarks are identified. Dragging intestines and blunt dissection are not advisable. Instead, interserosal spaces should be carefully identified and developed by clamping and cutting adhesions. If the serosa or seromuscularis of the bowel has been damaged, the defect must be carefully repaired by fine suturing using atraumatic needles and delayed absorption synthetic materials. The defect must be repaired in a direction that ensures no construction of the lumen. If a loop of intestines is badly damaged, resection anastomasis is required. The gynecological surgeon should be equipped to do that, or he should call for assistance.

Once the uterus has been identified it can be pulled upon by traction sutures and this serves to define extrauterine adherent structures. The fimbrial end of the tubes or the pearly white ovary can be important landmarks in the darkness of adhesions.

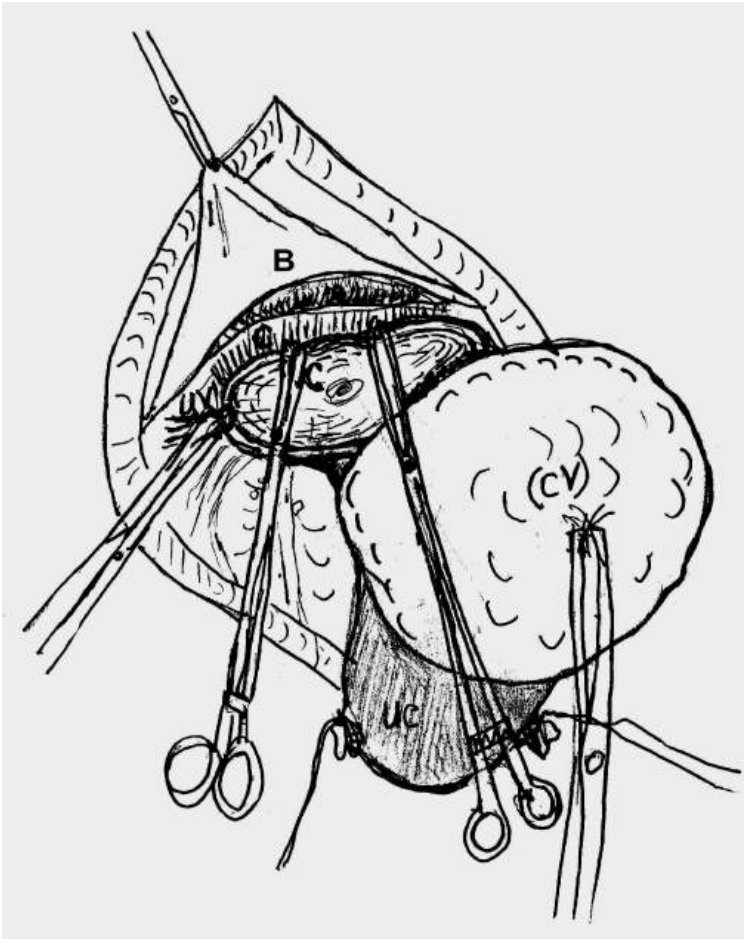
3. Difficulties with certain myomas

a. A low anterior wall or cervical myoma may raise the uterovesical pouch and displace the bladder upward which makes it liable to injury during opening the peritoneum.
b. The myomas can be large enough to interfere with the delivery of the uterus in the wound (see above).
c. Broad ligamentary and cervical myomas may result in great difficulty in hysterectomy. The important adjacent structures are displaced, notably the urinary bladder, ureters, uterine vessels and rectum and are vulnerable to injury if this is not considered with care. The best approach to this problem is to enucleate the myoma completely or partially before starting with the hysterectomy. The upper edge of the broad ligament is clamped as usual. The round ligaments stretching over the swelling are cut on both sides between ligatures. The peritoneum in between is incised. This is done just below an important landmark which is a usually present, in the from of a triangular dimple opening downward which is seen in the visceral peritoneum in the middle line at the level of transition from loosely attached to the firmly fixed peritoneum on the front

uterus. Cutting just below the dimple will ensure avoiding cutting in the bladder. The capsule of the myoma is then adequately incised transversely (occasionally longitudinally). Deep pulling sutures are inserted in the myoma. It is gradually enucleated from its bed by blunt dissection with occasional scissors snips (Figure 8). After the complete enucleation of the myoma, the bladder and ureter dissection is completed as usual but occasionally bleeding point may need be identified, caught and cauterized. The uterine vessels are secured as usual. The lower flap of the incision of the capsule usually needs be lifted by two Allis forceps in order to complete dissection of the bladder off the front of the cervix with the left hand inside the tumor bed and the right hand outside the cervix (Figure. 9). The cervix is usually completely removed.



Hysterectomy: Figure 8: Cervical myoma (CM) being enucleated through an anterior incision in the capsule. The uterine corpus (UC) is sitting on the top of the myoma.



Hysterectomy: Figure 9*: For cervical myoma (CM), which is almost completely enuculeated from its capsule (C). The capsule is pulled upon to complete the dissection of the bladder (B) and skeltoization of uterine vessels (UV). UC = uterine corpus.*

The author has always used this approach with occasional modification of opening the capsule of the myoma posteriorly when it is a posterior wall cervical myoma. Trial to remove the cervix with the myoma in place carries a risk of injury of surrounding structures.

4. Hemorrhage

Bleeding complications to an extent requiring blood transfusion are uncommon with abdominal hysterectomy: 1 - 2%. They are either in the form of (1) *intra-operative* (primary) hemorrhage, early *postoperative* (reactionary) and *late postoperative* hemorrhage.

- ***Primary Hemorrhage*** *is* particularly likely to occur from (1) tearing the blood vessels at the vaginal angles in total hysterectomy, or bleeding from (2) the severed edges of the vagina, or results from (3) slippage of a ligature on one of the vascular attachment of the uterus containing the uterine or ovarian vessels. Double ligation of these pedicles will safeguard this accident. Intraoperative bleeding should be generally dealt with by (1) tampoonading by packs until (2) suction is actuated, (3) light is brought to the required angle and the necessary clamp is ready to secure the particular bleeding point, which is

then ligated or cauterized. Applying clamps in pooling blood is a bad practice that results in traumatizing important structures like the bladder, ureter, rectum or bigger blood vessels.

- ***Reactionary Hemorrhage*** *should* be rare; it occurs within 36 hours of the operation and results from slippage of a vascular pedicle. This occurs as a result of immediate postoperative restoration or rise of blood pressure, or from coughing or sudden movements. Double ligation of pedicles, careful inspection of the field before peritonization and good postoperative sedation helps in avoiding this complication. Laporotomy is usually required, the bleeding vessels is secured and ligated. Vaginal-edge bleeding is usually mild and requires no more than a tight vaginal pack.
- ***Secondary Hemorrhage*** *is* rare and results from infection. The bleeding occurs 7 to 10 days after the operation and is usually in the form of vaginal bleeding which is usually mild but it causes alarm to the patient. It is usually preceded by a febrile postoperative period. It is usually controlled by a vaginal pack and this is followed by administration of broad-spectrum antibiotics. Rarely, abdominal exploration is required. Ligation of the anterior branch of the internal iliac may be required.

5. Injuries of Adjacent Organs

- **Bladder injuries**

The bladder can be injured during 1) opening the peritoneum, 2) dissecting down of adherent or displaced bladder off the cervix and vagina, 3) including the bladder in clamps applied to the vaginal angle, or 4) inclusion in suturing of the vaginal wound. It is not a major accident if recognized during the operation and repaired. If left unrecognized or imperfectly repaired it results in vesicovaginal fistula. The bladder injury is usually repaired by the gynecologist. He or she should assess the extent of the injury and its relation to the ureters. The wound is drawn taut between two bladder (Allis) forceps and repaired in two layers. The first is a continuous inverting Lambert suture not including the mucosa, but the bites are made to emerge as near to the mucosal edge as possible. This leaves to the inside of the bladder an even line without suture material. This tire is buried by another tire of inverting suture. Both layers are done by number 0 - 2 delayed absorption synthetic sutures. There is no need for abdominal bladder drainage but continuous bladder drainage depends on an indwelling Foley's catheter in the urethra. This is kept for 12 days, during which the flow of urine should be observed. Broad-spectrum antibiotics are given.

- **Ureteral injury**

There is no gynecologist with an average-sized practice who has not injured the ureter once or more in his practice. The ureter is most likely to be injured at the following sites:

a. ***During clamping the uterine vessels,*** an accident that can be avoided by (1) skeletonizing the vessels before clamping, (2) traction on the uterus upwards to the side and countertraction by pushing the parametrium down and to the other side and (3) applying the clamps at a right angle to the vessels.
b. ***During clamping and cutting the vaginal angles:*** One of the main difficulties in hysterectomy is to mobilize the termination of the ureter without opening up venous plexuses that lie in the region of the lateral vaginal wall. The ureter may be injured at this point. This injury is avoided if downward dissection of the bladder and ureters off the front of the vaginal is completed against an anterior fornix, which is stretched by fingers raising the fornix (the posterior approach of opening the vagina a described above). Applying clamps in blood pools should be strictly avoided (tamponade, suction, identification of the bleeding vessel).
c. ***During ligation of the infundibulo-pelvic ligaments:*** This should be avoided by lifting the ovarian vessels on the index finger before clamping them. One should consider the nearness of the ureter to this point particularly in difficult cases where there is a broad ligament tumor or dense pelvic adhesions.
d. ***During clamping the uterosacral ligaments:*** The ureter course forward in the base of the broad ligament lateral to the uterosacral ligament. Care needs be exercised to keep near to the uterine attachment of the ligament. The ureter needs be identified in difficult cases.

For repair of ureteral injury, end-to-end anastomosis, uretero-vesical implantation, or a Boare-flap is done according to the level of injury (see under Injuries). A ureteric catheter need be threaded from the urethra and made to bridge and scaffold the anastomasis site. Here, an urologist is summoned if the gynecologist is not familiar with these procedures.

- **Bowel injury**

The risk of bowel injury at the time of hysterectomy is highly correlated with the difficulty of the surgical procedure. Injuries to the bowel predominantly occur in two ways: (1) injury to the small bowel during breaking of adhesion and (2) injury to the rectum with dissection of the Douglas pouch. These should be avoidable.

Primary repair, in the form of closing a rent or of resection anastmosis is done. If there has been major injury of large bowel temporary defunctioning colostomy is done. A GIT surgeon is summoned if the gynecologist is not familiar with these procedures.

Infections

Infective complications after hysterectomy are first manifested by postoperative pyrexia that may complicate *one third* of cases and frequently resolve spontaneously. Few cases are complicated by pelvic cellulitis, which can form a vaginal cuff abscess or pelvic abscess. Urinary tract infection may complicate abdominal hysterectomy and is predisposed to by the catheterization and traumatization of the lower urinary tract. Abdominal wound infection should be exceptional.

Prophylactic antibiotics usually in the form of two or three IV injection of a second-generation cephalosporin (see above) reduce the incidence of these infective morbidities. Treatment of established infection requires 6 to 10 days course of broad-spectrum antibiotics. Before starting such course, urine culture and sensitivity should be done if cystitis is suspected. If an abscess (vaginal cuff or pelvic abscess) forms, it should be transvaginally drained.

- ***Infected granuloma(s)*** may form in the vaginal vault scar. These are *common* and cause purulent discharge and slight bleeding. The granulations are deep red, soft and bleed on manipulation. This might be mistaken for prolapse of tubal fimbria. The granutomatous polyps may not be recognized except after several weeks when they cause postcoital bleeding. These granutomas need be scrapped off and their site touched by cauterization.
- ***Other postoperative complications not specific to hysterectomy***
  - Wound infection.
  - Wound dehiscence.
  - Thromboembolic disease.
  - Pneumonia.

Vaginal vault prolapse

This is a delayed complication of hysterectomy whether abdominal or vaginal. During hysterectomy the ligamentary supports of the vaginal vault are severed, and if effort is not made to support the upper vagina, it will be progressively inverted under the weight of the abdominal viscera.

Dysfunctional complications of hysterectomy

These are subjective complaints after hysterectomy and may include: (1) psychosexual dysfunction, (2) lower urinary tract dysfunction, and (3) bowel motility dysfunction.

Psychosexual Dysfunction

Psychosexual dysfunction after hysterectomy is a poorly studied subject, which remains controversial. Most of the studies had not obtained adequate preoperative assessment. Hysterectomy is frequently done in the fifth decade of life, a time of common psychosexual changes, not only of the patient but also of her husband.

In terms of sexual function after hysterectomy, there are reports citing decrease in (1) libido, (2) arousability, (3) vaginal lubrication, (4) vaginal sensation and (5) frequency of orgasm. There can also be dyspareunia.

On the whole, the health related quality of life; HRQL has been reported to be impaired after hysterectomy. This can take the form, besides the above sexual dysfunction, the addition of weight, loss of interest in body figure, diminished self-esteem, which may be rarely associated with depression.

Earlier literature suggested an increase in these psychosexual dysfunction. More recent reports refute this and emphasize the following points: (1) It is now established that removal of the ovaries at time of hysterectomy has a strong detrimental effect on psychosexual dysfunction. Sometimes the ovaries left behind will, sooner than normal, lose their function, probably as a result of hysterectomy. (2) Healthy sexual function before surgery is the best determinant of healthy sexual function after the operation. Some patients may actually report improvement of sexual performance due to removal of the disease. (3) Proper preoperative counseling is a strong determinant of the postoperative satisfaction. This should include information about the indication of the operation, the nature of the operation and its implications and the superiority over other treatment options. The patient should give her fully informed consent. (4) The psychosexual dysfunction may be reflecting or resulting from a problem in the husband.

Dysfunction of the lower urinary tract

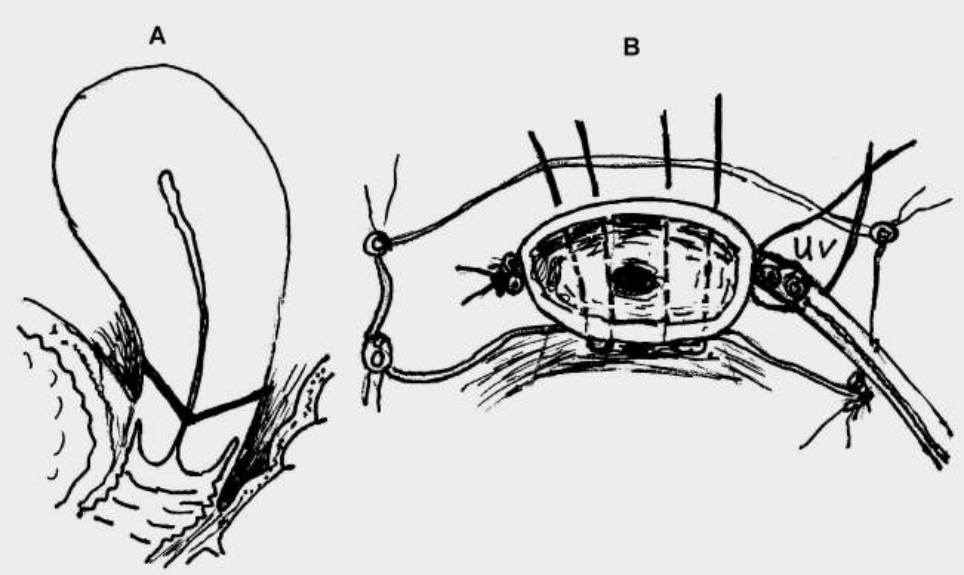
Old literature suggested that hysterectomy increases the incidence of lower urinary tract symptoms, like frequency, urgency, stress incontinence and chronic retention. More recent studies, which took in consideration the preoperative status, have failed to show these effects for hysterectomy. Urodynamic studies done before and after hysterectomy have failed to show any significant change.

Bowel dysfunction

Again, this is a controversial point. Old reports suggested increased occurrence of constipation and spastic colitis after hysterectomy. More recent reports that took in consideration preoperative symptomatology have failed to find any difference after the operation.

Technique of Subtotal Hysterectomy

The steps are the same up to the ligation of the uterine vessels. There is no need for completion of dissection of the urinary bladder from the front of the cervix. The corpus uteri are amputated by a scalpel at the level of the internal os. This corresponds to the point where the uterine vessels reach the cervix. The incision in the cervix is V-shaped or a conizing one (Figure. 10).



Hysterectomy: Figure 10: Subtotal hysterectomy *(A) V-shaped incision of the cervix (B) Ligation of uterine vessels (UV) and closure of cervical stump.*

This facilitates subsequent suturing of the incision. It also ensures removal of all the endometrium and obviates any possibility of return of any menstruation. The remaining part of the endocervix is cauterized by diathermy.

Two or three transverse mattress sutures approximate the edges of the cervical incision. The pelvis is peritonized as described under total hysterectomy. The cervical stump is suspended by suturing the ligaments as described in total hysterectomy.

Technique of Hysterectomy for Cervical neoplasia

(see under carcinoma of the cervix)

Technique of Vaginal Hysterectomy

Vaginal hysterectomy of a nonprolapsed uterus needs special experience and is more difficult than abdominal hysterectomy. The technique described below depends upon progressive downward mobilization of the uterus by progressive clamping and cutting of the vascular pedicles of the uterus just lateral to the uterus. The ligatured pedicles are fixed to the vaginal vault.

Two assistants are required in this operation. A spotlight need be adjusted to the inside of the vagina. Three right-angled long-bladed, long-handled retractors serve to retract lateral structures. A pair of aneurysm needles are usually used besides some 4 or 6 long curved *strong* Kocher clamps.

Positioning the patient

After receiving anesthesia, the patient is put in the dorsal lithotomy position in stirrups with the hips over the edge of the table and thighs well flexed on the abdomen. The hip joint *must not be externally rotated* or markedly abducted. *The assistant should never stand medial to thigh* or lean heavily on it. This can result in sciatic or femoral nerve injury.

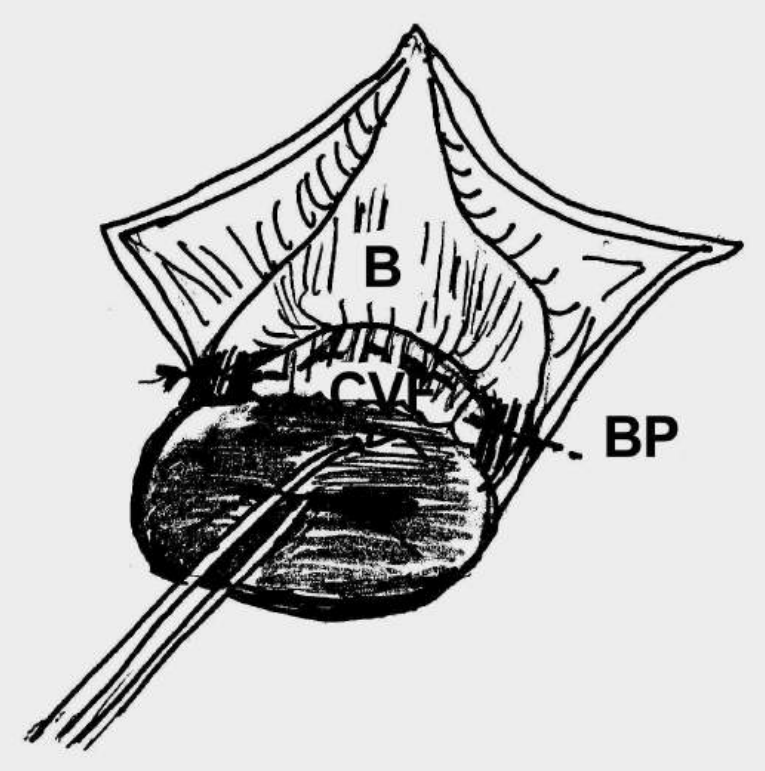
Examination

After sterilization of the operation field, it is draped. Careful examination under anesthesia is done. This comprises assessment of the extent of laxity of pelvic floor. The uterine cervix is pulled down by a volsellum. If the uterus is found firmly fixed high in the pelvis, one should reconsider the choice of the vaginal approach. The vaginal approach may also not be the better choice if the uterine size is more than that of 10 week pregnancy. Adhesions of inflammatory, endometriotic, or surgical origin make vaginal hysterectomy more difficult.

If the labia minora are hanging down, they are better fixed by silk suture to the skin outside the labia majora. A silk suture also anchors the drape to the perineal skin just in front of the anus serves to protect the operative field from soiling by discharge of fecal matter.

Widening muscle-cutting perineotomy (Schuchardt) incision is needed if the vaginal canal is narrow. A weighted Auvard's speculum of the correct size is placed in the vagina. Lateral right-angled vaginal retractors are needed in this operation.

Mobilization of the bladder (Figure. 11)



Hysterectomy: Figure 11: Vaginal hysterectomy cutting of cervicovesical fascia (CVF) and bladder pillar and bladder pillar (BP); the latter may need be clamped.

While pulling upon the anterior lip of the cervix by a volsellum, an inverted T-incision is made in the anterior vaginal wall. The transverse part is made at the junction of the cervix with the vagina. The longitudinal part extends down (anatomically down) the middle line. The incision should involve the vaginal skin *and the underlying vaginal fascia* to allow entering the plane between the vagina and bladder. Short Kocher forcepses are applied on the vaginal flaps on each side, which are demarcated, by traction. Any spurter is picked up by arteries and cauterized. With a combination of blunt and sharp dissection the anterior vaginal wall is separated from the bladder for a short distance on each side. There is no need to carry this dissection far laterally to under the pubic arch. This is unnecessary and will open big veins. The bladder is exposed between the flaps. Pulling the cervix down will allow identification of the bands of the *vesicocervical ligament* in the middle line. These are cut by a curved blunt scissors. This allows entering in the avascular plane between the bladder and the cervix. Entering this "space" allows easy mobilization of the bladder from the front of the cervix by the thumb. No forceful blunt dissection is required here; and the need indicates that one is not in the right plane. The angles of the bladder are fixed to the cervix by the bladder pillars, which are denser vascular lateral continuation of the vesicocervical ligament. While

retracting the bladder upward in the middle line and pulling down on the cervix, the pillars are cut by a scissors. Small blood vessels are thus opened up, and if bleeding is brisk, the vessels are caught in arteries and cauterized. After cutting the bladder pillars the bladder can be mobilized upwards together with the ureters from the anterolateral walls of the vagina.

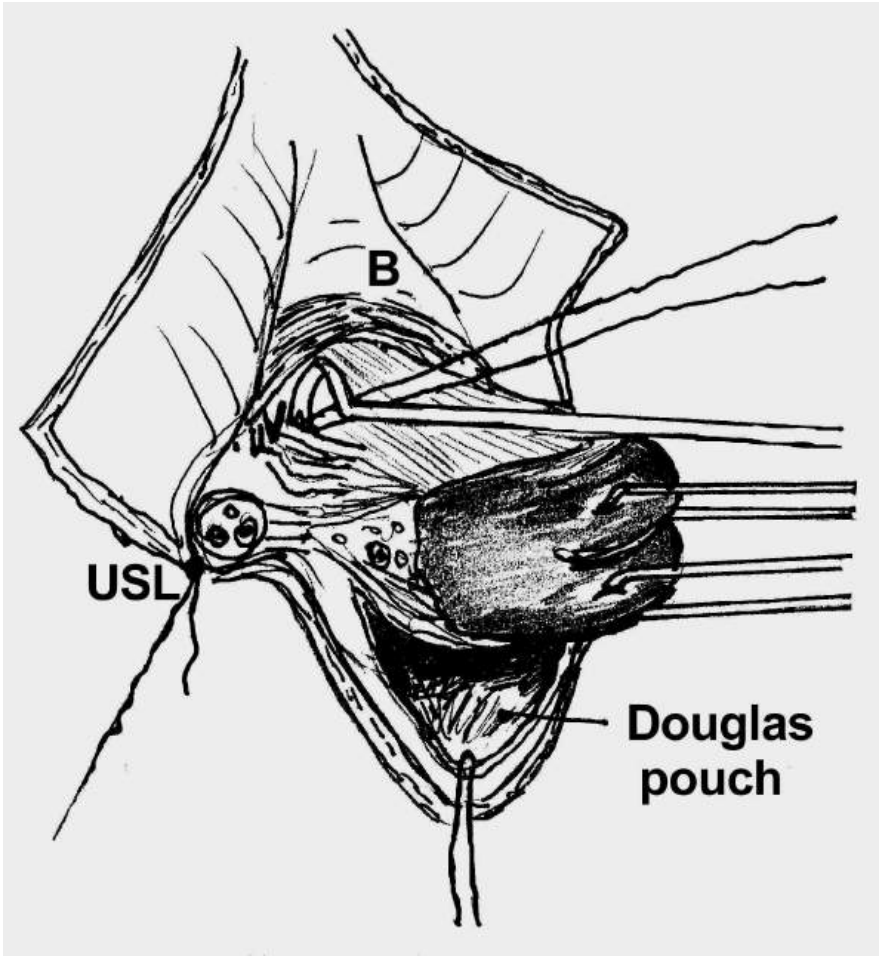
Opening the Douglas' pouch

The posterior lip of the cervix is held by a second volsellum and the circumcision of the cervix is completed by extending the transverse part of the vaginal incision around the sides and back of the cervix. The level is to be kept at the junction of the vagina and the cervix in order to avoid shortening of the vagina. The posterior vaginal is dissected away from the tissue behind the supravaginal cervix until the peritoneum of the pouch of Douglas is identified. Care must be taken to avoid dissecting the peritoneum from the back of the uterus since this will make it difficult to identify the Douglas pouch. The peritoneal pouch is sometimes not directly behind the cervix. The position of the pouch can often be identified by a shallow depression between the two-uterosacral ligaments, which is accentuated by pulling the cervix downwards and forwards. The pouch can be identified by rectal examination using doubly gloved left hand. The apex of the pouch is picked by a toothed forceps and snipped open by a scissors and the glistening peritoneum is identified. Some small amount of peritoneal fluid will come down. A stay-untied suture marks the posterior side of the Douglas pouch and the incision is enlarged laterally up to the uterosacral ligaments. Care should be taken not to injure the rectum. If this occurred, it should be repaired.

The back of the uterus should be palpated to exclude the presence of adhesions. If there are dense fixing adhesions, the surgeon may be opt to resorting to abdominal approach for hysterectomy. Not all hysterectomies started as vaginal could be completed with this approach.

Cutting the uterosacral ligaments

The cervix is pulled downward and laterally and the vaginal wall is dissected from the deeper structures on the side of the uterus. The lower part of the uterosacral and Mockenrodt's ligaments are thus exposed. They are together clamped by a long curved clamp, cut and doubly ligatured using No: 1 chromocised catgut. The procedure is repeated on the other side. One of the two ends of the ligature is kept long and hung on in an artery for later use to suspend the vagina. Cutting of the two-uterosacral ligaments allow more downward pulling the uterus.



Hysterectomy: Figure 12: Vaginal hysterectomy. *The uterosacral ligament (USL) has been transected and Douglas pouch opened. The bladder (B) has been dissected upwards, the right uterine vessels (UV) are being secured by an aneurysm needle.*

Clamping the Mackenrodt's ligament including the uterine vessels

This is the most critical step, and can be difficult with a non-prolapsed uterus. It is usually accomplished in one pedicle when the uterus is prolapsed (Figure 12). However, in a well-supported uterus it need be done piecemeal by two to four clamps each including a small bite of the parametrium. After cutting of tissue included in the inferior clamps on both sides, the uterus can be further pulled down allowing reaching to a higher level.

Care should be taken to avoid slipping of the pedicles since the tissues are drawn down under tension. The Mackenrodt ligaments should be double secured. It is the practice of the author to include the tissue first in a knot passed by an aneurysm needle, then to clamp the tissue medial to the knot by a curved long Kocher clamp. The pedicle is then cut medial to the clamp, ensuring cutting around the tip of the clamp. Since the uterus is always pulled down and is thus rendered ischemic, there is no need to place clamps on the specimen side of the uterine pedicles. After replacing the clamps by ligature, one of the ends of the knot is left long to be utilized in suspension of the vaginal vault. This single strand is tied to the single strand

left behind from ligature of the uterosacral ligament and one of the two strands is cut. This is repeated each time a pedicle on the side of the uterus is tied, until at the end two strands are left long gathering together all the uterine pedicles. These two strands will be fed on needles and passes through the vaginal edges before the final closure of the vault.

Another point need be observed during ligaturing and cutting the uterine pedicle, which is safeguarding the ureter. The ureter is just under the uterine and about 1.5 cm lateral to the supravaginal cervix. The ureter can be pulled down forming a knee-like bent if the uterus is pulled down while the ureter is still attached to the front of the vagina. This knee can be included in the clamps applied on the side of the uterus. This injury is avoidable through the following precautions: (1) cutting the bladder pillars and mobilizing the angles of the bladder from the front of vagina, (2) The Mackenrodt's ligament can be stretched and further dissected against an index finger inserted from behind through the opened Douglas pouch, (3) Before applying each clamp, the uterus is pulled to the other side while a narrow long retractor pulls the parauterine tissue away from the Mackenrodt's ligament. (4) Applying the clamps immediately later to the uterus.

Opening the uterovesical pouch

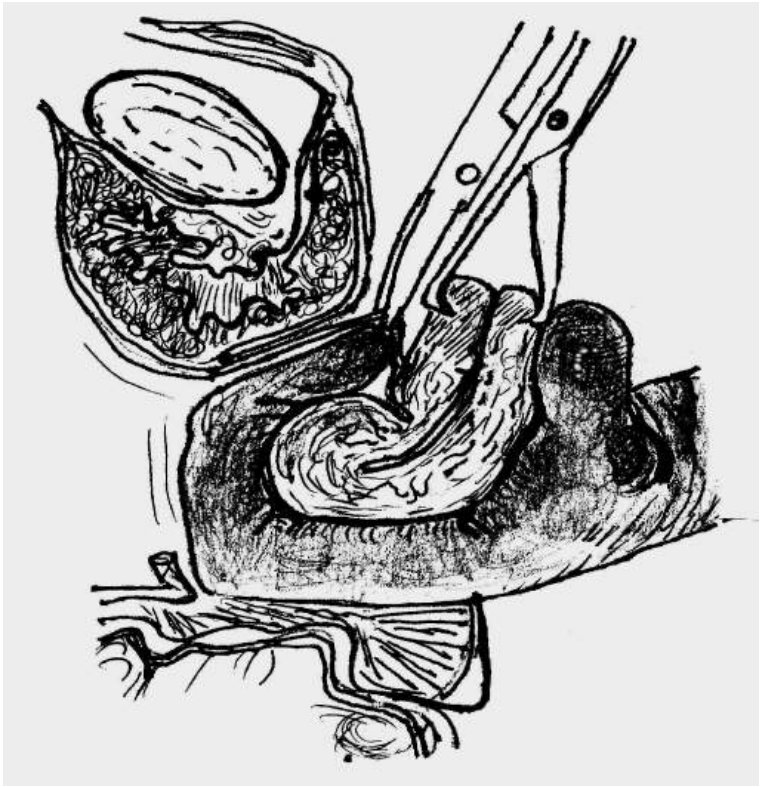
The severing of the Mackenrodt ligament mobilizes the uterus down to allow identifying the white crescentic fold of the uterovesical pouch. If there is doubt about this fold, the fingers of the left hand are passed from the Douglas pouch incision over the top of the uterus or broad ligament into the anterior pouch of peritoneum, which is snipped by scissors and then enlarged, laterally to the front of the broad ligament (Figuer: 13). A stay suture is passed in the anterior side of the peritoneal incision.

Delivery of the fundus uteri by anteflexion through the uterovesical pouch

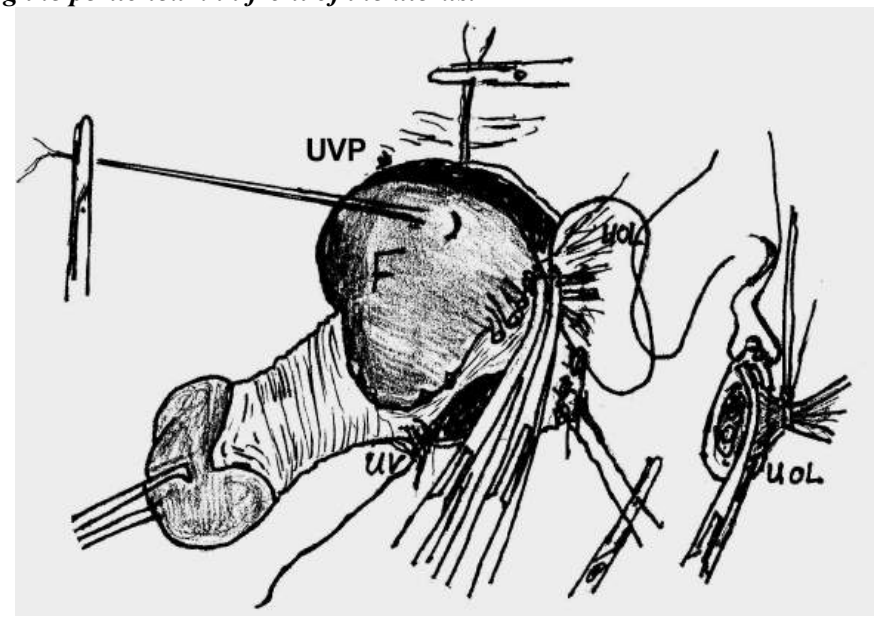
This is easily achieved by pushing from behind. Occasionally the uterus is pulled down by holding the front by a volsellum or Allis forceps. Sometimes, it is easier to bring the fundus out by retroflexion through the opened Douglas pouch. A sizable myoma may need be enucleated before the fundus can be turned out. If there are adhesion bands to the fundus, they should be *clamped* and cut next to the uterus. If the uterus is too big to be brought down through the peritoneal opening it can be bisected and each half is brought out separately. Having tied the uterine vessels, bleeding during bisecting the uterus is not marked. Each of the anterior and posterior walls are the uterus are cut by a strong scissors in the middle line.

The attachments of the round ligament, tube and ovarian ligaments are now exposed. They are double clamped by long curved Kocher's applied just lateral to the fundus uteri (Figure 14). Cutting the structures inner to the medial clamp will completely sever the uterus from this side. Pulling on the uterus allows easy application of the clamps to and severing the

other side of uterine attachment. The pedicles are doubly ligatured. The ends of the two pedicles are left long and hanged upon by an artery.



Hysterectomy: Figure 13 Vaginal hysterectomy. Opening the vesicouterine pouch of peritoneum by introducing the hand in the now-opened Douglas pouch around the fundus and stretching the peritoneum in front of the uterus.



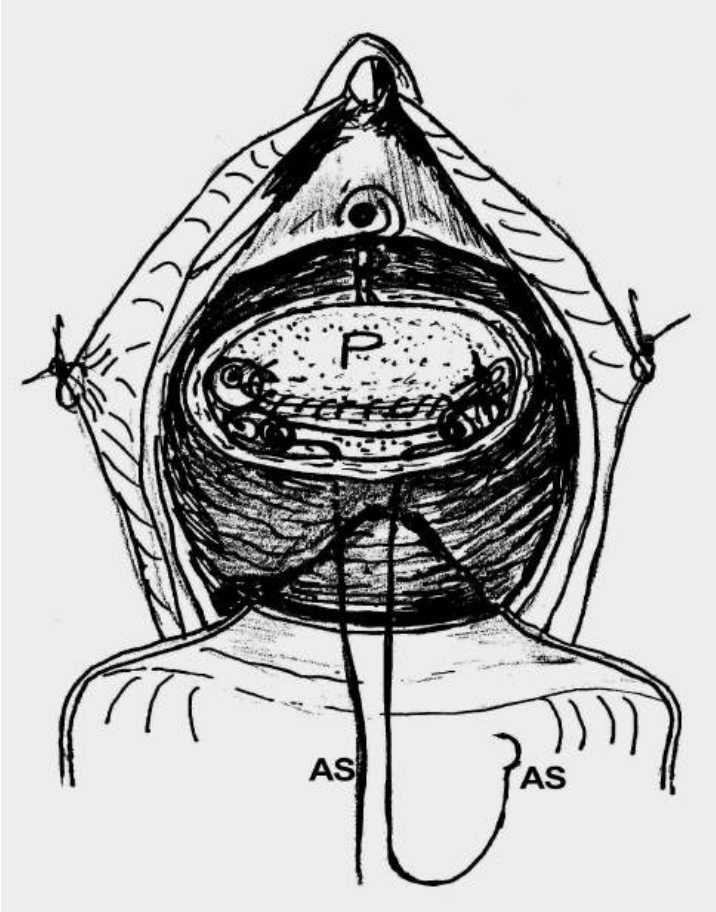
Hysterectomy: Figure 14: Vaginal hysterectomy. *The uterine fundus (F) is delivered by anteflexion through the opened uterovesical pouch (UVP). The left uterovarian ligament (UOL) is transected after being doubly clamped. The lateral clamp is replaced by a free knot, and the medial one by transfixation suture. The pedicle of UOL is shown tied on the right hand-side.*

If the *ovaries need be removed* they are delivered in the wound by holding them in ring forceps. Clamps are then applied on the infundiculopelvic ligament. This should be done with exercise of care to have intestines away by putting the table to Trendelenberg tilt. A swab on a swab hold forceps may need be used to push the intestines away. This pedicle is doubly ligated because it is usually held under tension.

Closure of the peritoneum

The pedicles are pulled out and inspected for any bleeding vessel. The peritoneal edge held on stay sutures are brought down and closed transversely reaching from one ovarian vessel pedicle to the other. All the pedicles of the uterus are thus left extraperitoneal.

Below the peritoneum the combined uterine pedicles of the two sides are sutured together by delayed absorption suturing material.



Hysterectomy: Figure 15: Vaginal hysterectomy. *The pelvic peritoneum (P) is closed by a continuous suture. The combined uterine pedicles are approximated below the peritoneum, and the ends of the approximating suture (AS) are passed through and tied to the posterior vaginal fornix.*

Closure of the vaginal incision

The field should be made dry before closure of wound in the vagina in a transverse direction. The two suture strands combining together the uterine ligatures are brought through and tied on the posterolateral angles of the vaginal vault. The vault wound is sutured by interrupted Dixon suture.

Modifications required in cases of vaginal prolapse

If a hernia of pouch of Douglas is present, the peritoneal pouch is dissected and excised. The uterosacral ligaments are approximated in the middle line to reduce the width of the pelvic hiatus. Care should be exercised not to include the ureters in this approximation.

When a cystocele is present, anterior colporrhaphy is needed. The last suture in the pubocervical fascia is passed through the combined uterine pedicles in the middle line. Kelley's stitch is done if there is mild stress incontinence. More elaborate surgery is done in the same sitting for more marked sphincteric weakness.

When a rectocele, or patulous vagina is present a posterior colpoperinearrhaphy (pelvic floor repair) is done.

Trimming of redundant vagina should be done with care not to overdo removal of vaginal length and width. The vagina should not be left too tight or short to make intercourse difficult. (Also see under chapter of Prolapse).

Postoperative points

The vagina is firmly packed with gauze soaked by Betadine, and a Foley's catheter is left in the bladder. Both are removed 24 hours later.

The patient is *encouraged* to resume sexual intercourse one month after the operation. Some couples are apprehensive and afraid to resume their relation after vaginal surgery. This fear must be dispelled.

Difficulties and complications of vaginal hysterectomy

Most of the problems and complications described under abdominal hysterectomy can occur with the vaginal operation. The likelihood of the complications depends upon (1) the experience of the surgeon, (2) the strength of ligamentary support of the uterus, (3) the uterine size and (4) presence of adhesions.

Considering the broad spectrum of the practice, the likelihood of intraoperative bleeding and injuries to adjacent structures are higher with vaginal hysterectomy than the abdominal operation; but infective complications are less likely with the vaginal operation.

Discharge from the hospital is generally earlier in the vaginal approach. However, there has never been a randomized comparative trial of the two approaches.

Although there is no general agreement on absolute contraindications to the vaginal approach for hysterectomy, the relative contraindications include:

1. Lack of surgical expertise.
2. Lack of uterine mobility: under anesthesia, the cervix cannot be pulled down to the vaginal orifice.
3. Need for exploration of upper abdomen.
4. Presence of adhesion to the uterus.
5. Presence of adnexal masses that require removal.
6. Contracted bony pelvis

The introduction of laparoscopically assisted vaginal hysterectomy has changed the picture through overcoming some of the difficulties in the vaginal hysterectomy.

Technique of Laparoscopically assisted vaginal hysterectomy (LAVH)

Although supravaginal and total hysterectomy by exclusively laparoscopic approach have been described, these operations have not yet established their place in gynecologic surgery. Their safety has not been documented and they require special expertise and instrumentation. The laparoscopic assistance of vaginal hysterectomy is, however, a possible addition to the acceptable operative procedures. *Three aspects* in the laparoscopic assistance are specially acceptable:

1. Exploration of the peritoneal cavity.
2. Removal or lysing adhesions to the uterus.
3. Transection of the ovaries when this is indicated.

Other aspects of laparoscopic assistance like opening the uterovesical peritoneal pouch and transection of the uterine pedicles have not established their place, are carrying increased liability to bleeding complications and injury to the adjacent structures and are not, at the present state of technology, warranted. After the laparoscopic procedure, the uterus (and the adnexa) are removed by technique of laparoscopically assisted vaginal hysterectomy as described hereafter.

Positioning

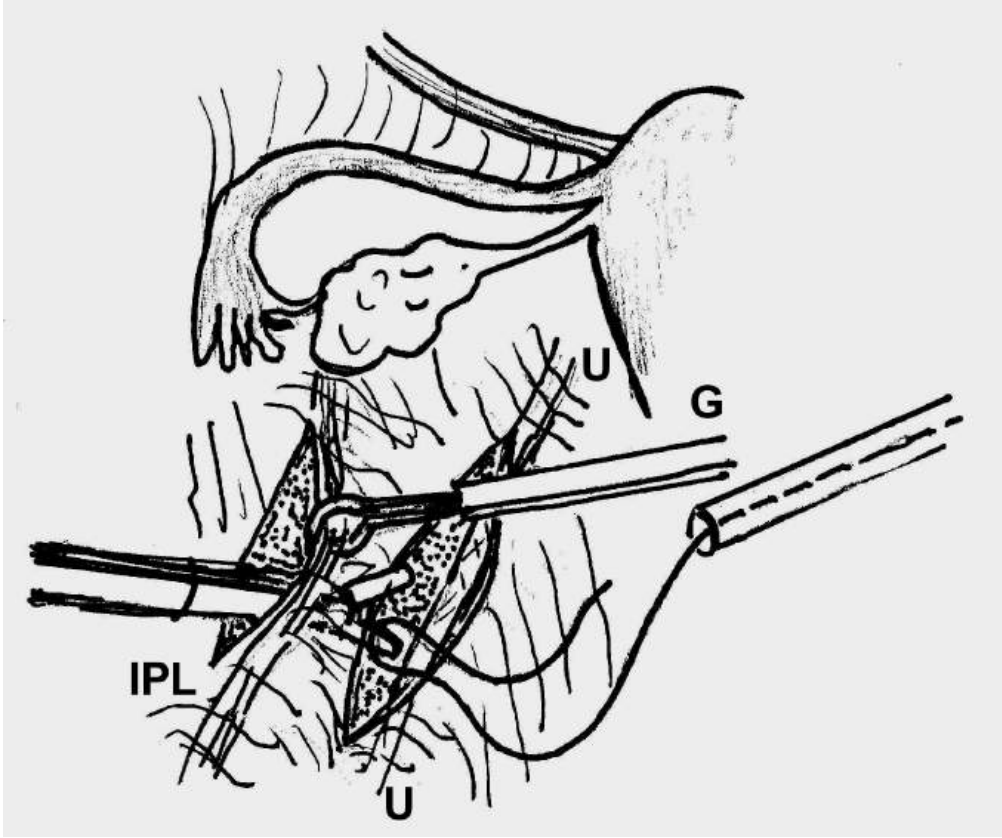
The Allen stirrups should be low, not acutely flexing the thighs on the abdomen. This in order to allow access to the lower quadrants of the abdomen for the insertion of the

instrument ports. After completion of the laparoscopic part of the operation and removal of the lower quadrant ports, the patient is re-draped in the traditional lithotomy position to facilitate the vaginal procedure.

A strong double-angled uterine manipulator is important for the laparoscope procedure. The umbilical port should be kept till the end of the operation to inspect the pelvis for hemostasis.

Exploration of the abdomen and clearing the uterine adhesion

This step is essential to decide the feasibility of the LAVH. The adhesions are cauterized by bipolar forceps as near to the uterus as possible and are then cut by a scissors.



Hysterectomy: Fig. 16 Hysteroscopically assisted hysterectomy: *An incision in the peritoneum above the infundibulopelvic ligament (IPL). Another incision below the IPL above the ureter (U), which is pushed medially. A window beneath the IPL is created using a blunt grasper (G). An extra corporeal loop suture is being passed around the ligament.*

Transection of the infundibulopelvic ligament

This is done *when the ovaries need be removed.* In this procedure the ureter need be identified and dissected away from the ovarian vessels (Fig. 16). The ureter can be seen as a

raised glistening structure crossing down the side of the pelvic brim just behind the infundibulopelvic ligament. In difficult cases the ureter is catheterized transoystoscopically. Ureteric catheter with splashing light is available in order to safeguard the ureters. This increases the cost of the operation. The peritoneum above the ureter is grasped and tented away from the sidewall of the pelvis and incised above the ureter. A grasper from the contralateral port retracts the lower peritoneal edge medially. An irrigator fluid dissector is used to bluntly dissect the retroperitoneum to further expose the ureter. Another incision is made in the peritoneum above the infundibulopelvic ligament. The infundibulopelvic ligament is held in an atraumatic grasper introduced from the contralateral port and pulled medially while a tunnel beneath the ligament is created by fluid dissection joining the incision below it. A vicryl suture is passed around the ovarian vessels, tied extracorpareally and cinched down. A second tie is similarly made next to the first one to ensure double ligation. A third tie is made 2 cm medial to the second and the ligament cut between the second and third ties. Alternatively the ligament is secured by a stapler ligator device. Diathermic coagulation and cutting of the infundibulopelvic ligament is not to be done. This is not secure enough and the radiated heat can damage the ureter.

After securing the ovarian vessels, the peritoneal wound below the ureter is continued in the posterior leaf of the broad ligament down to the uterine side. The wound above the infundibulopelvic ligament is continued on the anterior leaf of the broad ligament down to the round ligament, which is cauterized by bipolar diathermy forceps at two points and cut in between by a scissors. The procedure is completed on the other side.

Transection of the upper edge of the broad ligament

This is the alternative used if *the ovaries are conserved.* The peritoneum above the ureter is incised. The bipolar cautary is used to coagulate the round ligament at two points and it is cut in between by a scissors. The same is repeated on the tube. The stapler ligature device is used to ligate the ovarian ligament together with the ovarian vessels. With the broad ligament previously opened by transection of the round ligament and the peritoneum above the ureter also open, the lower jaw of the endoscopic staple-ligator is introduced through the peritoneal window beneath the uteroovarian ligament, the upper jaw above the ligament and the staple is fired, thus severing the ovarian vessels. Use of staple ligator to cut through the round ligament and the fallopian tube is usually unjustifiable cost and the procedure can be safely accomplished by the bipolar diathermy. An alternative approach is to tie the ovarian vessels by a vicryl loop tied extracorporeally. The procedure is repeated on the other side.

Opening the uterovesical pouch

The incisions in the broad ligament resulting from transection of the round ligaments are enlarged medially and the loose peritoneal reflection from the bladder to the uterus is tented and incised. The bladder is pushed down by fluid jet dissection.

Securing and cutting the uterine vessels

The lateral stump of the round ligament is lifted by an ipsilateral grasper and the connective tissue mesentery of the round is cut by fluid irrigator inserted in the contralateral port. By tilting the uterus by the uterine manipulator to the contralateral side, the uterine vessels can be seen. They are secured at two points by a stapler ligation device. Care should be exercised not to include the ureter.

It is still the opinion of a reasonable majority of gynecological surgeons to skip the last two steps and leave them to the vaginal part of the operation. Injury to adjacent structures is a definite risk during dissection of the uterovesical pouch and transection of the uterine vessels. Also intraoperative bleeding can result and this usually needs converting the procedure to laparotomy and abdominal hysterectomy.

Place of LAVH

The introduction of laparoscopic assistance of vaginal hysterectomy has in some centers enlarged the indication of vaginal hysterectomy. This assistance allowed vaginal removal of more firmly supported and larger uteri or uteri suspended by adhesion. However, there is still a good deal of controversy about LAVH. This controversy is about the following issues:

1. When to use LAVH: indications.
2. What to do: extent of assistance.
3. Could the whole procedure be completely accomplished vaginally?
4. Lack of sizable data documenting the outcome of LAVH.
5. Safety of LAVH in the hands of a good number of gynecological surgeons other than enthusiastic promoters of the technique is not established.
6. Need for structured, supervised and certified training.
7. Cost of equipment and consumables

Changing Trends in Hysterectomy

This subject will not be again dealt with in this section. It has been covered under previous headings. The discussion should include:

1. Widening the indications of the increasing resort to hysterectomy in benign conditions. Elective hysterectomy.
2. Changing indications: alternative to hysterectomy.
3. Subtotal versus total hysterectomy - changing trend.
4. Abdominal versus vaginal hysterectomy.
5. Removal of the normal ovaries with hysterectomy.
6. Technical improvement, improved safety.
7. Laparoscopic approaches including LAVH.
8. Ethical aspects of hysterectomy.
9. Health-related quality of life (HRQL) after hysterectomy.

Recommended Readings

- Te Lindes Operative Gynecology 8th Edition. J.A. Rock and JD Thompson, Eds Philadelphia, New York Lippincott - Raven, 1997.
- Shaw's Textbook of Operative Gynecology. J. Hawkins Ed. Baltimor, The Williams and Wilkins Company, 1968.
- Clinical Obstetrics and Gynecology - The changing Status of Hysterectomy. T.G. Stovalt Ed. Vol 40 No 4, 1997. Philadelphia, Lippincott - Raven Publisher.
- Operative Gynecologic Endoscopy - Second Edition. J.S. Sanfilippo and R.L. Leine, 1996. New York, Springer – Verlag.

Chapter 28

CONTRACEPTION AND FAMILY PLANNING

Contents

Combined Oral Contraception

Also called combined pills, COCs, OCs, the birth control pills, and the Pill

Contents

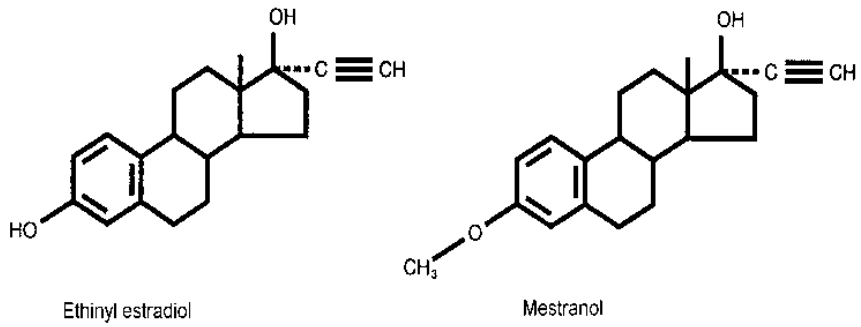
Introduction:

Combined oral contraception was first introduced in the fifties by Pincus, Rock and Garcia. The first contraceptive pill contained a combination of a synthetic progestogen, norethynodrel and a synthetic estrogen, ethinyl estradiol. The progestogens have been shown to inhibit ovulation and the estrogen is added to ensure regular menstrual cycles. The first field trial was done in Puerto Rico; and since then it has gained wide worldwide acceptance and become the most widely used temporary contraceptive. It is estimated that about 100 million throughout the world are using COCs. Over the years, there have been many important changes in the composition and use of these preparations. Most importantly, the content of the progestogen and the estrogen has been markedly decreased, multiphasic formulations marketed and new progestogens introduced. The risk benefit ratio of use of the pill has become better understood. Furthermore women using this method of contraception are now more properly selected than in the past.

Composition

Combined contraceptive pills contain a synthetic estrogen and a synthetic progestogen, in addition to bulking inert substances.

Estrogens

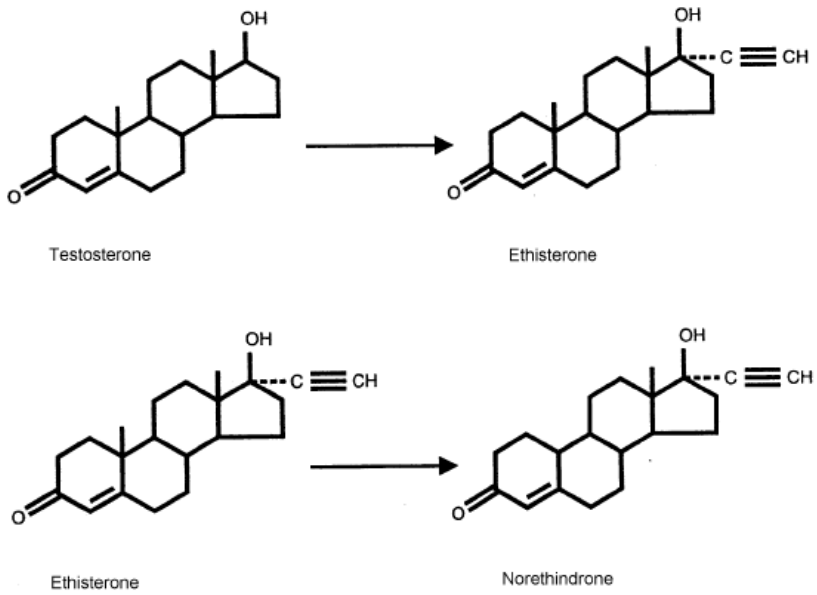


Contraception: Figure 1 structure of Ethinyl estradiol and Mestranol

The synthetic estrogen component of COC is ethinyl estradiol (EE) that is active when taken orally. This is, at least, 20 times more active than the natural estradiol. Few COC formulations contain mestranol, the 3-methyl ether of ethinyl estradiol. Mestranol may be slightly less active than EE and needs to be transformed in liver to EE (Figure 1). Old COC formulations contained 100 ug of EE, but the estrogen content has progressively been decreased to 50, 30, and 20 ug. Most of the preparations available contain 30 or 35 ug of EE. Pills containing less than 50 ug are described as low-dose COCs. Formulations containing > 50 ug are no more available in most parts of the world; they are rarely available in Egypt e.g. Ovral and Anovlar.

The estrogen components of the combined pills serves to 1) suppress FSH secretion thus preventing selection and emergence of a dominant follicle. 2) In addition the estrogen serves to maintain endometrium preventing it's shedding. 3) The presence of estrogen is necessary for progestogen effect.

Progestogens



Contraception; Figure 2: ***Formation of Norethindrone***

Also called progestagens, and progestins. The progestogens used in contraceptive are synthetic steroids, which have some of the effects of the natural progesterone and are active when taken orally. The 19-nortestosterone derivatives are the more commonly used type of progestogens. The removal of methyl group from position 19 of testosterone results in the formation of 19 – nortestorenes(Figure 2). This change result in 1) loss of most of the androgeinc effects of testosterone, 2) acquisition of progesterone-like effects, 3) while keeping some of the anabolic effects of testosterone. 4) Some progestogens have some antiestrogenic and estrogenic effects. Several progestogens have been produced in attempt to diminish the androgenic metabolic effects while enhancing the progestogen properties e.g. gestodene, desogestrel and norgestionate.

Synthetic progestogens used in contraceptive formulations have the following effects in human:

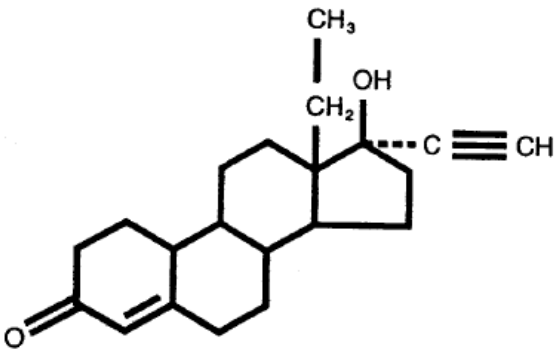
1. Inhibition of ovulation if taken orally on daily basis starting from early in the menstrual cycle and continued for at least 20 days. This effect is synergistically enhanced by the EE concurrently included in the combination pill. Inhibition of

ovulation is evidenced by prevention of mid-cycle LH peak and also the luteal phase elevation of progesterone production.

2. Postponement of menstruation if given to normal women before day 20 of the cycle.
3. Production of some secretary changes in the endometrium. These effects are much less marked than those produced by the natural progesterone. The endometrial cells show subnuclear vaculation but the glandular secretion is not marked. The stroma shows patchy decidual changes. Prolonged administration result in atrophy of the glands. The endometrium is definitely much less prepared to receive a fertilized ovum should this occur.
4. A increase in the viscosity and loss of spinnbarkeit of the cervical mucus; thus rendered less penetrable by sperm.
5. Some of the anabolic effects of testosterone are maintained by 19-nortesterones as mainly evidenced by inducing a decrease in high-density-lipoprotein cholesterol.

The two most widely used progestogens in presently available contraceptive formulations are:

- Norethindrone (norethisterone) and norethindrone acetate.
- Norgestrel, particularly the spacial isomer; levonorgestrel of the racemic ixture (Figure 3).

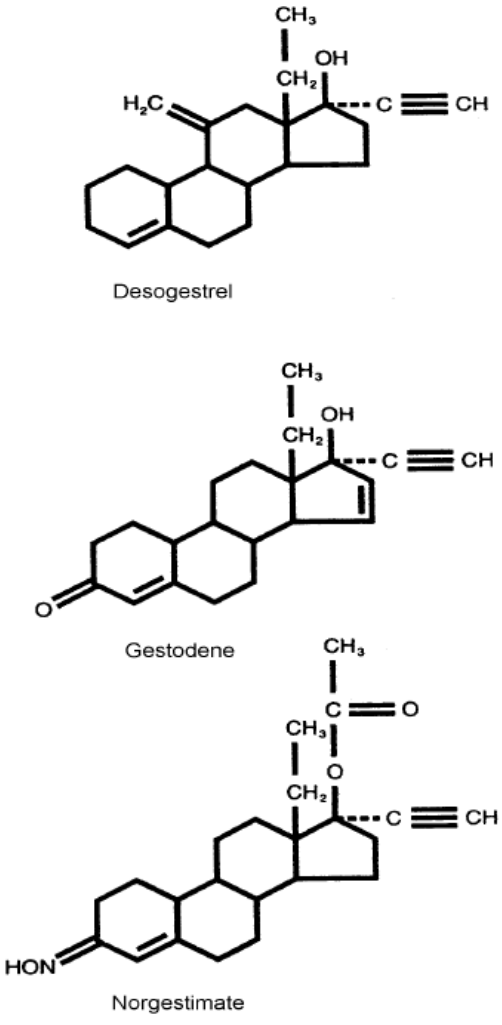


Levonorgestrel

***Contraception: Figure 3** structure of levonorgestrel*

Along with the reduction of estrogen content of combination pill in presently available COCs, there has been a reduction in the progestogen content. For example the norethindrone dose has been reduced from 10 mg down to 0.5 mg, and levonorgestrel from 250 ug to 150 ug (e.g. Microvlar 30, and Nordette containing 30 ug EE plus 150 ug of levonorgestrel). Recently, three newer progestogens have been introduced in contraceptive formulations.

These are gestodene, desogestrel and norgestimate (in the doses of 75 ug, 150 ug and 250 ug respectively) (Figure 4). These newer pills are currently available in the Egyptian market under the brand names of Gynera and minulet (containing gestodene), and Marvelon (containing desogestrel) and Cilest (containing Norgestamate). They are essentially derivatives of levonorgestrel and the third one norgestimate is metabolically converted in vivo into levonorgestrel. These three progestogens are claimed to be less androgenic than levonorgestrel and norethindrone, e.g., producing a more favorable impact on the lipid metabolism. They have been described as "third-generation progestogens". However this designation is not warranted, since they are close relatives to levonorgestrel (all are 19-nor-testosterones); and there has not been any agreement on classification of progestogens in generations. The hopes that they have lower incidence of cardiovascular complications have not, so far, been substantiated in epidemiological studies (see later).



***Contraception: Figure 4** Structure of the new Progestogens*

Types of combined oral contraceptives

1. **Fixed dose regimens (monophasic pills)** contain 21 pills containing similar doses of the estrogen and progestogens. A pill is taken daily starting from the fifth day of the cycle and continuing for 21 days. A menstruation like bleeding will occur few days after the end of the regimen. The next course should begin on the fifth day of this menstruation. Alternatively, the users should leave 7 days after the last pill and start on a new package on the 8th day after the end of the previous packet. This alternative method of use of the pill has the following advantages:

- Making the day of the week on which the user begins on a new packet fixed, and easier to remember.
- The user may not be certain when her menstruation start. Occasionally, the menses starts as spotting, and consequently the beginning of pill use may be delayed.
- Rarely, the long term user misses a period, and if she delays beginning on the next cycle of treatment waiting for the occurrence of menstruation, she can get pregnant (the user should be clearly instructed to begin on the next package after the 7 day interruption regardless of the occurrence of the period; pregnancy is highly improbable if she has been using the pill regularly during the previous cycle).

Some of the fixed-regimen preparations in the market contain 28 pills: 21 active pills and " 7 reminder pill " which are placebos containing no hormones, so that the user will use the pill continuously. The reminder inert pills in some formulations contain iron (advantageous in anemic populations). With these preparations adequate explanation should be given to the user to begin with the first " active " pill usually marked 1, and not with the reminder pills which have a different color. Such type of mistake can lead to inadvertent pregnancy.

2. **Sequential regimen:** In this regimen the first 14 pills contain estrogen only and the last 7 pills contains progestogen in addition to the estrogen. This was in attempt to mimic the natural ovarian hormonal production. This regimen is no longer used; because of higher estrogen dose and slightly lower effectiveness.

3. **Triphasic formulations:** In this regimen low estrogen and progestogen doses are closely adapted to the corresponding phases of the " normal " menstrual cycle. The commonly used triphasic regimens (e.g. triovlar or trinordiol) comprise:
   - Six tablets containing 30 ug EE + 50 ug levonorgestrel (LNG).
   - Five tablets containing 40 ug EE + 75 ug LNG.
   - Ten tablets containing 30 ug EE + 125 ug LNG.

In total, such package contains less progestogen per cycle of treatment but slightly more of EE. The incidence of intermenstrual spotting, break-through bleeding and missing of a period is low and equal to the corresponding incidence with low dose-COCs of the fixed-dose regimens. Both regimens are equally effective in preventing pregnancy. No real merits have so far been shown to use of these triphasic formulations as regard the cardiovascular risks (see below). The low progestogen content is a merit for women with acne, seborrhea or hirsutism. The triphasic pills are sold in the local marked for a price slightly higher than that of comparable levonorgestrel containing fixed dose formulations. Another possible disadvantage of triphasic is that taking pills out of order results in an incorrect dose. This might reduce contraceptive effectiveness and may result in break-through bleeding or spotting.

Mechanism of contraceptive effect

1. Complete prevention of ovulation is achieved if the pill is used correctly. This results from inhibition of normal secretion of gonadotrophins by an action on the hypothalamus and pituitary. The estrogen and progesterone components contribute to this inhibition.
2. The cervical mucus changes is a secondary safeguard should ovulation occur as a result of incorrect use.
3. The endometrium is not suitable for nidation.

The latter two effects are not of a great significance in case of combination pill because of consistent inhibition of ovulation. They can be of a value in reducing chance of pregnancy in women who irregularly use the pill.

Contraceptive Effectiveness

Among women using combined oral contraceptives correctly pregnancy is most unlikely----0.1 pregnancies per 100 women per one year (i.e. 1 in every 1000 users). This is the " theoretical or ideal " effectiveness. In real practice, women sometimes use the pills incorrectly by failing to start them at the proper time, or missing to use them on daily basis or by stopping the intake on the occurrence of spotting or breakthrough bleedings. Consequently, the actual or " use effectiveness " or " typical effectiveness " is much less than the ideal effectiveness. It is in the order of 3 to 8 pregnancies per 100 women per year (1 in every 34 to 12 user). The pills compares favorably with other contraceptive methods (Table 1). The failures are commoner in less motivated groups particularly in developing countries. They may be slightly higher with low dose or triphasic formulation; escape of the pituitary-ovarian axis from the inhibition is more likely to occur upon missing a pill or two.

Table 1:Faliuer rates during the first year of use, United States

Methods	Percent of women with pregnancy	
	Lowest Expected	Typical
No methods	85.0%	85.0%
Combination pill	0.1	0.3
Progesterone only pills	0.5	0.3
IUDs		
Levonorgestrel IUD	0.6	0.8
Copper T 380A	0.1	0.1
Norplant	0.05	0.05
Female sterilization	0.05	0.05
Male sterilization	0.1	0.15
Depo-provera	0.3	0.3
spermicides	6.0	26.0
condom		
male	3.0	14.0
female	5.0	21.0

Advantages of COCs:

1. Very effective contraceptive, particularly when used correctly. By preventing unwanted pregnancies and enabling women to choose the time of births, COCs, like other reliable contraceptive contribute to both maternal and child better health.
2. The use of the pill is under the control of the women. She can stop taking the pills at the time of her choice.
3. No need to do anything at the time of sexual relation.
4. Increased sexual enjoyment resulting from not worrying about occurrence of pregnancy.
5. Can be used by women who have children and by those who do not have children i.e. it is equally safe in nulliparae.
6. Fertility returns soon after stopping. Delay in return of fertility is most exceptional and only occurs in women who are basically subfertile. There is no increased risk of abortion or any congenital fetal abnormality after discontinuation of pill use.
7. Monthly periods are regular. Fewer days of bleeding and lighter periods usually result.
8. Prevent ectopic pregnancy.

9. Spasmodic dysmenorrhea and premenstrual tension syndrome are alleviated. These conditions are features of ovulatory cycles.
10. Can prevent or decrease iron deficiency anemia.
11. COCs use protects the women from developing functional (corpus luteum and follicular) ovarian cysts.
12. COC use lowers the risk of benign breast disease (fibroadenoma and fibrocystic breast disease).
13. Diminish the risk of pelvic inflammatory disease.
14. Diminishes the risk of endometrial cancer. The risk of this cancer is reduced by 50 % after one year of use; and the effect persists long after stopping pill use.
15. Diminishes the risk of epithelial ovarian cancer by 50% after 6 months of pill use; the risk decreased further with longer use. The protection against ovarian cancer persists long(> 10 years) after women stop using COCs.

Disadvantages of COCs:

1. ***Not effective unless taken every day.*** The need to remember taking the pill every day is the main problem in using the pill for some women. Irregular use results in unwanted pregnancy and increases the occurrence of break-through bleeding.
2. ***Common side effects of minor significance***: These include:
    a. Nausea. This is common in the first few months of use; and disappears thereafter; low dose COCs are less likely to cause nausea. If the woman vomits within 2 hours of taking the pills, she should take another pill.
    b. Mild headaches are also expected in the early months of use. Severe headache, severe migraine, blurred vision should indicate shifting to a method without estrogens; such headaches indicate higher risk to cerebral stroke.
    c. Bloatedness is rarely complained of with newer low-dose COCs.
    d. It is caused by some water retention.
    e. Slight weight gain. Some women may find this advantageous.
    f. This partly due to water retention and partly to adding fat.
    g. Mild breast tenderness, usually temporary.
    h. In a few women OC use causes mood changes including depression and less interest in sex. These are usually transient. If they are persistent, the women are shifted to non-hormonal methods.
3. **Changes in menstrual pattern:**

a. The menstrual periods become regular, but tend to decrease in duration and amount. This may be taken as an advantage; it can improve existing anemia. However, these

changes may cause unnecessary anxiety in some women about possible harmful effects resulting from keeping in the body some noxious substances that the body gets rid of in menstruation.

b. Intermenstrual spotting and breakthrough bleeding are expected in about 10% of users during the early months of use. These are particularly noticeable with low-dose COCs but usually disappear after the first few cycles of use. Breakthrough bleeding can be caused by irregular use of the pills. However if a woman has been taking the pill regularly for some time without breakthrough bleeding and then develops intermenstrual bleeding, an organic cause needs to be excluded. This includes assessment of endometrial thickness by VUSG and a diagnostic D&C.

c. Missing a period is a rare occurrence in long-term users of COCs. This results from atrophic changes in the endometrium. The problem is that the user may delay beginning the new packet by waiting for the period, and this can result in occurrence of pregnancy. The user should be instructed to begin with the new packet of pill after the lapse of 7 days after the last pill in the previous packet.

d. Post-pill-amenorrhea may be defined as the absence of menstruation for two months or more after ceasing to take COCs. This is a very rare phenomenon and usually resolves spontaneously. Persistence of amenorrhea is usually associated with other causes like pregnancy, hyperprolactinemia and polycystic ovary syndrome. Post-pill amenorrhea and delay in occurrence of pregnancy is more likely to occur in women who had delayed menarche and oligohypomenorrhea before using the pill. The condition should be managed as any secondary amenorrhea.

e. The use of pills improves primary dysmenorrhea and premenstrual syndrome.

4. ***Not suitable for breastfeeding women***. COCs decrease the quantity of milk and adversely affect its quality. If initiated in the early postpartum month they result in early weaning. These unfavorable effects on lactation are caused by estrogen components and are not seen in users of progestogen-only pills. It has been suggested that low-dose pills may be initiated after the 6 months postpartum when the infant is not totally dependant on the mother's milk. However, even at this stage they can adversely affect breastfeeding and are better being avoided all together during active breast feeding. Another possible disadvantages of using COCs during breastfeeding are the secretion of the contraceptive steroids in the milk. This occurs in very small amounts and the ingestion of them by the breastfed infants have not yet been shown to cause adverse effect on their infants. However, the possibility of subtle effects that can influence future maturation and development of the offspring cannot be ruled out completely.

5. ***Do not protect against sexually transmitted diseases (STDs)*** including AIDS. However, most studies have not established any link between COCs use and the transmission or progress of HIV infection or any other STD. COCs use, on the other hand, have been shown to be associated with diminished incidence of pelvic inflammatory disease which results from upward spread of lower genital tract infection to the tubes, ovaries and peritoneum. Low dose COCs dose not increase the chance of devolving vaginal candidiassies or trichomniasis.
6. The wide and easy availability of the " pill " has ***encouraged, in certain societies, extramarital sexual relations,*** particularly between adolescents.
7. ***Hair loss****:* this is a rare reaction to pill use and indicates, if significant, shifting to one of mechanical methods.
8. ***Acne and seborrhea***: may be accentuated by pill intake. The use of newer formulation containing one of the newer progestogens like gestodene, desogestrel or norgestamate may be of advantage in such subjects.
9. ***Dark pigmentation of the face:*** This is a very rare occurrence that should indicate shifting to a non-hormonal method.
10. ***Breast atrophy:*** This is a very rare occurrence that should indicate stopping of the pill use.
11. ***Drug interaction****:* contraceptive hormones can interact with certain other drugs that OC user may take, reducing the effectiveness of OCs, or changing the efficacy of the other drugs. Pregnancy and breakthrough bleeding may rarely occur due to interference with contraceptive hormones. This can result from activation of certain liver enzymes, which are involved in the breakdown of contraceptive steroids at an enhanced rate.

The following drugs may possibly reduce contraceptive efficacy and predispose to breakthrough bleeding

1. Amidopyrine (aminophenazone).
2. Phenacetin.
3. Anticonvulsant and antidepressant drugs including barbiturates, phenytoin, primidone, carbamazepine and ethosuximide.
4. The antituberculous antibiotic refampin. *The use of other antibiotics like ampicillin, aminoglycosides and tetracycline do not interfere with contraceptive steroids action.*
5. The antifungal drug griseofulvin.

In these cases the COCs use can be combined with the additional use of condom, or the patient is shifted to another contraceptive like the IUD.

On the other hand, oral contraceptives may occasionally alter the dose required for the following group of drugs.

1. Anticoagulants.
2. Tricyclic antidepressants.
3. Corticosteroids.
4. Insulin or oral hypoglycemic.

12. ***Interaction with Diabetes Mellitus:*** *COCs influence carbohydrate metabolism in two ways:*

a. Estrogen increases glucose levels and interferes with insulin action.

b. Progestogens can stimulate overproduction of insulin; hyperinsulinemia is a risk factor for vascular complications. However, low-dose COCs do not initiate diabetes in euoglycemic women. They can be used in patient with short-term uncomplicated diabetes and in women with history of gestational diabetes. The dose of insulin or oral antidiabetic may rarely need to be increased as a result of pill intake. The use of COCs in longstanding diabetics (> 20 years) and in patient with cardiovascular or renal complications should better be avoided.

13. ***Dyslipidemia*** (causing high levels of serum total cholesterol, triglycerides, low-density lipoprotein cholesterol or low levels of high-density-lipoprotein cholesterol) may be enhanced by use of COCs. This condition can, very rarely be familial. Women known as having these abnormalities in the lipogram should better avoid using COCs to obviate an increased risk of cardiovascular diseases.
14. ***Gall bladder disease:*** Epidemiological studies have shown no increased risk of developing gallbladder disease in COC users. However, COCs are better avoided in patients with gallstones since the estrogen may increase the level of cholesterol that can enhance the growth of gallstones.
15. ***Liver diseases:*** Women with past-viral hepatitis can safely use low dose COCs. However, viral carriers or women with active disease are at an increased risk of deterioration of their liver functions on use of COCs and should avoid using them. However, it should be remembered that liver dysfunction is a commonly made clinical diagnosis, usually on no real basis and this should not deprive the women from the benefit of using the pill expect in the are mentioned circumstances.
16. ***Effect on blood pressure:*** both estrogens and progestogens tend to produce a slight increase in blood pressure, with lowest doses having least effects. COC use has been observed to produce a small but statistically significant blood pressure increases but the blood pressure mostly remain within the normal range. Women with moderate or

marked hypertension are better avoid using COCs particularly since hypertension is a risk factor for developing arterial cardiovascular morbidities like myocardial infection and cerebral stroke. Normotensive women, however, do not run increased risk of these conditions on use of COCs and can safely use low-dose COCs up to the age of menopause. If COCs are prescribed to a mildly hypertensive women the blood pressure should be monitored in succeeding months, the pill is discontinued if there is any exacerbation of hypertension.

17. ***Concern about cardiovascular disease (CVD) risk in combined oral contraceptives users:*** Since their early introduction in 1960s, the association of COCs with increased risk of certain cardiovascular complications of thrombotic nature have been suspected and suggested by clinical trials and epidemiological studies. On the arterial side, there has been a reported association with myocardial infection (MI) and cerebral stroke (both hemorrhagic and ischemic); and on the venous side with venous thrombosis and embolism (VTE). Except for VTE these risks were concentrated in older COC users who smoked or who have risk factors for these conditions. These associations were quite rare but have resulted in apprehension towards the pill in the mind of the general public and members of the medical profession. This is due to the fact that the pill users are healthy and should not take any risk whatever minimal in heir contraceptive practice:

    The cardiovascular risks of COCs have been suggested by A) epidemiological studies and B) clinical pharmacology trails:

    A. Epidemiological studies have mainly involved cohort and case-control approaches.

- ***Cohort studies*** compare the experience of women exposed to COCs with that of women not using (but still eligible to use them). The two groups of women are followed forward in time, in order to determine the occurrence of cardiovascular diseases. Since cardiovascular diseases are uncommon in women of reproductive age, cohort studies need to observe a very large number of subjects for a prolonged period of time in order to detect enough cases to allow a meaningful analysis.
- ***Case-control studies*** require the collection of a group of women with cardiovascular diseases (cases), and an appropriate comparison group without these problems (controls), the purpose is to compare the frequency of use of COCs (and other risk factors) in the two groups. Therefore, cohort studies start from a healthy condition and proceed to development of disease, while case-control studies start from the diseased condition and explore the present and past histories of the patients for current and past exposure to risk factors including the use of hormonal contraceptive. Consequently, case-control studies usually require less time and effort.

    In cohort studies, the strength of the association between exposures to a risk factor (in this case the use of COCs) is usually measured in term of *relative risk* (RR). In cohort studies, this can be measured directly by calculating the ratio of the observed incidence rate of disease among exposed individuals to the observed incidence rate in non-exposed control. A relative risk of 1.0 means that the incidence rate in the exposed group is the same as that found in the non-exposed group. Relative risks greater than 1.0 occur when the incidence rate in the exposed group is grater than that occurring

in the non-exposed group; suggesting an adverse effect of exposure. Conversely, relative risks of less than 1.0 result from a lower incidence rate among exposed individuals, implying a protective effect. Case-control studies calculate a different measure of association, the *odds ratio* (ratio of the odds that cases have been exposed to the factor of interest (in this case the use of COCs), to the odds of exposure in the controls which provides an estimate of the relative risk.

In interpreting relative risk values, four points need be taken in consideration:

1. ***The extent of variability of data (spread) around the value of the relative risk.*** By convention, most studies calculate ***the 95 % confidence interval***. This is the range of values within which the effect will be observed on 95 % of occasions if the process for obtaining the data were repeated 100 times. When the 95% confidence interval exclude 1.0, the finding is traditionally thought to indicate significant alteration of the risk; i.e. the RR is thought unlikely to have occurred by chance.
2. A statistically significant association between exposure (e.g. pill use) and the development of disease (e.g., certain type of neoplasia or cardiovascular disease) can occasionally result from: problems in design or implementation of the epidemiological study.
   a. Bias between groups in the process of selecting study subjects and the controls, the extent of recalling the exposure to risk factors (e.g. use of COCs) or the care made in ascertaining of the diagnosis of the diseased conditions. These result respectively in selection, recall, or detection biases.
   b. Confounding effect (effect modification) of other exposures e.g. smoking, age, … etc.

   Epidemiological studies should always try to avoid these bias and confounding effects. If this not possible in the design, their effect should be taken care of by special statistical analysis.
3. ***Absolute (attributable) risk***, measuring the public health importance: an Absolute risk depends upon the size of the relative risk and the underlying incidence of the diseased condition in the particular population exposed. Occasionally the case fatality rate of the disease should also be taken in consideration. For example, if the incidence of venous thrombosis among women using COC is 15 per 100,000 women-years, and the incidence in women not using this method of contraception is 5 per 100,000 women-years, then the attributable or absolute risk is 10 per 100,000 women using oral contraceptive for one year. Given the low case-fatality of VTE of 1 percent, the use of the pill can result in an extra one death due to VTE per one million women exposed to pill use for one year.
4. The risk of the alternative of not using the contraceptive on the occurrence of a disease (for example the risk of VTE) should be considered along with the risk of pregnancy in causing this disease, and the dangers entailed in induced abortion of such pregnancies.

B. Clinical pharmacology trails:

These are prospective controlled trails testing the effects of COC use on certain chosen biological parameters, which are surrogates for cardiovascular diseases. The changes in these parameters have already been known to be risk factors for developing cardiovascular disease.

1. The changes in lipid and lipoprotein metabolism induced by COCs have been taken to represent increased risk to arterial diseases. The latest results of clinical pharmacology trials indicate that low-dose COCs increase fasting triglyceride levels, produce only minor increase on L.D. lipoprotein and total cholesterol. The effect on H.D lipoprotein depends upon the balance of estrogen and progestogen in the pill. Estrogens produce an increase, and progestogen (particularly those with androgenic effects) produces a decrease in this " protective " lipoprotein.
2. COCs alter the plasma contraception of the blood coagulation factors (hemostatic system). These included an increase the procagualtion factors including factors V, VII, VIII. IX. and X (particularly F VII) and a decrease in the antithrombotic factors, antithrombin III, and protein C. These changes are at

least partially balanced by enhanced fibrinolytic activity that is evidenced by a rise in plasminogen and its activators. These changes were less evident with low-dose COCs.

3. COCs cause modest elevations in plasma glucose and insulin response to an oral glucose challenge; and increase insulin resistance. These changes may increase the risk to arterial disease. Their clinical significance in healthy young women is uncertain.

4. Comparative studies of low-dose COCs suggest that the dose and type of the progestogen component influence the effect of the various formulations on lipids and lipoproteins and homeostasis. On the whole contraceptive formulations containing the newer progestogens gestodene, desogestrel or norgestimate have less pronounced biochemical effects than older formulations containing levonorgestrel or norethindrone.

Fortunately, ***recent epidemiological studies have given reassuring indications;*** which can be summarized as follows:

1. Healthy women, who do not smoke, have had their blood pressure checked, and who do not have hypertension, or diabetes mellitus run no increased risk of myocardial infraction upon use of low-dose combined contraceptive pill ***regardless of their age***. Smoking, particularly heavy smoking, and hypertension markedly increase the risk of MI in current COCs users. Past users of COCs are not having increased risk of MI.

2. Similar statements can equally apply to the hemorrhagic stroke. The risk of the less common ischemic stroke is only slightly increased in pill users who are not hypertensive and do not smoke, but the risk is increased by these two cofounders.

3. COCs users have a slight increase in the absolute (or attributable) risk of venous thromboenbolism which is nonetheless three to six fold higher than that in non – users (see before). The risk is highest in the first year of use and declines thereafter, and rapidly disappears after discontinuation of use. The risk of VTE attributed to COCs uses rises with increasing age, obesity and recent surgery. Recently, interest about genetic predisposition to thrombosis in subjects with Factor V Leiden genetic mutation, which is probably the cause of increased resistance to the antithrombotic effect of activated protein C. Oral contraceptive users with this mutation (and the consequent increased thrombotic tendency) have a 30-fold increased risk of venous thromboembolism compared with noncarriers of this mutation using COCs. This genetic mutation has been found to be relatively commoner in certain Western European populations.

The lately improved picture of COCs as regard the cardiovascular risks has resulted from three factors:

1. Effort on the part of clinical epidemiologists in more recently reported studies, to avoid bias in the study design and implantation and to segregate the influence of COC use from that of cofounders like smoking or hypertension.

2. Selective prescription of COCs, and avoidance of their use in women at risk of cardiovascular diseases.
3. Marked reduction of estrogen and progestogen dose contained in the pill; most of the currently used pills contain less than 50 ug of ethinyl estradiol together with low dose of a progestogen.

The suggestion that low dose COC formulations containing gestodene, desogestrel or norgestimate carry a lower risk of cardiovascular risks have not yet been substantiated by epidemiological studies. On the contrary, COCs containing gestodene or desogestrel have been shown to carry a small increase in the risk of venous thromboembolism beyond that attributable to COCs containing levonorgestrel.

18. **Concern about neoplasia in COC users**

There have been concern that the prolonged use of contraceptive hormones might increase the risk of certain types of neoplasia, particularly that of the breast and cervical cancer. There have been plenty of epidemiological reports on this subject, which raised some controversies. The following is a summary of the present position on neoplasia and COCs:

1. The use of COCs results in pronounced and long lasting protection against endometrial cancer (see above).
2. The use of COCs results in pronounced and long lasting protection against epithelial ovarian cancer.
3. On the whole, the current and past use of COCs dose not increases the risk of breast carcinoma. However, the use of COCs by young women (< 35 years) and by nulliparous women may, if prolonged (≥ 5 years) increase the risk of development of breast cancer, particularly the development of the disease in young age. It needs to be remembered that breast cancer in this age group account to only 10-15 % of cases of this carcinoma.
4. Epidemiological results of OC and cervical cancer have been inconclusive
   - A number of studies reported an elevated RR of preinvasive (CIN) cervical cancer in ever-users of COCs, but the RR varied greatly.
   - A slightly increased risk of invasive cancer in ever-users of CO has been reported. However, the confounding effect of a number of influences could not be eliminated as contributing to this slight increased risk particularly the effect of certain sexual behaviors like early beginning of sexual life, multiple sexual partners, and multiple partners of the partner(s). Cervical cancer is increasingly considered as a sexually transmitted disease dependent on contracting sexually transmitted infections e.g. certain viral infections (see under carcinoma of the Cervix).

5. There are reports of increased risk of liver cancer in ever-users of COC in developed countries that are at a lower risk of this disease. It is unclear how these findings apply to developing countries with high prevalence of viral hepatitis; the finding in the developing countries most probably do not apply to locations where hepatitis where endemic. In these countries Hepatitis B is a risk factor for hepatocellular carcinoma.
6. Hepatocellular adenoma is commoner in CO users than in nonusers. The main clinical problem resulting from this tumor is the development of rupture of the tumor with occurrence of severe internal hemorrhage that requires immediate surgery. However, the incidence rate of liver adenoma is extremely rare making the absolute risk extremely low.
7. There are conflicting reports on the association of COCs and development of malignant melanoma varying from 3 fold increase to no increase.

Concluding notes on complications of COCs*: On the whole the presently available COCs are nicely tolerated and safe. The common side effects like nausea, headache and menstrual irregularities are usually mild and temporary. The significant side effects particularly interaction with disease risk or drug action are minimal and questionable.*

Eligibility of use of combined oral contraceptives

In spite of the disadvantages listed above, the pill continues to be the most popular temporary contraceptive worldwide particularly in developed countries.

I. In general most women can use the low-dose COCs after proper counseling even if they:

- Of any age
- Women who are aged 35 or above can safely use low-dose COCs, if they do not smoke cigarettes and are not hypertensive.
- In this age group the use of COCs have the following extra merits.
    1. High reliability; pregnancy in this age group is a most unwelcome occurrence.
    2. The use of COC results in regular menstruation and prevent the occurrence of dysfunctional bleeding which, in this age group, is common, raise suspicion of organic lesions and results in use of more risky hormonal treatments like the use of ethindrone and danazol.
    3. Relieves climacteric symptoms like hot flushes and sweats and vaginal dryness occasionally complained of in the premonopousal women.

4. It remains to be seen whether the prolonged use of combined contraceptive help in protection against postmenopousal conditions like osteoporosis and coronary insufficiency.

- Have no children--------concern that the use of the pill before the first child causes future infertility is unfounded.
- Are adolescent--------the pill the mostly commonly used methods by adolescents in different parts of the world.
- Are fat or thin.
- Smoke cigarettes but are under age of 35.
- Have just had abortion or miscarriage----they can be initiated immediately after evacuation.
- Have iron deficiency anemia.
- Have dysmenorrhea or premenstrual tension syndrome (These improve upon pill use).
- Have benign breast disease.
- Varicose vein, but not history of VTE disease.
- Mild headaches.
- Dysfunctional bleeding-i.e. after exclusion of an organic cause.
- Have Schistosomiasis.
- Have thyroid disease.
- Have diabetes for < 20 years and without, vascular, eye or renal complications.
- Have fibroids.
- Have endometriosis.
- Benign ovarian tumors.
- Pelvic inflammatory disease.
- Past ectopic pregnancy.
- Past trophoblastic tumor.
- Tuberculosis (unless taking rifampcin).
- Family history of breast cancer.
- History of pregnancy induced hypertension.

II. The following list include women who run certain proven or theoretical risks on using the pill **but can still use the low-dose pill if the alternative methods are not available or acceptable:** The advantage of using the pill in these groups of women outweigh the theoretical or proven disadvantages. Generally they need to be kept under observation, which is essentially only a clinical surveillance. The use of COC should follow careful counseling.

- Smokers who are above of 35, if they can be talked in stopping the habit.

- Moderate hypertension < 160/110.
- Are breastfeeding a child more than 6 months old.
- History of jaundice after exclusion of viral carrier state.
- Uncomplicated valvular heart disease.
- History of gestational cholestasis.
- Mild cirrhosis of schistosomal nature.
- Sickle cell disease.
- Epilepsy (see drug interactions).
- Tuberculosis (see drug interaction).

III. The following conditions should represent contraindications for using COCs:

- Heavy smokers above the age of 35.
- Severe hypertension > 160 / 110.
- Breastfeeding women with a child < 6 months old, and women who are keen on preservation of the function of lactation.
- Advanced, long-term or complicated diabetes.
- History of DVT.
- Planning to undergo surgery (within one month time), which will entail prolonged immobilization.
- History of ischemic heart disease.
- Complicated valvular heart disease (with pulmonary hypertension, frequent extrasystoles, history of subacute bacterial endocarditis).
- Severe headache with focal neurologic symptoms.
- History of breast cancer.
- Active hepatitis.
- Severe cirrhosis.
- Patient using anticonvulsants, rifampin or griseofulirn.

Procedural Guidelines in COC use

1. Use of COCs should follow, like other contraceptive methods adequate counseling.
2. Nonmedical providers can be trained to offer low-dose COCs.
3. Start on the first packet any time during menstruation but not later than the fifth day in menstruation. If this not possible provide the client with condoms which can be used until the next cycle.
4. She can start 3 weeks after the delivery if she is not breastfeeding.
5. In the first 7 days after first or second trimester abortion.

6. When shifting from another method: If she is an IUD user start the pills one month before removing the IUD. If she is using injectables begin at the end of the term of efficacy of the last injection without waiting for the occurrence of a menstruation.
7. Begin on the subsequent packet after the lapse of 7 days after the last pill.
8. Regular intake should be emphasized.
9. She should continue on using the pill if she gets untimely spotting or bleeding. She should be told or reminded with the rules of El-estahada (Vide infera) If she complains about the bleeding, she can use an extra pill until the bleeding stops, the extra pills should be taken from another packet. If the irregular bleeding is repeated for more than 3 cycles, investigation for an organic cause should be made. This is particularly needed if the bleeding arises *de novo* after having normal cycling. The possibility of irregular use of the pills should be excluded.
10. Missed pill: If she misses to take one pill she should take the missed pill once she remembers, and then take the pill of the day as usual. If she missed 2 or more in a row she should take two pills on the day she remembers and continue on the packet as usual, but the rest of this cycle should be considered unprotected; the couple may either abstain from sex or the husband uses the condom or any other back up method until she has begun with the next packet. Breakthrough bleeding is expected.
11. There is no need what so ever for periods of rest from using of the pills. This practice usually results in pregnancy.
12. Mention the common side effects like nausea, mild headache, tender breast, spotting and breakthrough bleeding in preuse counseling. Explain the benign nature of such symptoms, and their tendency to disappear spontaneously within 3 months.
13. If she vomits shortly after taking the pill she should take another pill from a separate packet. If she has severe diarrhea for more than 24 hour, she should know that this is not caused by the pill and should continue on taking them while receiving the treatment of her diarrhea, but the couple should use additional contraceptive like the condom for the rest of this cycle.
14. Elderly woman should continue on the pill until she is 52 year old, and then stops; ut the couple should continue on using the condom plus spermicides until menopause is ascertained. The complete absence of the risk of pregnancy can be ascertained only after the having two years of amenorrhea. Alternatively, she can stop the barrier contraception after only one year of amenorrhea; or if serum FSH assays 6 months of amenorrhea shows marked menopausal elevation.
15. A physical examination is not generally required before initiating use of COCs, but careful assessment of clinical history is necessary. However measuring the blood pressure

is advisable in women above the age of 35. There is generally no need for any laboratory test prior to COC use except for ***very few risk subjects*** as indicated above.

16. The users should be encouraged to visit the clinic whenever she has unexpected symptoms particularly frequent headache or bleeding. It is reasonable to provide the users with a 6-12 month supply of pills. At the time of these 6 and 12-months visits the medical history should be revised and the blood pressure is measured (in women above 35 years).
17. There is no need to modify the scheme routinely used for early detection cervical cancer because of use of the pill.

Progestogen-Only Pills: Minipills

Contents:

- Mechanism of action
- Efficacy
- How to use
- Advantages and disadvantages
- Eligibility criteria
- Procedural guidelines

The progesterone-only pills (POP) or Minipills were developed in the early 1970s in response to reports that estrogen was responsible for the thrombotic side effects and for the inhibition of breastfeeding. They are now mostly used by breastfeeding mothers, but can be also used by other women who have other indications for avoiding estrogen use.

Progestogen-only pills contain one half to one tenth as much progestogen as combined oral contraceptives, hence the name minipill. There are two brands of minpills in the Egyptian market: Microlut (30 ug of levonorgestrel and Exlutone (500 ug of lynestrinol) the packet contains 35 such pills. Minipills are taken continuously, with no pill-free intervals between packets.

Mechanisms of contraceptive effects

1. Ovulation is prevented in about only 50 % of cycles of use of POPs. However, when ovulation occurs, the subsequent luteal phase is usually deficient reducing the possibility of implantation of any fertilized ovum.

2. The continuous availability of the progestogen results in thickening of cervical mucus, making it difficult for sperm to pass through.
3. The endometrium is rendered thinner, with inadequate secretary transformation, making it not suitable for implantation, should fertilization occur.

Contraceptive efficacy:

The minipill is very effective when used correctly and consistently during breast feeding (theoretical effectiveness)-0.5 pregnancies per 100 women during first year of use. This figure means less theoretical effectiveness than COCs. However, since minipills are usually used in breastfeeding women who are in a phase of reduced fertility, and since mistakes in pill taking are less likely with minipill because the user takes the same pill every day without break, the use (typical) efficacy is high-about 1 pregnancy per 100 women in first year of use. This means that minipill is more effective than combined oral contraceptive as commonly used (figures on pregnancy rate for minipills as commonly used by women **not** breastfeeding are not available). The minipill is most effective when taken about the same time every day.

How to use

POP is taken one pill every day. Because of the small amount of the progestogen contained, it is to be taken at approximately the same time of the day in order to ensure effective blood level over the 24 hours. POPs, in contrast to COCs are to be taken continuously without an interval of pill-free days between packs of pills i.e. when the user finishes one packet, she should take the first from the next packet on the very next day. This ensures less likelihood of wrong use.

The breastfeeding mother can start using the minipill 6 weeks after childbirth. Initiating use few days after childbirth is not advisable because of fear of interfering with the establishment of lactation. Postpartum women not breastfeeding can initiate taking this pill at any time during the first 4 postpartum weeks. After first or second trimester abortion POP can be started during the first 7 postabortion days. In women having menstrual cycles POP is started during the first 5 days of menstruation, preferably on the very first day. It is generally advisable that women who are not breastfeeding should use an additional contraceptive like barrier methods or spermisides during the first two weeks of minipill use, during which time efficacy is not certain.

At the preuse counseling the women should be told that menstrual irregularities might occur. These can be in the form amenorrhea or untimely spotting or bleedings. The latter is not heavy enough to affect her health, and usually diminishes after the first few months of

use. These menstrual irregularities are less bothersome for lactating women because of irregularities, particularly amenorrhea that result from breastfeeding. The use of POP has been shown to prolong lactational amenorrhea. However, regular menstruation, albeit reduced in amount, are expected in the majority of POP users who are not breastfeeding.

Advantages

1. Progestogen-only pills like other progestogen-only methods can be safely used by breastfeeding women. In contrast to combination pills (COCs) that contain estrogen, progestogen only methods including POPs have been shown not to inhibit milk yield or alter its qualities, or influence the growth, health and development of the breastfed infant. Even, some studies have indicated that the use of POP may increase the quality or improve the nutritional value of the breast milk.
2. POP can be also used by women who have special contraindication for use of estrogen containing contraceptive e.g. women with hypertension or past history of venous thrombosis (see below).
3. Less likelihood than of COCs of causing metabolic changes, like changes in the lipid or lipoprotein metabolism, glucose tolerance and insulin resistance and hemostatic parameter. These lesser effects are due the absence of estrogens and the small amount of progestogen contained in the minipill.
4. Immediate resumption of normal fertility and regular cycling after discontinuation of POPs. This is in contrast to occurrence of few months of delay in the resumption of fertility and regular menstruation after discontinuation of progestogen-only injectables.

Disadvantages

1. The main disadvantage of POP is the likelihood of causing menstrual irregularities (see above). These are more tolerated by breastfeeding women who expect amenorrhea as a result of lactation. Unlike injectable progestogen-only injectables, these menstrual irregularities immediately abate after discontinuation of the use of the minipill; while menstrual irregularities may persist for some weeks or months after discontinuation of the injectables.
2. Slightly lesser efficacy in preventing pregnancy (relative to COCs) in non-breastfeeding women.
3. Less effective in preventing ectopic pregnancy than COCs. This should not be taken as minipill predisposing to ectopic pregnancy. In fact POP diminishes the absolute number of ectopic pregnancies, but in case of contraceptive failure, the ratio of ectopic to uterine pregnancy is higher than the usual ratio in non-contracepting women. This phenomenon

is undoubtedly due to disturbance of tubal function in POP users, which delays the passage of the fertilized ovum along the tube.

4. POP should be taken in approximately the same time in the day. For women who are not breastfeeding, even taking a pill more than a few hours late increase the risk of pregnancy, and missing 2 or more pills increase the risk greatly.
5. Side effects like nausea, headache or breast tenderness may occur but are definitely less common than in COC users. Slight depression, mood change or diminished libido may be occasionally complained of.

Medical Eligibility

Progestogen-only pills contain no estrogens. Many of the criteria that restrict use of combined oral contraceptive do not apply to POP. The minipill ***can be safely used (in addition to all indications of use COCs) by the following groups of women:***

1. Breastfeeding women.
2. Smokers.
3. Women who are mildly or moderately hypertensive (< 180 / 110).
4. History of DVT.
5. Valvular heart disease.
6. Biliary tract disease.
7. Sickle disease; in fact progestogen-only methods may reduce the incidence of sickling crises.

POP are better not be used by women with;

1. History of breast cancer.
2. Present or past ischemic heart disease.
3. Present active hepatitis.
4. History of ectopic pregnancy.
5. Users of drugs as phenytoin, carbamezapine, barbiturates or primidone for epilepsy, or rifampin for tuberculosis, or griseofulvin for tinea infections.

Procedural guidelines in POP use:

- The minipill should be started in the first day of menses and a backup method should be used for the first 7 days. The pill should be taken in the first time every day. If more than 3 hours late in talking a pill, a backup method should be used for 48 hours.
- If a pill is forgotten or gastrointestinal illness impairs absorption, the minipill should be resumed as soon as possible, and backup method should be used for at least 7 days. If 2 or more pills are missed in a row and there is no bleeding in 4-6 weeks, pregnancy test should be obtained.

Progestogen-only Injectable contraceptive (POIC)

Contents

There are two progestogen-only injectables available in the market:

1. **Depot medroxyprogesterone acetate (DMPA)**, 150 mg, known by the brand name *Depo-Provera* (Upjohn pharmaceutical company) given by injection every 3 months (12 weeks).
2. **Norethindrone enanthate (NET EN)** 200 mg, known by brand name *Noristrat* (German Schering AG), given by injection every 2 months (8 weeks).

Evolution of progestogen-only contraceptive injectables

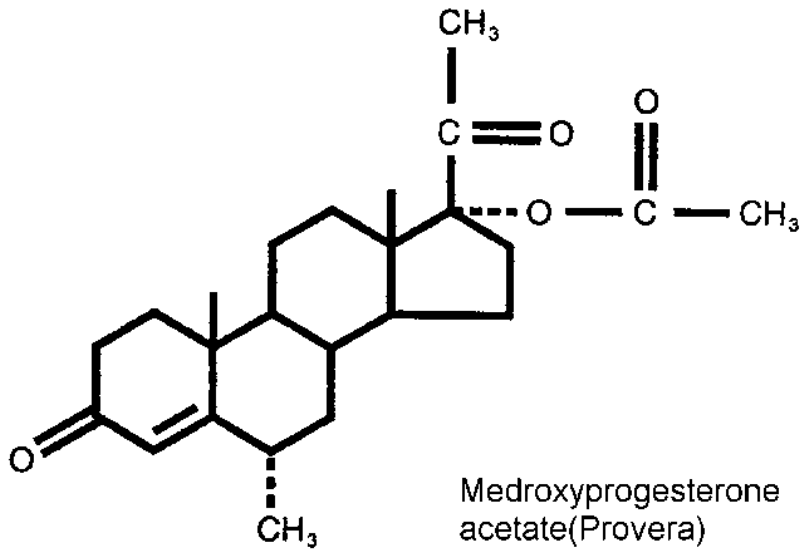
Research on progestogen-only contraceptive injectables began in the late 1960s; motivated by the special use merits of injectables, and by the realization that estrogen component in combined oral contraceptives may cause nausea and vomiting and predispose to certain side effects of thrombotic nature. It has been apparent from the beginning that the progesterone-only injectables contraceptives fulfilled many of goals of effectiveness, reversibility, ease of administration, and non-interference with lactation. However, their wide use in the public sector was delayed because of difficulties in registration of the preparations by regulatory authorities. Notably, the Food and Drug Administration of the USA (the regularity body responsible for registration of drugs in the USA market) denied DMPA approval for many years. This long delay was based on theoretical concerns based on tests of DMPA in beagle dogs and monkeys. Beagles developed breast tumors, and some monkeys developed uterine tumors. This attitude in the USA influenced the attitude of parallel regularity bodies in many developed and developing countries, and consequently the extent of use of these injectables worldwide. However, it has become apparent that results in experimental animals do not apply to man. The World Health Organization extensive and

careful studies demonstrated that the use of DMPA does not increase the risk in women of breast, cervical or ovarian cancer and in fact is protective against endometrial cancer. In 1992 the US-FDA granted approval of DMPA as a contraceptive.

DMPA has now been registered in more than 100 countries including Egypt. It has been estimated in 1995 that injectable contraceptive were being currently used by more than 12 million women world-wide; and its use has been rising since then. Noristrate has been registered for contraception in more than 60 countries including Egypt. Worldwide, DMPA has been more widely used, due to difference in marketing energy.

Formulation of progestogen-only injectable contraceptives

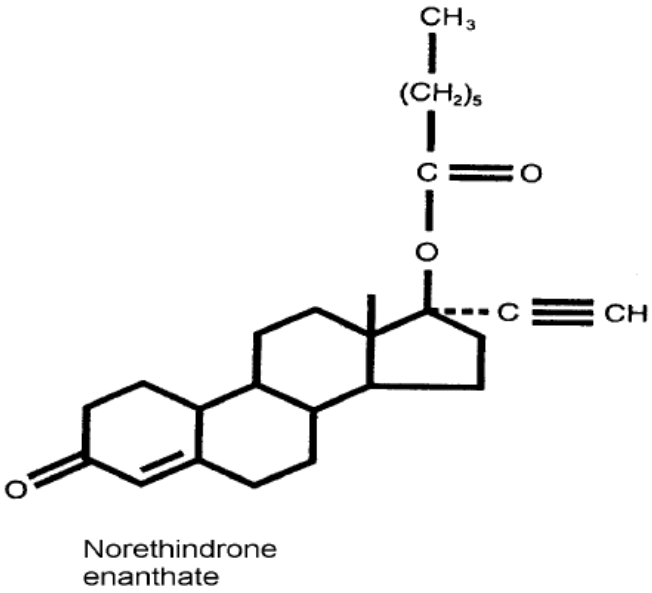
- **Dep-Provera (DMPA)**



Contraception: Figure 5 Structure of Medroxyprogesterone actate

The synthetic Medroxyprogesterone acetate (Provera) is a C21-17 acetoxyprogesterone (17 alpha-hydroxy-6 alpha-methylprogesterone acetate) (Figure 5), whose effects are similar to those of progesterone naturally produced in the body. Provera is a progestogen that has been widely used for many gynecological indications. Depot medroxyprogesterone acetate is an aqueous suspension of microcrystals of provera (DMPA). Deep gluteal or deltoid intra-muscular injection of 150 mg of this suspension results in prolonged availability of MPA in the circulation in levels that ensure effective contraception for 3 to 4 months.

- **Norethindrone enanthate (NET EN)**



***Contraception: Figure 6** Structure of Norethindrone enanthate*

The synthetic progestogen norethindrone (also called norethisterone) is a 19 nor testosterone progestogen (Figure 6), which has been widely used as oral progestogen, and enters in the formation of number of oral contraceptives. Its enanthate conjugate has a prolonged effect when injected intramuscularly. NET EN contraceptive injectable contains 200 mg of this conjugate in an oily suspension that ensure prolonged availability in the circulation of contraceptive levels of this steroid for 2 to 3 months.

Effectiveness of progestogen-only injectable contraceptives

Both DMPA and NET EN are highly effective contraceptives, comparable in efficacy to voluntary sterilization, Norplant and T Cu 380 IUD. The pregnancy rate reported for both formulations is 0.3 pregnancy per 100 women in the first year; the rates are less for subsequent years. The efficacy depends on timely and correct injection. It is equally effective for prevention of ectopic pregnancy.

Mechanism of Action:

- Progestogen-only contraceptive injectables act principally by suppression of ovulation, as evidenced by absence of both the mid cycle LH peak and the rise of progesterone to level indicative of ovulation. Folliculogenesis seems to be inhibited and estrogen production is inhibited; particularly with depo-provera

- Under the effect of these injectables, the cervical mucus becomes thick and impermeable to sperm.
- The endometrium becomes unsuitable for nidation; it gets thinner with scanty glands and shows minimal progestational changes.

Return to fertility

The use of progestogen-only injectables does not cause infertility. However, there can be few-month delay in return to full fertility after discontinuation of their use. Women who discontinue injectable in order to conceive achieves this, on the average, after 9 months of the last injection i.e. 6 months after the end of its effective term. By comparison, women conceive within an average of 3 months after removal of an IUD. This delay of return of fertility after discontinuation of injectable is due to persistent release of the contraceptive steroid from the depot injection site. Amenorrhea and irregular menstruation also persist for several months after women discontinue injectable. There is no difference in time of return of regular menstruation and fertility between long-term and short-term users of DMPA.

Side-effects and complications

1. ***Disruption of regular menstruation:***

This is the commonest side effect, and most important cause of discontinuation of progestogen-only injectable. Women should be informed during preuse counseling that is expected that they will have irregular menstruation. This can be in the form either prolonged, more frequent or untimely bleedings; or long episodes of amenorrhea. ***Only about 10 % of DMPA users have normal cycles in the first year of use.*** With continuation of use of DMPA, irregular bleeding become less common, *but amenorrhea gets commoner*. NET-EN has somewhat less effect on the bleeding pattern than DMPA. There can be regional (possibly ethnic) and personal differences in occurrence of bleeding abnormalities or the percentage of women reporting them. Obese women tend more to have amenorrhea than slim ones.

The extent to which the women are bothered by these menstrual irregularity seems to depend upon the attitude of women towards their menstruation, and upon the quality preuse counseling and the attitude of their treating physicians. When the bleeding irregularities are expected they are better tolerated. Women may fear that the bleeding will cause weakness and anemia. However, this is not expected because the bleedings are generally not heavy enough; though lasting for longer days. Women who get amenorrhea may suspect pregnancy. They should be reassured that this is most unexpected because of high efficacy of injectable contraceptive provided they are timely given. However, the absence of pregnancy can be

reassured to the user by performing a rapid pregnancy test. Women of certain cultures may dislike the amenorrhea because of fear that it represent keeping in the body of noxious substances; they need to assured that this is not the case. On the other hand certain women may appreciate the amenorrhea because of not being bothered by monthly menstruations.

Muslim women may have special cause to dislike untimely and prolonged bleeding days because of the religious attitudes toward menstruation. During menstruation the Muslim woman is not allowed to observe the following religious duties: 1. Prayers, 2. Ramadan fasting, 3) going on pilgrimage, 4) entering a mosque; or 5) or reading (but not reciting) or carrying the Koran. Although she is subsequently required to fast the same number of days she missed during menstruation, she is not required to catch up on prayers she missed. No sexual intercourse is allowed during menstruation. It is not widely appreciated, however, that above rule apply strictly to menstruation (Heid) and do not extend to any other vaginal bleeding whether cyclical or not, and whatever its cause. These non-menstruation bleedings are called in religious text Estehada, which means menstruation like bleeds; and they should not prevent the women from observing the above obligations and functions. The Prophet Mohammad (God's prayer and peace upon him) was careful to clarify this point when he was asked about a woman whose bleeding exceeded her usual days of menstrual bleeding. He advised that she should act according to her own previous " habit " (one of the names for menses in Arabic), and treat the extra days as an Esthada. The woman should abstain only during days equal to her normal menses, then she has the general bodily bath she normally has at the end of her menses, and resume observing all her required functions. However, before each prayer she needs to have a vulval wash and perform Wodooa (the washing of certain body parts normally done before prayers) before each individual prayer i.e. she is not required to have a total body wash for each prayer on the event of occurrence of bleeding. It is even less widely appreciated that the women is sinning if she knows these rules, but does not observe her religious functions during the day of the Esthada. These points may not be clear in the minds of some Muslim women, and their treating physician and other health care providers. These points should be part of counseling women upon the use of methods of contraception that may cause spotting, breakthrough or irregular bleedings.

The management of menstrual disruption associated with injectables. Some women using progestogen-only contraceptive injectable cannot accept frequent bleeding despite counseling about its benign nature. Even if they decide to discontinue using injectables, they have no choice but to continue for several months, until the effect of depot injectable wears off. (In contrast, menstrual disruption end by discontinuation of use of progestogen-only pill (the

minipill) or removal of Norplant implants). Health care providers have used several approaches for treating these bleeding irregularities. However, none of these approaches always works in correcting the problem; in fact, they may not be more effective than simple reassurance, after conducting a careful gynecological examination which exclude an organic cause for bleeding. If estrogens are not contraindicated, combined oral contraceptive can be given for three weeks. These may be repeated after one-week interval. Anti-inflammatory drugs (except aspirin) for 10 days can be of help in some cases. Ibuprofen and other nonsteroidal anti-inflammatory drugs block the synthesis of prostaglandins, which may be inducing bleeding. Giving the next injection of DMPA or NET EN early can temporary reduce bleeding among women who want to continue despite bleeding problems? Injections generally should however, not be given sooner than four weeks after the previous injection.

Women with heavy or prolonged bleeding-twice as much or twice as long as usual for them are exceedingly rare. In these a D & C is needed to reduce the blood loss. Histopathological examination should be done if an organic cause is suspected.

Giving COCs to induce bleeding in amenorrheic DMPA user is not recommended, reassurance should be enough. Shifting from one brand of progestogen-only injectable to the other does not correct the menstrual pattern.

In menstrual disruption prove unacceptable; the women should be shifted to another method of contraception e.g. IUD or COC at the end of the time of effectiveness of the last injection. The women should however be informed that the menstrual irregularity which has been caused by the injectables can persist for some months after their discontinuation. During this time she should continue with her new method despite of persistence of bleeding irregularity e.g. she should use COC on the three weeks on, and one week off schedule.

2. ***Delay in return to fertility (see above).***
3. ***Weight gain.***

Most users of injectables gain weight. On the average, DMPA users gain 1.5 to 2.0 kg in the first year. Some users (not all) may continue to gain weight thereafter at about the same rate. Such women should be advised to be careful with their diet. The reason for weight gain is unclear. The extra weight is mainly from fat rather than water retention (which is contributing to occasional weight gain in COC users). Adding weight can be an effect of getting older. The attitude towards weight gain is personally and culturally determined, for some women it may be an asset. Weight gain can be a cause some women to discontinue the use of injectable.

4. ***Headaches and Dizziness*** is complained of by 5 to 20 % of users; they are usually mild and tolerable. However headache and/or dizziness can cause discontinuation of progestogen-only injectables (in 1 to 2 % of clinical trials). There is however, no medical

reason for women to discontinue injectable because of headaches, unless the headaches are severe or associated with focal symptoms like difficulty in seeing, speaking or moving. Such few women are predisposed to cerebral stroke and should be immediately shifted to use of non-hormonal methods of contraception.

5. ***Concern about effects or lipid and lipoprotein metabolism.*** DMPA and NET EN increase the levels of total cholesterol and LDL cholesterol and decrease HDL cholesterol. LDL cholesterol has been linked to atherosclerosis, while HDL cholesterol reduces this risk. Atherosclerosis is a major cause for coronary insufficiency (heart attacks and stroke). There is little epidemiologic evidence, however, that current use of injectable contraceptives causes increased risk of these cardiovascular disease.
6. ***Concern about effect on bone density***

   There is a concern that prolonged use of DMPA may reduce bone density through causing a prolonged state of hypoesrogenemia. Such bone depletion will not have an immediate effect but may result in low bone density after the menopause that predisposes to minimal-trauma fractures. Concern has been centered on the prolonged use of DMP by young women (< 20 years old), at the time of maximal gain of bone mass. Results of bone density studies have so far yielded conflicting results as regard bone depleting effect of prolonged DMPA use. The bone density on old age and the occurrence of osteoporosis after menopause are influenced by a number of factors including ethnicity, diet, and bodily activities. So far, no concrete data are available to warrant a change in policy of use of DMPA on the basis of this concern about bone density.
7. ***Concern about effect of progestogen-only-injectables on cancer risk***

   This concern is mentioned here in order to negate:

   (Most of available data were obtained on use of DMPA; no comparable data are available on less widely used NET EN).

   a. *Breast cancer:* An effect of DMPA use on risk of breast cancer has been given a special importance because: 1) the studies on beagle dogs which had shown that the use of DMPA resulted in development of breast tumors; and 2) breast cancer is the second common cancer in women (after skin cancer). Big epidemiological studies have found no overall increased risk of breast cancer among women using DMPA. However, young women faced a slightly but significantly increased risk of breast cancer (PR = 1.4) and mainly during the first 5 years after starting use of DMPA (i.e. if women had not developed breast cancer within five years after starting DMPA, they faced no increased risk). This pattern of increased risk in recent users but not in users during the distant past suggests that DMPA may speed up the growth of existing tumors rather than turn normal cells into cancerous cells. Since breast cancer

is relatively rare in women below the age of 40 years (15 % of all cases), the public health consequence of the slightly increased risk to breast cancer in young recent users of DMPA should be small, estimated to be an increase of an average of 1.3 cases per 100,000 women per year. Therefore, these findings do not justify restriction of DMPA use or even warning prospective users on this possibility during counseling. The use of DMP suppresses fibrocystic hyperplasia and the other related benign breast conditions.

b. *Endometrial cancer:* DMPA use produces a protective effect against endometrial cancer (i.e. a RR = 0.2), which last for many years after discontinuation of use.
c. *Cervical cancer:* Epidemiological studies controlling for sexual behavior of women and their sexual partner have shown no increased risk of invasive cervical carcinoma.
d. *Epithelial ovarian cancer:* No association was found between use of DMPA and epithelial cancer of the ovary. A protective effect similar to that resulting after use of COCs has not been demonstrated for DMPA. This is surprising since DMPA, like COCs act by suppression of ovulation.
e. *Liver cancer:* No increased risk has been demonstrated.

8. ***Effect on fetal and child development:***

A fetus could be exposed to contraceptive hormones in the very rare event that injectables fail to prevent pregnancy, if a women receives an injection while pregnant, or if a women become pregnant shortly after discontinuation the method (but hormones are still in the bloodstream). Studies on the effect of fetal exposure to this progestogen have reported no increase in congenital abnormalities or interference of subsequent development of the resulting child. Consequently, there is no solid basis for termination of such inadvertent pregnancies by induction of abortion.

Advantages of progestogen-only injectables

1. Highly effective.
2. Long-term effect; one action, having the injection causes contraception for 2-3 months.
3. No need to take a daily decision as entailed in using COCs.
4. Administration by injections may be more acceptable in certain culture, which value this route of administration over taking medication by mouth.
5. Failures due to incorrect use less likely than with COCs.
6. A leeway (grace period) of two weeks in case of DMPA and, one week in case of NET EN is affordable i.e. variation in the timing of repeat injection will not result in failure; allowing some flexibility in use.
7. Does not interfere with sexual relation.

8. The quantity and quality of breast milk do not seem to be affected. Both types can be used safely during breastfeeding. No effects on use of DMPA or NET EN by lactating mothers have been demonstrated upon the growth, development or health of breastfed infants. On the contrary, some studies reported positive effects on such infants (greater increment in infant weight).
9. No estrogen side effect: Progestogen-only injectables obviate the risks of estrogen-related complications like myocardial infraction, stroke and thromboembolism. Smoker aged above 35 years can safely use DMPA or NET EN.
10. Prevent ectopic pregnancy.
11. Non-contraceptive health benefits including:
    a. Prevents iron deficiency anemia. Due to an overall diminution of the amount of menstrual blood loss; blood hemoglobin levels in DMPA or NET EN users tend to increase.
    b. Fewer and less severe sickle-cell crisis.
    c. May make epileptic seizures less frequent.
    d. May reduce the risk of PID.
    e. Helps in prevention of pelvic endometriosis and may make symptoms of existing disease less severe.
    f. May check development of existing fibroids.
    g. Decreases the risk of endometrial cancer.

Disadvantages of progestogen-only injectables

1. Common side effects (see above).
    a. Menstrual disruption.
    b. May cause weight gain.
    c. May cause mild to moderate headache and or dizziness.
2. Requires more careful and caring preuse counseling and support of users in order to keep them using injectables despite menstrual irregularities.
3. Delay in return of fertility (see above).
4. Requires repeated injections every 2 or 3 months.
5. Does not protect against STDs.
6. May result in transmission of hepatitis virus (and other viruses) in case the same syringe is reused.

Eligibility

- ***Progestogen-only injectables can be used by most women even if they are:***
    1. Breastfeeding.

2. Regardless of their age.
3. Childless.
4. Fat or thin.
5. Smoking.
6. History of or present mild or moderate hypertension.
7. Uncomplicated or complicated valvular hear heart disease.
8. Recurrent headache (with no focal neurological symptoms).
9. History of ectopic pregnancy.
10. Varicose veins.
11. Deep venous thrombosis (present or past).
12. Sickle cell disease.
13. Schistomiasis and schistosomal.
14. Uterine fibroids.
15. Epilepsy.
16. Tuberculosis.
17. Uncomplicated diabetes: However, the dose of insulin may need readjustment.

- ***Progestogen-Only injectables can be used in the following circumstances if alternatives are not available or acceptable***; the advantages outweigh the theoretical or proven disadvantages:

1- Women with heavy menstruation.
2- Women < 16 years old.
3- Severe hypertension.
4- Complicated diabetes mellitus.
5- Liver cirrhosis.

- ***Progestogen-only injectables should better not be used in women with:*** (The following apply to all progestogen-only contraceptives).

1- Suspected pregnancy.
2- Breastfeeding women less than 6 weeks postpartum. There are concerns that the neonate may be a risk of exposure to steroid hormone during the first 6 weeks of life, or that they may interfere with establishment of lactation.
3- Current and history of ischemic heart disease.
4- History of stroke.
5- Severe headache with neurological focal symptoms.
6- Current or past breast cancer. Breast cancer is hormonally sensitive tumors.
7- Benign or malignant liver tumors.
8- Active hepatitis.

9- Using anticonvulsants.

10- Undiagnosed vaginal bleeding.

Procedural Guidelines

1. ***Preuse counseling:***

- Careful counseling about injectables and other progestogen only contraceptive should precede their initiation. Besides emphasizing the advantages of the method the, high likelihood of menstrual irregularity should be made clear to prospective users. If they expect the irregularity, their reaction to them is better. Prospective users of the injectables should be told that there could be a delay of 3 to 6 months in the return to fertility after discontinuation of the injections. This does not apply to prospective users of POPs and Norplant in whom no such delay occurs.
- The users should be encouraged to come to the clinic whenever she has any complaint. Users of progestogen-only-contraceptive generally require more reassuring care during use, they require " a service that cares " to ensure continuation of use (see above).

2. ***When to start***

- Any time it is reasonably certain that the women are not pregnant. It may an advantage in public practice to begin during the first 7 days of the menstrual cycle.
- In breastfeeding women the use can start 6 weeks postpartum. Fully or nearly fully breastfeeding effectively prevents pregnancy for up to 6 months provided menstruation has not been resumed (see under LAM). In such women progestogen-only contraceptives can be initiated any time if they choose to have extra protection. The progestogen-only contraceptive can be begun any time if the three requirement of LAM, the chance of her being pregnant at that time is very low. If one of the terms of efficacy of LAM has expired, P-O-contraceptive is initiated within the first 7 days after beginning of the menstruation.
- If the woman is not breastfeeding progestogen-only contraceptive can be initiated immediately postpartum or at any time during the first 6 weeks postpartum.
- Immediately after an abortion.
- Immediately at the time of stopping other method e.g. removal of an IUD.

3. ***Giving the injection***

- A 2 or 5 ml syringe and a 21-23-gauge intramuscular needle is used.
- Disposable syringes and needles are better used. If disposable syringes are not available, reusable syringes needles and syringes can be used provided they have been properly sterilized. New, one-use delivery system; UniJect and autodestruct syringes may simplify infection prevention. The unique feature of UniJect is a plastic blister that

is filled with the medication. The provider presses the blister to deliver the medication through the attached needle. UniJect has a one-way valve between the needle and blister that prevents it from being refilled and reused. Use of UniJect systems may entail an affordable increase in service delivery cost.

- The injection is made deep in the upper arm (deltoid region) or in the gluteal region. The site of the injection should be not massaged; this may result in a rapid absorption of the steroid.
- Give the client a card giving the data of next injection, but encourage her to come to the clinic whenever she develops any unexpected symptom.
- No extra contraception is required in the early days of use of injectables or Norplant. However, this required during the first 2 weeks of use of POP by non-lactating mothers (see above).

Follow-up visits

This to ask for and manage side-effects (see above).

- The next injection should be given in time. However, there is an affordable leeway (grace period) of 2 weeks in case of DMPA and of 1 week in case of NET EN. Longer delay in taking the next injection increase the chance of contraceptive failure.

Combined Injectable Contraceptive (CIC)

Contents

Formulation

Combined injectable contraceptives (CIC) contain a natural estrogen plus a progestogen, and act through inhibition of ovulation. Two formulations have been widely tested (mainly in WHO sponsored trials) as ***monthly injectables:***

1. Cyclofem = medroxyprogesterone acetate (DMPA) 25 mg plus estradiol cypionate 5 mg.
2. Mesigyna = norethindrone enanthate (NETEN) 50 mg plus estradiol valerate 5 mg.

The estrogen used in CICs results in approximately physiologic dose of " natural " estrogen (estradiol), as opposed to synthetic estrogen (ethinyl estradiol) used in combined oral contraceptive (COCs). The estradiol released from both CIC formulations is present in the body for only the first 8-11 days of the month and has a concentration in the range of the normal menstrual cycle. Because the estrogens in the CICs are more physiologic, have a shorter duration of action and are less potent compared to the synthetic estrogen in the COCs, the type and magnitude of estrogen-related side effects, and metabolic changes associated with CICs may be different from those occurring in COC users. However, while the effect of the hormonal load associated with COCs and POP use can be reduced immediately by discontinuation of their use, this is not the case with CICs, whose effect continues for some time after method discontinuation.

Evolution of Combined Injectable contraceptives

The development of monthly CICs has been encouraged by the desire to combine 1) the merits of administration of contraceptive by long-term injections to, 2) insurance of monthly menstrual bleedings as that occurring with the use of COCs. The development of CICs began in the late 1960s and involved a number of pharmaceutical companies notably Squibb, Upjohn, and Schering companies; and the World Health Organization. Clinical trails of the above two formulations: Cyclofen and Mesigyna have been conducted in a number of countries including Egypt. They demonstrated high efficacy, reasonable menstrual cyclicity and good acceptability. One or both preparations have been approved for use in a number of countries including China, Latin American countries, Thailand and Indonesia and Egypt (Mesigyna has been approved)

Contraceptive Effectiveness

Monthly injectables are highly effective giving a failure rate of 0.2 or less pregnancies per 100 women per year. The effectiveness of CIC depends on the timing of the first injection and adherence to the injection schedule. The first injection is better to be given during the first 7 days of the menstrual cycle, but can be given at other times if it is certain that the woman has not already conceived. The grace period of the repeat injections is much shorter than with POICs; the repeat injection of a CIC should not be later than 3 days after the monthly appointment. If the user comes any later, the provider must be reasonably sure that she is not pregnant before giving the next injection. Client may have the repeat injection 3 days earlier.

Mechanism of action of CICs

Combined injectable contraceptives act principally by inhibition of ovulation. An added protection is caused by cervical mucus changes and the incomplete secretary changes in the endometrium. The return of fertility is expected to be slightly delayed after discontinuation of the injections, i.e. the delay is far a much shorter than the delay in return of fertility after the discontinuation depot progestogen-only injectables.

Changes in the menstrual cycle

With monthly injectables, women tend to have better bleeding pattern than with the use of progeston-only injectables. About half of women have regular bleeding during the first year of use. Users tend to have irregular or prolonged bleeding in the first three months and then increasingly regular patterns by the end of the first year. In particular, the first bleeding interval may be shorter than usual. With monthly injectables, most women have bleeding 10 to 15 days after the first injection and then every 30 days after that. Thus women tend to have regular bleeding 10 to 15 days after each injection at the time of waning off of the estradiol effect. There is no difference between the bleeding patterns associated with the two types of monthly injectable.

Advantages of monthly CICs:

1. Highly effective.
2. Reversible.
3. Injections are more acceptable in certain cultures.
4. No need for daily decision to take the medication. This makes use-failure less likely.
5. The estrogen contained is natural estradiol that is less likely to result in estrogen related side effects. There is lesser incidences of nausea, headache, and weight gain than with COCs and POICs.
6. The metabolic changes e.g. changes in lipogram and coagulation parameters are less marked than in users of POICs and COCs.
7. Reasonable and more acceptable bleeding pattern than that in users of progestogen-only contraceptives.

Disadvantages of monthly CICs:

1. The need to take a monthly injectable.
2. The shorter grace period (relative to POICs).

3. Menstrual irregularity, particularly during the early months of use.
4. Not suitable for breastfeeding mothers. The estrogen content may changes the quantity and quality of breast milk.
5. Does not protect against STDs.

Eligibility:

CICs are relatively new contraceptive method, and there is little epidemiologic data on their long-term effects. In spite of the fact that estrogen load to which the body is exposed in users of CICs is less relative to users of COCs, it is wiser at the present time, to extrapolate the medical eligibility criteria of COCs to CICs.

Intrauterine Contraceptive Devices (IUD)

Contents

- Evolution
- Widely used methods and their methods of insertion.
- Mechanism of action
- Continuation of use
- Side effects and complications
- Advantages and disadvantages
- Procedural guidelines
- Eligibility criteria

It is estimated that IUD is the second most commonly used reversible family planning method after the COCs worldwide. In different part of the world, the IUD is number one method, and its use is rising. In Egypt it is the most popular method of contraceptive. It has a long-term effect and is the least expensive method to use.

Evolution of the intrauterine contraceptive devices

The idea is old, the Arab nomads used to insert date seeds in the uterus of the female camel during long journeys to prevent them getting pregnant. In the 1920s Grafenberg of Germany introduced the first IUCD in clinical practice. It was in the form of a spiral ring made of silver-copper alloy and had no tail. The use of this ring resulted in serious

complications mainly, bleeding, pain, perforation., pelvic infection and intestinal obstruction. These, besides the need for operative removal have resulted in bad reputation of the IUCD, and the practice was condemned.

The idea was revived in the early 1960 by the use of the biologically inert plastic: polyethylene and provision to the device of a thread tail that allows easy removal. Many shapes for IUCD were tried, including the loop (Lippes loop), the spiral (Margulis spiral), double spiral (Saf-T. coil), the bow (Brinberg Bow), the shield (Dalcon shield) and the T-shaped. In the early stages emphasis was on increasing the area of contact of the IUD with the uterine wall. This was best ensured in the Lippes loop which had the lowest pregnancy and expulsion rate, but suffered from high incidence of bleeding and pain. In contrast the T-shaped device had less incidence of bleeding and pain but had a high pregnancy rate. The loop dominated the field during 1960s and early 1970s and the loop has become synonymous to the IUCD and was widely used worldwide. Nowadays it is rarely used after the introduction of medicated, mainly the copper carrying IUD.

In the late 1960s researcher discovered that adding copper to a plastic IUD frame increased contraceptive effectiveness. This enhanced the effect of small IUD like T-shaped and 7 shaped IUDs. The first copper IUDs--the Cu – 7 (Grave Gard), and T Cu – 200 (T Cu 200) proved to combine reasonable effectiveness (2-4 pregnancies per 100 women-years) to fewer side effects such as pain and bleeding. These IUD gained wide popularity during the 1970s. It was thought however that these IUDs would have to be replaced every few years.

In an attempt to enhance the efficacy and prolong the term of effectiveness, the surface area of the plastic frame covered by copper was increased from 200 mm2 (as in Cu 7 and T Cu 200) to 380 mm^2. Therefore, a second generation of copper IUDs was developed including the T Cu – 380 A, the Multiload – 375 (ML Cu 375) (see below) and others. The expectations were proved: these IUDs are more efficient (failure rate of less than 1 per 100 women/year) and a long-term effectiveness of 10 years or more has been ensured. The T Cu 380 A has gained a wide popularity particularly after international donor agencies have subsidized its availability in developing countries

Another type of medicated IUD have been introduced in 1970s, and 1980s, namely the hormone-releasing IUDs which constantly release small amounts of progesterone or a progestogen, levonorgestrel (LNG) in the uterine cavity. By exerting a local effect on the endometrium and the cervical mucus such steroids enhance the efficacy of the carrier frame. The vertical limb of the T is surrounded by a steroid-containing cylinder; the wall of the cylinder is made of a rate-controlling membrane made of a material (Silastic) similar to the one used in Norplant capsules. Progestasert, released progesterone at a rate of 65 ug per day for one year. The high price and the need to yearly replacement resulted in limited use of progestasert; it is no longer avialble. The LNG--20 IUD contains 52 mg of levonorgestrel,

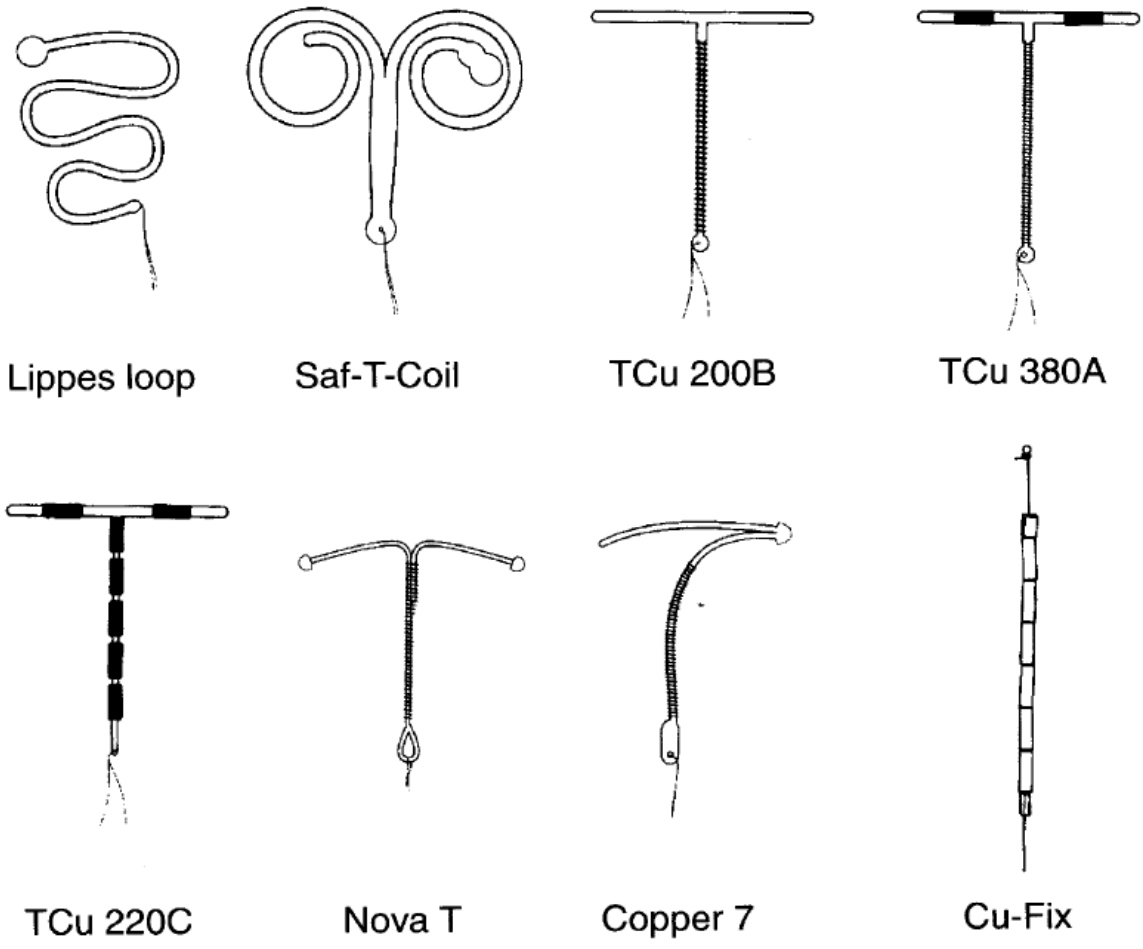
which is released at a rate of 20 ug per day, and lasts for five years. The LNG 20 IUD has already been approved in a number of countries (Merina). It is, at least as effective as T Cu--380 A. Due to local effect of the IUD on the endometrium its use results in decrease in the amount of menstrual flow and amenorrhea. This is an advantage over the T Cu 380 particularly in women who are having heavy periods or who are anemic. This LNG 20 IUD (occasionally called intrauterine system) has been found to be effective in treating menorrhagea. However, women may not like the amenorrhea (if not properly emphasized in the initial counseling) and can ask for removal because of this occurrence.

Research continues to develop new IUDs that may reduce expulsion rates and side effects. Among the devices being considered are the frameless IUD consisting of six copper sleeves carried on a surgical nylon thread, which is called Flexi-Gard 330 and Gyne-fix. The upper end of the surgical nylon thread has a tiny knot. This knot is driven in the inner layer of the myometrium of the fundus during insertion with a notched needle that works like a miniature harpoon. The device has no frame, hence it is flexible, and is expected to cause no irritation of the uterus, and therefore results less incidence of bleeding, pain, and less PID. Due to fixation to the fundus and small size, this device is rarely expelled. The effect of such IUD depends upon the effect of copper ions released from the 330 mm^2 of copper surface in the uterine cavity. Clinical trials have been promising, and the use of generics has been approved in the European Union.

Widely used Intrauterine Devices and Their Methods of Insertion

1. **Lippes Loop** (Figure 7): It is an un-medicated IUD which has been be the most widely used IUD in the 1970s, but is now giving place to T Cu 380 A. Lippes loop has the form of two compressed letters of S, and has a triangular external outline. It is made of polyethylene with barium sulfate added for the sake of visibility on X-rays. Four sizes are available designated as A through to D in order to suite the varying length of uterine cavity. It has two strings. It is inserted by push-out technique: The device is aseptically threaded into the *lower* end of the plastic insertion tube. The latter have a fixed shoulder that will hold at the external os while allowing the tip to reach above the internal os. The loop is transferred to the uterine cavity by pushing by a plunger. The duration of efficacy is unlimited.
2.
3. **T Cu 200 and Gravi-Gard:** (These have been replaced by T Cu-380 A).

Figure 7: Types of IUD



Source: Speroff and Darney (1992)

Contraception: Figure 7; Different types of IUD.

4. **T Cu 380A IUD**

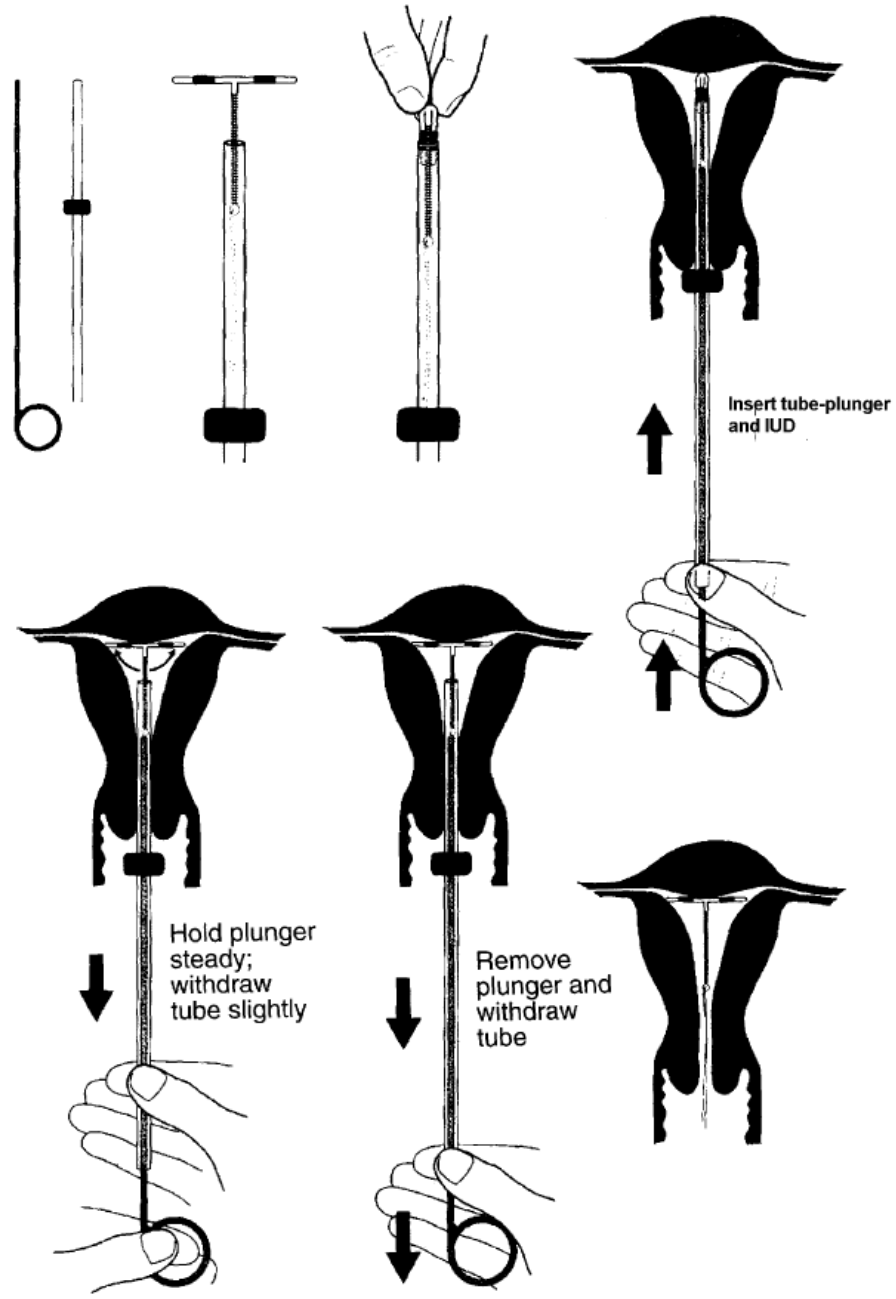
This is the most widely used IUD worldwide. It is made of a T-shaped frame of polyethylene with barium sulfate added for visibility on X ray. It has a fine copper wire wound around the vertical stem with two solid sleeves in each transverse arm. The total area of the T covered by copper is 380 mm^2 (hence the name). The stem has a ball at it lower end and two attached threads. A variant of T Cu 380 is the T Cu 380 slimline (T Cu 380 C) in which the copper sleeves are placed at the end of the arms and are recessed into plastic instead of covering upon. The slim transverse arm is easier to load in the inserter. This variant has not yet been proved to be better than the original version.

T Cu 380 has been approved for use for duration of 10 years

T Cu 380 A is inserted by the withdrawal method (Figure 8): The following steps need be strictly followed:

1. Proper counseling to develop a joint user/ provider agreement to use the method. The method of insertion should be explained to the patient. If it is expected that the client is apprehensive a tablet of prostaglandin synthetase inhibitor like ibuprofen is given 30 minutes before insertion.
2. Infection-preventive procedures should be followed: including 1) Use of high level disinfected instruments, 2) wash hands with disinfectant and wear a sterile glove. Alternatively a non-touch technique insertion is used (The IUD is loaded into the inserter while both are still in the sterile package in which it is supplied). 3) The cervix and the vagina are cleaned several times by water-based antiseptic e.g. Betadine. The sterile sound and tip of the inserter should not touch the vagina.
3. Bimanual and speculum examination. The bimanual examination determines the size, position, consistency and mobility of the uterine and identifies any tenderness, which indicate PID (a contraindication for insertion). A retroverted uterus requires special care.
4. While gently pulling on the cervix (in order to diminish the angle of flexion), carefully insert a uterine sound to determine the direction and the length of the uterine cavity.
5. Loading of the IUD in the *upper* end of the inserter. The IUD is supplied in a sterile package with the longitudinal stem of the T already in the inserter. The arms are bent into the tip of the inserter. Usually this can be accomplished through the covering of the package before, or after it is opened (no-touch technique). After opening the package the plastic shoulder is moved down the insertion tube to a length from the tip equal to the length of the uterine cavity. The shoulder should be oriented in the same plane as that of the transverse plane of the IUD. The plunger is passed up the inserter tube until it touches the ball at the end of the vertical stem. This latter step ensures fundal placement when the IUD is released in the uterine cavity.
6. The loaded inserter tube is passed into the uterine cavity (again while pulling on the cervix) until it reaches the fundus. The shoulder is oriented to conform to the transverse plane of the uterus; this will ensure releasing the T in the transverse plane of the uterus, which is the proper orientation. The insertion tube is then withdrawn while the plunger is held steady, this will release the IUD into the uterine cavity without any pushing. The plunger needs then to be withdrawn before the inserter tube is pulled out. This will avoid pulling down on the threads that may occasionally get entangled between the tubal wall and the plunger. This methodology of inserting the IUD ensures fundal placement and diminishes the chances of perforating the uterine.

7. All the steps should be exercised slowly and with care in order to ensure proper placement and avoid perforating the uterine wall with the inserter.
8. The two threads are then shortened.
9. The patient should be informed of the possible occurrence of slight post insertion bleeding and of relatively heavier periods in the first few following cycles.

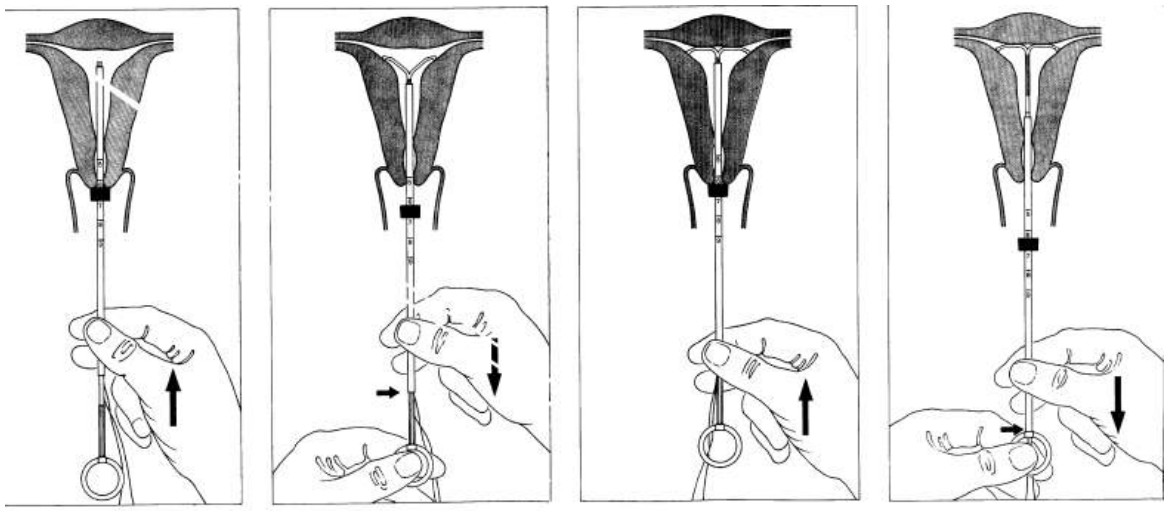


Source: Speroff and Darney (1992)

Contraception Figure 8: ***withdrawal technique of IUD insertion***

4. Nova T and Cu Nova T

This is made of polyethylene with barium sulphate added. It has soft arms each ending in ball, which is thought to fit in the uterine cornu. Nova T has 200 mm^2 copper wire with silver core which, is wrapped around the vertical stem (the addition of silver was claimed to diminish the possibility of breaks in the copper wire). CU Nova T has 380 mm^2 wire wrapped around the stem. The Nova T has been approved for use for 5 years. This IUD is inserted by withdrawal approach (as above). The difference is that the transverse limbs are loaded into the inserter tube by pulling down on the two long thread tails that are projecting beyond the lower end of this tube. This makes the no-touch loading of the IUD into the insertion tube easy. Another difference in the insertion method is that after the tip of the loaded inserter has touched upon the fundus, it is slightly withdrawn down for few mms to allow the emergence of the transverse arms upon withdrawal of the inserter tube. In order to ensure fundal placement the inserter tube is then pushed back to touch the fundus again. The inserter is further withdrawn to allow the complete release of the IUD in the uterine cavity (Figure 9). To avoid entangling the long threads between the inserter tube and the plunger, the latter is completely withdrawn before the tube is taken out. These fine but important differences need to be emphasized.



***Contraception: Figure 9** Insertion of Nova T IUD*

5. Multiload -250 (ML Cu 250) and 375 (ML Cu 375)

This is made of polyethylene impregnated with barium sulphate and has two flexible (soft) arms, which are bent down and have spurs on their outer aspect. ML Cu-375 is approved for 5 years use. These spurs are thought to prevent downward displacement of the IUD.

The multiload IUD is inserted by withdrawal technique, but the arms need not be folded in the inserter tube. It is claimed to have lower bleeding, pain and expulsion rates due

to it soft spurred arms. Removal of this IUD is occasionally more painful than removal of T shaped devices. ML Cu 375 is slightly less effective than T Cu380A. It is available at higher price that is not warranted by any proven merit over the subsidized T-Cu-380 A.

6. Levonorgestrel (LNG-20) Intrauterine device or system (Mirena / Levonova)

This IUD has a T shaped frame; a levonorgestrel-containing cylinder surrounds the stem. The cylinder covering is made of a rate-controlling membrane. The release rate is 20-ug levonorgestrel per 24 hours. The life span demonstrated in clinical trials is 5 years that can be extended in the future pending on accumulation of data. Levonorgestrel IUD is inserted by withdrawal in exactly the same way as the Nova T devices.

Mechanism of action of the IUDs

The mechanisms involved in the action of IUDs are not precisely known; ***the following mechanisms are contributing to their contraceptive effect:***

1. The presence of the intrauterine device stimulates a foreign body reaction in the endometrium characterized by an increase in the concentration of various types of leucocytes, and macrophages, prostaglandins, and enzymes in the uterine fluid. These changes are more pronounced with copper bearing IUDs particularly in those with bigger surface area covered by copper. These changes may interfere with transport of sperm in the genital tract and may damage them. In most studies fewer sperm are found in the tubes of IUD users relative to nonusers.
2. The presence of the device in the uterus causes an increase in motility of the fallopian tubes, expediting the progress of the ovum through the tube and reducing the opportunity for fertilization and early division which usually take place there. Research has demonstrated that ova were less likely to be recovered by washing the tubes of women using the IUD than in women not using contraceptive. In women who have had a recent sexual intercourse none of the ova recovered from these tube showed evidence of fertilization; in contest half of the ova recovered from nonuser did show such evidence. These results provide the clearest evidence that IUDs work chiefly by preventing fertilization. In accord with this mechanism of action is the observation that the presence of the intrauterine device does not only prevent uterine pregnancy but also markedly decreases the *absolute* incidence of tubal pregnancy.
3. It has been suggested that the presence of the IUD interferes with the implantation of the fertilized ovum in the endometrium. However, research findings suggest that this is unlikely to be a significant mechanism of action. With the advent of highly sensitive and specific radiommunoassy of β-hCG, fertilization can be detected within 7 to 10 days after ovulation, before implantation of a fertilized ovum is completed. Studies of women using mainly copper

IUDs have found hCG assays indicating fertilization in less than one per cent of menstrual cycles.

In the past emphasis was put in the geometry of IUDs and on increasing the area of contact between the device and the endometrium, in order to diminish the area of normal endometrium ready to receive fertilized ovum. With the proven high efficacy of the frameless copper IUD e.g. Gyn-Fix. with minimal contact with the endometrium this idea has lost its ground.

4. The presence of the devices particularly those with a tail projecting through the cervix, the cervical mucus become less permeable to sperm.

5. The hormone-carrying IUDs have additional local effects (systemic effects on the hormonal milieu of the body is triveal): The released progesterone or progestogen renders cervical mucus thick and less permeable to the sperm. The endometrium diminishes in thickness (becoming atrophic) and has lesser numbers of glands and consequently less supportive to the sperm and fertilized ovum viability.

Assessment of the clinical performance of IUDs (and other contraceptives):

After obtaining promising results in animal model experiments of any new medication, it is evaluated in a series of *clinical trials*; the scale of which (the number of individuals involved in the trial) enlarges gradually. In *phase I* clinical trial of any medication the contraceptive failure and the important side effects are tested in a small number of subjects, who usually volunteer for the purpose. After ensuring reasonable effectiveness and freedom of major complications, the trial is enlarged to bigger numbers of subjects in phase II trials done in specialized centers, which can ensure proper selection of subjects and close observation. In phase III a wider clinical trails is done on bigger numbers of varying populations and different settings with reasonable observation that can be ensured in the usual routine clinical practice. These monitor contraceptive effectiveness and estimate the incidence of side effects (which are technically referred to as *events*). After obtaining reasonable outcome, the medication is approved for clinical use by the authorizing governmental bodies, i.e. the medication is released in the market. Subsequently, the early stages of use of the medication in the public practice is usually monitoring by what is described as post-marketing surveillance (sometimes called phase IV trials) in which the performance of the medication in public health services is assessed, and the occurrence of uncommon side effects (e.g. urinary tract infections, skin changes. etc) is recorded. The rare and remote side effects e.g. cardiovalur effects and effect on cancer risk can not however be assessed in clinical trials; they are usually assessed *by epidemiological-type of studies* e.g. cohort and case control study (see above under COCs). Epidemiological and demographic *surveys* can monitor the extent of use by the general public, usually relatively to other methods of contraception. These can usually assess the extent of continuation of use for a reasonable duration of time. These latter two features reflect the usefulness of the medication (e.g. contraceptive) to fulfill certain purpose of public health or epidemiological nature (in this case family planning).

The first " event " that needs to be monitored in clinical trials of a contraceptive is the occurrence of unwanted pregnancy i.e. contraceptive failure. In addition, clinical trials assess the incidence of other important side effects (events), for example, bleeding and pain, expulsion perforation, removal for other medical reasons, and estimation of discontinuations of use of IUD as a result of these occurrences. A

summary of the contraceptive usefulness is measured by the continuation rate which reflects the percentage of those who started using the contraceptive method who have continued using it for a given period of time, for example, one, two or five years.

- *Pearl's Index:* The first procedure for evaluating contraceptive efficacy in clinical trials was the Pearl's index. To calculate this, the total unplanned pregnancies are divided by the total months of exposure and multiplied by 12 and by 100 to give the number of pregnancy per 100 women / years. The total months of exposure are the sum of completed months of use of the contraceptive by all the women involved in the trial; some of them would have used for many months while others have just recently joined the trial.

$$\text{Pearl index} = \frac{\text{Number of unplanned pregnancy}}{\text{Sum of months of use of IUD by all women}} \times 12 \times 100 = \text{pregnancies per 100 women/ years}$$

The main problems of pearl index:

a. It does not dissect the influence of varying duration of use of contraceptive on the occurrence of failures e.g. it will not tell whether failure are more likely during early use relative to long-term use.
b. If the population under study contains a large number of poorly motivated individuals who are careless in their use of a contraceptive (like the COC) or in reporting suspected expulsion when using the IUDs, this results in artificially high pregnancy rate in short-time use.
c. As successive months of exposes elapse, the problem-prone subjects are selectively removed from the study by discontinuation, and the bulk of data is accumulated from the most strongly motivated group, giving an artificially low pregnancy rate in a long-term study. The latter effect automatically results if the population contains a high proportion of potentially subfertile women (e.g. elderly women or women who are breastfeeding).

- *Life table method:* This analysis uses an *actuarial* procedure in calculation of the likelihood of occurrence of events including the occurrence of unplanned pregnancy. This procedure has long been used in calculation of life expectancy in insurance plans and consequently the premiums. The actuarial statistics reassess the status of participation in the study after each successive month of exposure excluding from the denominator all discontinuations that have occurred in the previous months of exposure and those who are lost to follow-up (on which data are unavailable). In this way, the occurrence of pregnancy or discontinuations due to other reasons are removed month by month from the denominator i.e. those who are included in the evaluation are only those that have utilized the method for this period of time. At a certain cut-off date, the likelihood of discontinuation due to pregnancy and other mishaps (events) can be calculated. Cumulative discontinuation rates can readily be broken down according to cause: pregnancy, expulsion, removals for various reasons The cumulative continuation rate can be also calculated up to this cut-off date. These discontinuation and continuation rates are either *net or gross rates*. For calculation of *gross rate* a single decrement table is used, and this measures the incidence of each type of events (e.g. pregnancy) separately, independent of that of other events. Gross cumulative rate are useful for comparison of a single type of event (e.g. pregnancy or expulsion of the IUD) among several different devices or several different groups of users. *Net cumulative rates* are useful for assessing the incidence of each type of event in the presence of all other types of event, and are used to assess the overall performance of the method (e.g. the IUD). This net rates are computed by using a multiple decrement statistics. Net cumulative rates have useful property that they are additive. The sum of the net rates for discontinuation due to different reasons, gives a total discontinuation rate which when subtracted from 100 gives the continuation rate up to the

specified cut-off date. The life-table rates are readily available in computer programs for computation of either gross or net discontinuation rate but they can be hand processed. A pregnancy (or any other discontinuation) rates obtained by a life-table procedure is presented per 100 women-years. A standard error is usually computed along with these rates. It should be understood, however, that this is not a sampling standard error with a given number of degree of freedom, like that usually presented with the means of a series of numerical observations. The standard error given with life table rates is an approximation to the standard error had the study been done in a large population. Large samples (at least of 100 women) are required before mathematical deduction can be made as to the significance of a difference between two rates found for the two types of contraceptives compared. A common assumption is that if the standard error added or subtracted from the rate overlaps, then the difference between rates in the two groups has not been demonstrated to be of importance. However, if the standard errors do not overlap, no real difference necessarily exists, except in large sized observation.

Life table rates diminish but do not rule out completely the sources of possible bias indicated for Pearl-index approach. Life table approach has generally facilitated acquisition of data, which can be used for comparison of contraceptive efficacy in a short period of time.

- *Use-effectiveness*: In clinical trials the situation is idealized, the prospective users are well selected (according to specific inclusion, and exclusion criteria), are specially motivated to use the contraceptive in an ideal way, counseled with care, and subjected to special supportive follow-up care. Therefore the clinical performance does not represent the status of use in the usual public practice. An *ideal* or *theoretical effectiveness* is the contraceptive failure rate when the contraceptive is used properly. The *use-effectiveness* or typical effectiveness represent the failure rate in actual conditions, of practice where no special care is exercised in selecting users or there monitoring. Difference between these two rates is likely to be big, if the correct use requires careful use, for example the daily intake of a contraceptive pill over a specified time, or the proper use of condom. The difference is much less marked with a method not liable to use failure like the IUD; in fact this is one of the major merits of IUDs. However, in case of the IUD the use effectiveness is still subject to some provider's error, for example, poor counseling, improper insertion, and failure to provide supportive care during use will influence the removal rates. Proper training programs of service providers can overcome these problems.

Contraceptive effectiveness of IUD

The IUD is one of the most effective methods of contraception. Pregnancy rates for earlier devices (first generation of IUD) like T Cu-200, Cu 7 and Lippe's loop are about 2 to 5 per 100 women in the first year (Table 2).

Contraception Table 2: First Year Clinical Trial Experience in Parous Women

Device	Pregnancy Rate	Expulsion Rate	Removal Rate
Lippes Loop	3%	12-20%	12-15%
Cu-7	2-3	6	11
Tcu-200	3	8	11
Tcu-380A	0.5-0.8	5	14
Levonorgestrel IUD	0.2	6	17

Among the widely used copper IUDs, T Cu 380 A, and ML Cu 375 (second generation of IUDs), the pregnancy rates are less than one per 100 women per year. They are as effective as male or female sterilization, Norplant and injectable contraceptives. The LNG-20 IUD has an equal or slightly higher effectiveness. The pregnancy rate does not increase and in fact decreases upon long-term use (Table 3). In an ongoing international trial sponsored by WHO and the population council, the *cumulative* pregnancy rate for the T Cu-380 A was 2.1 per 100 women. For the LNG-20 a pregnancy rate of 0.3 has been reported after five years of use. The decline of pregnancy rates in prolonged users is partly due to the women growing older (with less natural fertility), and the drop out from use of women with complications like partial expulsion, perforation and women with poorly fitting IUD who would have bleedings and pain that should have motivated removal.

On wide-scale use of IUD outside the care exercised in clinical trial, the IUD remains one of the most highly effective methods. Use failures (typical failure rates) are much less likely than in the case of pills or condom use. This good performance is expected, if proper training of service providers backs up the wide scale use of IUD in public health service.

Contraception Table 3:Ten-Year Experience with TCu-380A

Rate per 100 users per year

	Year									
	1	2	3	4	5	6	7	8	9	10
Pregnancy	0.7	0.3	0.6	0.2	0.3	0.2	0.0	0.4	0.0	0.0
Expulsion	5.7	2.5	1.6	1.2	0.3	0.0	0.6	1.7	0.2	0.4
Bl./pain removal	11.9	9.8	7.0	3.5	3.7	2.7	3.0	2.5	2.2	3.7
Medical removals	2.5	2.1	1.6	1.7	0.1	0.3	0.1	0.4	0.7	0.3
Continuation	76.8	78.3	81.2	86.2	89.0	91.9	87.9	88.1	92.0	91.8

Data from Population Council (n=3=3,536) and WHO (n=1,396) trials

Continuation of IUD use

The usefulness of IUD as a contraceptive is measured by another important parameter, which is the extent of continuation of use (Table 3). This is not only the function of effectiveness but is mainly determined by the incidence of side effects and their management. The IUD is having a very high continuation rates. In a big international study sponsored by WHO 45 % of women continued to use of the IUD for 10 years after its insertion. Even outside the care of clinical trails, IUD continuation rates are high and are much higher than the continuation of use of COCs, injectable contraceptives and condom. However, these continuation rates depend upon the availability and quality of care given to

initiation and support of continuation of contraception in public health services, which may vary from one setting to another.

Side effects and complications of IUDs

1. Contraceptive failure: pregnancy

The second generation IUD is highly effective contraceptives (see above). In the few incidences of failure, pregnancy is attended by complications. Spontaneous abortion is the most frequent complication of pregnancy with the IUD in the uterus. Some 60 % of such pregnancies spontaneously abort if the IUD is left in place. More than half of these abortions occur in the second trimester. An IUD left in place during pregnancy also increases the risk of preterm delivery. Therefore, if pregnancy occurs in an IUD user, removal of the IUD should be made if the thread is visible in the cervix. This improves the outcome of the pregnancy. However, if the IUD is left behind (because of the tail not available at the cervix), its presence does not increase the risk of birth defects, genetic abnormalities or molar pregnancy. The IUD will usually come out at delivery together with the placenta and membranes, and should be searched for in the afterbirth.

Another important complication of pregnancy with the IUD inside the uterus is the occurrence of intrauterine infection. The infection usually ascends to the uterine cavity along the intracervical tail threads. This increased risk of infection was particularly associated with a certain type of IUD, the *Dalcon Shield*. The serious complication that resulted from septic abortion with Dalcon shield in place had resulted in withdrawal of this type from the market, but has seriously affected the reputation of the IUD in general, particularly in the USA, in which the use of the IUD has remained low since this incidence. Removal of the IUD with visible thread removes the risk of ascending infection. However, if the thread is not visible, the IUD should be left in the uterus until the delivery; the intrauterine manipulation needed to remove such missing IUD is more serious than leaving it behind.

2. Ectopic pregnancy

IUD protects against ectopic pregnancy but less efficiently than the protection against uterine pregnancy. Thus, when an IUD user become pregnant, the pregnancy is more likely to be ectopic (i.e. the ectopic to uterine pregnancy ratio is higher) than in a pregnancy in a non-contracepting woman. In IUD users the chance of ectopic pregnancy is estimated to be one in 25 pregnancies while this chance is usually less than one in 100 or 250 pregnancies in women who are not contracepting (Table 4)(see under Ectopic pregnancy).

Contraception Table 4:Ectopic Pregnancy Rates per 1000 Women-Years

Non-contraceptive users, all ages	***3.00-4.50***
Levonorgestrel IUD	**0.20**
Tcu-380A IUD	**0.20**

3. Bleeding and pain

Increased bleeding and pain are usually occurring together, are the most common problems of IUD. Both are the commonest reasons for removing the IUDs; accounting for about 10 % of removal during the first year. They are less common with T shaped IUD than with lippes loop. Post-insertion bleeding usually stops after few days. Heavy menstrual periods or inter-menstrual spotting or bleeding usually disappear after 2 or 3 cycles. If they persist this indicates poor orientation of the IUD in the uterus. However, in general the days of menstrual bleeding tend get longer in IUD users and the amount of blood loss can be increased. The kind of counseling and the support the women receive and their attitude towards using the IUDs influence the rates of discontinuation due to bleeding and pain. Women who want no more children may be more tolerant to these complaints. Bleeding is rarely so heavy to cause anemia. Several approaches have been tried to diminish the blood loss in IUD user including the use of prostaglandin synthetase inhibitor, or tranexamic acid during the bleeding; and administration of progestogens during the second half of the cycle have been tried; However these measures usually fail; removal of the IUD is the usual end result.

It has to be remembered that abnormal pain and bleeding associated with IUD may be due not to the IUD itself but to pelvic inflammatory disease, ectopic pregnancy, ovarian dysfunction or even malignancy. In these conditions the complaints will persist after removal of the IUD.

Unlike other IUDs, hormone-releasing devices decrease menstrual blood flow or, in the case of LNG-20, amenorrhea may develop. This decrease in the menstrual flow results from local effect of the progestogen released on the endometrium. In fact, the LNG-20 has been used successfully to treat menorrhagia. However, unless properly counseled and supported by medical advice, the women may have the IUD removed because of diminished menstrual blood or amenorrhea-some women may get unnecessary apprehensive about keeping in the body of some noxious material which the body normally gets rid of in menstruation. Other women may find it more advantageous to have long periods or amenorrhea. In fact, this LNG-IUD may be the better choice for anemic women.

4. Expulsion

Uterine contractions can push the IUD downward, causing complete but usually partial expulsion. Most expulsions occur in the first year and especially during the first three months after insertion. Because partial or complete expulsion can be undetected, this can lead to unplanned pregnancy. Therefore some providers advise IUD users to check for the IUD threads frequently and to report to the clinic whenever, they fail to feel the thread. Since the expulsion occurs during menstruation or follows upon an episode of bleeding, it is usually sufficient for the patient to personally check for the threads after any episode of bleeding. If she has regular menstruation of average amount, expulsion is most unlikely. Women, particularly those who dread the idea of getting pregnant may over report expulsion.

Expulsion rates vary from less than one to more than 7 per 100 women in the first year. With softer and smaller T-shaped devices, the expulsion rate is usually lower than with the bigger Lippes' loop. Correct insertion, with the IUD placed up to the fundus and in the transverse plain of the cavity reduces the chance of expulsion. Fixation to the fundus of frameless IUDs like Flexi-Gard 330 and Gyne-Fix is an attempt to reduce the complications including expulsion. The available data about these latter devices have so far indicated fulfillment of this aim in clinical trials. Whether this will be also fulfilled in wider-scale use remains to be verified.

5. Perforation

`Perforation of the uterus may occur during the insertion, by the sound, inserter tube or the device itself; the IUD, as a result, is partially or completely inserted outside the uterine cavity. The perforation can occur at the fundus if the inserter or the IUD is pushed too deeply in the uterine cavity, but it can also occur in the cervix if the internal os offers resistance or the uterus is acutely ante-flexed. Careful insertion can prevent most perforations. If perforation is suspected at any time during the insertion, the producer should be stopped and the IUD should be removed. If the service provider suspects that she or he has done a perforation, the case should be referred for assuring the diagnosis. If the IUD has not been inserted, nothing is done, perforation heals spontaneously. It is most doubtful that a properly inserted IUD can borrow its way through the myometrium; perforation needs someone to do it.

The perforating IUD usually projects in the peritoneal cavity but it is occasionally held within the broad ligament. It usually keeps its attachment to the uterus; the threads may be visible at the external as. The perforating IUD usually, but not invariably result in omental and intestinal adhesions. Perforation of the uterus during IUD insertion rarely cause special symptoms and the condition can go on unsuspected until difficulty is encountered in

removing the IUD or the patient comes for missing the threads. Ultrasonography can usually diagnose that the IUD is partially or completely outside the uterine cavity. After the availability of ultrasonography, X-ray is rarely required to visualize perforating IUD. To detect by X-ray whether the IUD is outside the uterine cavity, a lateral view of the pelvis is taken with a sound in the uterine cavity. Laparoscopy (occasionally combined with hysteroscopy) is rarely required to make the final diagnosis, together with removal.

Operative laparoscopy is the usual approach used for removal of a perforating IUD. Laparotomy is rarely used to remove a perforating IUD. The general opinion however is that a perforating IUD is to be removed only if it is causing symptom; they rarely cause problem. However, they should be considered unreliable as a contraceptive.

6. Missing the threads of the IUD

This frequently results from the threads being curled or pulled up into the cervical canal or the uterine cavity, less commonly results from unnoticed expulsion and rarely from uterine perforation. The management should follow the following plan of management:

1. Speculum examination frequently reveals the presence of the threads or that they can be straightened downs the cervical canal by an artery forceps without pulling upon the device.
2. If the above cannot be achieved, pregnancy should be ruled out by clinical history, pregnancy test and/or sonographic examination; the latter examination usually reveals that IUD is inside the uterine cavity.
3. If the patient is found pregnant, no attempt should be made to remove the IUD; the women should be encouraged to complete her pregnancy. She should be assured that no harm would be caused to the pregnancy, other than increasing the likelihood of abortion.
4. The possibility of the pregnancy being ectopic should be excluded (see above).
5. If the patient proves to be not pregnant and is not having any complaints related to the IUD, and USG shows that IUD is in the uterine cavity the IUD should be left and the user is assured of continued contraceptive effect.
6. If perforation is suspected proceed as given above (under perforation) to verify the diagnosis and manage the condition.

7. Pelvic inflammatory disease (PID) and the IUDs

It should be emphasized from the start that for women in mutually faithful marriage, as the majority in this country, IUDs pose little risk of reproductive tract infections. Reproductive tract infections can be either unrelated to sexual practice or related to this practice i.e. sexually transmitted disease (STDs). Pelvic inflammatory disease is a broad term

for infection ascending from the cervix into the uterus, fallopian tubes, ovaries and pelvic peritoneum. STDs commonly causing PID include gonorrhoea and chlamydial infections. Their primary site of infection is the cervix, urethra, and bartholin glands. The symptoms of lower genital tract may go unnoticed and they manifest first by PID. In addition to STDs, post-abortion and postpartum infections are major causes of PID in this country.

The *clinical sign* of PIDs include: lower abdominal or pelvic pain; pain on manipulating the cervix, tenderness of the adnexa; high temperature; abnormal cervical discharge; intermenstrual bleeding and; tender adnexal masses. To ensure that cases of PID do not go untreated, the presence of any of the first three signs in absence of an alternative diagnosis should be taken as indicating PID, particularly if they develop shortly after IUD insertion or after a certain intercourse with a new partner.

The *consequences* PID can be serious. Even a single infection can permanently damage of the fallopian tubes. The pathology is usually bilateral and may damage the lining of the tube or kink them or surrounded them with adhesions. This may completely block the tubes causing infertility; or narrow them, predisposing to ectopic pregnancy. The infection may remain dormant in the tubes and can be flared up every now and then.

Data from developed and some of the developing countries indicate that women using IUDs are twice as likely to develop PID. ***The following factors were found to influence the risk of PID in IUD users.***

a. *Insertion producer*: women are most likely to develop PID just after insertion, within the first month. Thereafter, the incidence drops. In most cases the infection is introduced from without. The chance is minimized if infection-prevention procedures (see before) are carefully followed. However, the insertion of the IUD may flare up a dormant undetected infection in the tubes. Controlled trial did not, however, show a value of prophylactic administration of antibiotics after IUD insertion. In fact, these may mask early manifestations of infection, which will flare up later on or cause silent tubal damage.

b. *Exposure to STDs*: Much of the risk of PID in IUD users, apart from that occurring in the first month after insertion may be due to sexually transmitted infection. The risk is related to the sexual life of the user, including the diversity of her sexual partners and diversity of the partners of her partner(s).

c. *Young age*: Younger women particularly if nulliparae are more likely to develop PID. This may be caused by increased chance of contracting STDs.

d. *Type of IUD*: The Dalcon shield-which is no longer used was linked to PID. There is no difference in PID risk among users of different types of the second generation IUDs. There are claims that LNG-IUD entails less risk of PID.

e. The chance of PID does not seem to increase with the *duration of use of IUD*. On the contrary, the use of IUD with longer duration of effectiveness will diminish the chance of PID by reducing the number of required replacements, since PID is highest in the few weeks following the insertion.

Mechanisms of occurrence of PID in IUD users

a. *Introduction of infection during the insertion procedure.* The bacteria are introduced from without through careless aseptic and antiseptic technique. The vaginal cavity and cervix are impossible to sterilize completely and an infections must result from the inevitable carriage of vaginal or cervical bacteria in the uterus. In general, bacteria introduced during insertion are usually eliminated; the uterine cavity becoming sterile again within 30 days. The migration of white cell into the uterine cavity, which occurs in response to presence of the IUD, helps to eliminate bacteria.

b. *Nonbacterial inflammation of the fallopian tubes* is common in IUD users than nonusers. This inflammation may reduce the resistance of the tube to ascending infection secondary to STDs.

c. *Ascent of the bacterial along the thread tail of the IUD has been suspected.* One proposed explanation for the high rate of infection with Dalcon Shield is its multifilament string that permitted bacteria to rise along this tail into the uterus more readily. Threads on all currently available IUDs are monofilament.

Management of PID in IUD users:

a. Broad-spectrum antibiotics usually in combinations should be initiated and given in full course. Evidence suggesting the presence of an STD should be searched for by careful history taking including asking about whether the husband has developed symptoms suggestive of STDs recently, and also by bacteriological examination of any urethral or cervical discharge.

b. Removal of the IUD. Generally, the presence of the IUD may impede the eradication of infection. If possible, one may delay IUD removal for 2 to 4 days for treatment to take effect another contraception should be advised.

c. Follow up visit within few days and weeks to ensure that PID has completely subsided.

d. Such a patient should better not insert the IUD again.

8. Difficult or painful insertion

This usually results from poor contraceptive motivation, misconceptions or pervious bad experience of the patient or a friend. These women may fail to relax to allow the

deliberate insertion procedure, and attempt to wrestle with the problem may predispose to perforation. A tight internal os may make sounding difficult. One should not exercise any degree of force in pushing the sound because this can result in creation of a false passage and perforation of the cervix or the fundus. The procedure should be stopped and the patient is asked to return during menstruation when the internal os is usually more open. If the service provider feels that she or he has gone into a false passage, he or she should not insert the IUD. Syncope rarely follows the insertion procedure in an anxious patient.

9. Increased vaginal discharge

This may denote introduction of infection, bacterial or otherwise, by use of non-sterile speculum. That the presence of IUD predispose to bacterial vaginosis has been suspected but has not been proven in controlled trial.

10. Infertility:

Except in the population groups predisposed to PID (see above) the IUD does not result in permanent infertility. More than 90 % who remove the IUD in order to conceive achieve this within one year.

11. Difficulty in removal:

This usually results when the IUD string is missing from the cervical canal. (see above). After exclusion of pregnancy and unnoticed expulsion of the IUD; the IUD can usually be removed as an outpatient procedure. The presence of the IUD can be " felt “ by the sound. A patulous cervix can usually allow the introduction of a Spencer Wells artery forceps, which can be slightly opened to get, hold of the string or the IUD stem, which is pulled out. A special instrument designed for the purpose of removal of a missing IUD is available. It is a malleable tube, which contains a malleable forceps ending in two fine jaws. After passing the instrument in the uterine cavity the jaws are separated by external manipulating device, which are then closed to get hold of the device and this can be pulled out. In some cases dilatation of the cervix under anesthesia is required and the device is held by a fine ring forceps. Operative hysteroscopy is rarely used to get out a missing loop in the uterine cavity.

12. Discomfort of the husband

The penile perception of the IUD thread is not expected. When this complaint is reported, a downward displacement of the stem of the T is frequently found.

Advantages of the IUD

1. A single decision leads to effective long-term prevention of pregnancy.
2. Long-term effect. The most-widely used IUD-the T Cu 380 A lasts for at least 10 years. The LNG-20 IUD has a term of at least of 5 years.
3. Highly effective; the failure rate is < 1 per 100 women–year. The failure ate diminishes with prolongation of use of IUD; 1.4-2 pregnancies per 100 women after 10 years of use: as effective as tubal sterilization.
4. No interference with sexual practice (like with barrier methods).
5. Increased sexual enjoyment because removal of worry about pregnancy.
6. No hormonal side effects.
7. Immediately reversible (see above).
8. Copper-bearing and inert IUDs have no effect on the amount or quality of breast milk. The LNG IUD will not, most probably, have any effect on breast milk.
9. Can be inserted immediately after birth (except for hormone-releasing IUDs) or after abortion (if no evidence of infection is suspected).
10. Can be used until establishment of menopause.
11. No interaction with drugs.
12. Helps to prevent ectopic pregnancy.
13. Minimal cost.
14. Require less time from medical care, relative to other methods.
15. Frequent visit to the clinic are not required.

Disadvantages of the IUD

1. Common and rare side-effects (as given above).
2. Medical procedure needed for initiating the use. This may be disliked or unnecessarily feared of.
3. Client cannot stop IUD use on her own; this needs the care of health provider.
4. Does not protect from STDs. The IUD is not a good method for women who are at special risk to develop these infections. However, the available information does not suggest that the use of the IUD increases the risk of the women or her partner of contracting HIV infection and AIDS.
5. Is not usually suitable for nulliparae: due to higher incidence of bleeding and pain, and may be; PID.
6. Not suitable for women with congenital abnormalities in the shape of uterine cavity.

7. The women may find it difficult to check for the presence of the strings. In fact this is not needed except in women who complain of heavy or untimely bleedings or cramping pains.

Practical aspect in using IUDs: Procedural guidelines

These should cover the following points

1. Eligibility for use of IUD.
2. Time of insertion.
3. Method of insertion.
4. Side effects.
5. Follow-up of women using the IUD.
6. Removal of IUD.

   Most points except the first, second and fifth have been discussed before.

Eligibility for IUD

Eligibility for using IUD does not only depend upon medical conditions but also depends upon personal preference of users. An interactive counseling is needed before IUD is inserted.

Many women can use IUDs safely and effectively: including

- Parous women of any age.
- Fat or lean.
- If breastfeeding.
- If smoking.
- Previous caesarean section.
- Previous myomectomy.
- Just had an IUD removed because its period of effectiveness has ended. Removal of the old IUD and insertion of a fresh one can be done in the same sitting.
- IUD was expelled and client would like to try again.
- Women with cervical tears ----these women are generally not especially liable for expulsion.
- Women with genital prolapse.
- Women that have just given birth---see under postpartum IUD.
- Women who have recently aborted provided there is no likelihood of retained parts or infection.
- Diabetics. The fear of increased risk of PID in diabetic is unfounded.
- Hypertensive and, dyslipidemic.

- Past or present ischemic cardiac disease, past or present VTE.
- Headaches.
- Cervical erosion (ectopy).
- History of CIN.
- If taking any medication.
- Schstosomiasis, Malaria, Thyroid disease, breast tumors, liver or gall bladder disease.

***For the following group of women, the advantages of use of IUD usually outweigh theoretical or proven disadvantages*:** They generally can use IUDs if alternative contraceptives carry particular risks, or are not acceptable.

- Nulliparae. (Smaller IUDs e.g. a minigravi-gard is suitable for them).
- Dysmenorrhea.
- Vaginitis--- does not contraindicate immediate insertion of IUD. Careful sterilization of the cervix is needed. Treatment should be prescribed for the probable cause.
- Uterine fibroids not causing abnormal bleeding.
- Endometriosis.
- Non-pelvic tuberculosis.
- Mild or moderate anemia.
- Valvular heart disease. Antibiotic cover is better advised to diminish the chance of bacterial endocarditis.

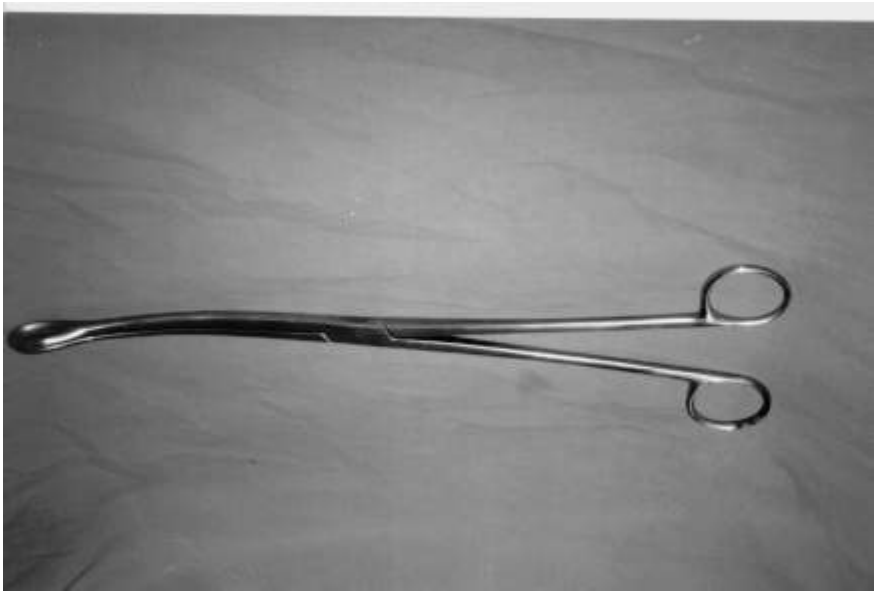
The following few women should not use IUDs:

- Present and past PID.
- Women predisposed to STDs. (because of style of sexual relations).
- Women with suspected presence of an STD.
- Past ectopic pregnancy.
- Congenital anomalies of the uterus like septate or bicorneate uterus.
- Abnormal uterine bleeding of undiagnosed cause.
- If pregnancy is suspected.

Time of Insertion

- ***Any time during the menstrual cycle:*** (not necessarily during menstruation) is suitable provided it is reasonably certain that the woman is not pregnant. If the woman has been using a reliable contraceptive she can have the insertion at any time.

- ***Postpartum IUD insertion:*** Immediate postpartum insertion of the IUD has been fraught with the risk of infection and increased chance of spontaneous expulsion. However, controlled trails have shown that if aseptic precaution are followed, the incidence of puerperal morbidities are not increased and spontaneous expulsion is less than 10 %. During the hospital stay after childbirth, if the women has decided voluntarily, in advance, to use this method, the IUD can be inserted by hand within 10 minutes after delivery of the placenta (post placental insertion). It can also be inserted any time within 48 hours after childbirth. This is usually done by a special forceps (Kelly's forceps), which is essentially a long ring forceps (Figure 10). The IUD can also be left behind in the uterine cavity after caesarean section. Special training is required for doing the postpartum IUD insertion and special provisions are required to ensure aseptic technique. After PP insertion the threads are left long. The patient needs to be seen 6 weeks postpartum in order to check that spontaneous expulsion has not occurred, and in order to shorten the long threads. If expulsion has occurred women frequently accept insertion of another IUD at this visit.



Contraception; Figure 10: Kelly forceps for postpartum IUD insertion.

The idea of postpartum IUD insertion is to promote acceptability of the IUD; the immediate postpartum time can be an opportunity in which the women avails herself to medical care. If this opportunity is missed, the women may fail to come to medical care before she gets pregnant again. She can forget the need for contraception, and she can be discouraged to come to hospital again because of her other overwhelming obligations at home; or by the need to travel a long distance to reach the hospital. The women should

not be pushed to use postpartum IUD against her preference; adequate time should be given to her to consider the idea. This can be done during antenatal care.

The usual time for inserting IUD after childbirth is the ***6-week postpartum***, after the uterus has involuted to the pre-pregnancy condition. Usually, intercourse has not been resumed before this time. If she comes later than this time, absence of pregnancy should be ensured before an IUD is inserted. If the women has been exclusively (or almost exclusively) breastfeeding since childbirth, and she is having lactational amenorrhea and is still not later than 6 months postpartum, the chance of her getting pregnant with these three provision is less than 2 %. This particular woman can have an IUD inserted without waiting for resumption of menstruation (see under LAM). If any of these three provisions is not fulfilled she can have the IUD inserted during or shortly after a spontaneous or induced menstruation.

- The IUD can be inserted ***immediately after an abortion*** provided that there is no chance of having retained parts or infection.

Follow-up procedure:

A follow-up visit is usually required any time between 3 and 6 week after insertion. At this visit a check-up exam make sure that her IUD is still in place and no infection has developed. After this one visit, no further routine visits are required. However the women is advised to come to the clinic if she feels something hard like a match stick in her vagina if she have excessive or untimely menstruation, or pelvic or lower abdominal pain, or if she misses her period; and whenever she feel the need for medical consultation. She should be informed (or given a card) about the type of the IUD that has been used and its duration of effectiveness.

Emergency contraceptives (EC) or Postcoital contraceptives

Contents:

- Introduction
- Possible mechanism of action
- Methods
- Side-effects

Emergency or postcoital contraceptives refer to methods women can use to prevent pregnancy following unprotected sexual intercourse. Such need may arise from either 1) unplanned sexual intercourse in a non-contracepting women as in sexual assault, return of the husband from an absence, resumption of sexual relation after an abortion or before beginning of use of an effective contraceptive. 2) The need can arise from a contraceptive accident as breaking of the condom, or occurrence of an intercourse during the fertile period in couples practicing the rhythm method. Although the need for emergency contraception should be rare, the occurrence of such emergencies can frequently occur in practice. Knowledge about the existence of emergency contraceptive and their availability can serve as a back up of contraceptive programme. By offering EC information and services to these clients, family planning programmes can help women avoid unintended pregnancy, and consequently avoid the demand for induction of abortion, which may not be safely available. EC service also may serve as a first contact point of the woman with a family planning service and usually results in her use of regularly used or long-term contraceptives. It should be clear that ECs are not intended for regular use, such use is impractical, and not equally effective as the regularly used methods.

Possible mechanisms of action of EC

EC intercept one or more of the sequence of events in the menstrual cycle which yield to the establishment of a pregnancy, has an unprotected sexual intercourse occurred. These include the following possibilities:

1. ***Interfere with ovulation. This rarely occurs, and only when emergency contraceptive*** pills are given during the pre-ovulatory phase.
2. ***Interference with fertilization of the ovum***. This can be achieved by methods that interfere with ascent of sperm to the tubes, and / or the tubal secretion and motility critical for occurrence of fertilization.
3. ***Interference with implantation*** of the fertilized ovum (the blastocyct in fact) in the endometrium seems to be the most probable mechanism of action. This is possible since the duration from fertilization to establishment of implantation is approximately 5 days. This interference with implantation is achieved by rendering the endometrium not suitable for nidation.
4. ***Induction of an early abortion***. If " menstruation induction " are excluded from ECs, this is mechanism the least probable one i.e. emergency contraceptives commonly used are not abortifecients. Menstruation is usually not delayed after the use of ECPs, and

sensitive assays of hCG done at the time of the subsequent menstruation after EC did not show any increase in the incidence of rise of this hormone in users relative to non-users

Emergency Contraceptive Methods include:

1. *Emergency contraceptive pills (ECP)*

a. ***Estrogen pills***: This was the earliest regimen used. It mainly consisted of ethinyl estradiol administered by the 5 x 5 regimen, i.e. 5 mg daily starting within 72 hours after the unprotected intercourse and continued for 5 days. This regimen is no longer used because of high incidence of side effects as nausea, vomiting, breast tenderness and disturbance of menstruation.

b. ***Combined estrogen-progestogen pill.*** This is known as Yuzpe regimen. This entails initially giving either two high dose pills e.g. those containing 0.25 mg of levonorgestrel (LNG) + 50 ug of ethinyl estradiole (EE) (e.g. Ovral) or four low dose pills containing 0.15 mg LNG + 30 ug EE (e.g. Nordette or Microvlar) *within 72 hours (3 days) of unprotected intercourse*. This is followed by giving *a similar dose 12 hours later*. These pills are usually cut out of the packet of COC, or available as special packet dispensed for the purpose of EC (not yet present in the Egyptian market). The effectiveness of this regimen is high but not 100 % sure. It fails to prevent pregnancy in about 2 % of women who use it correctly. This represents a 75 % reduction in risk of pregnancy compared to use of no method; in the absence of ECP use approximately 8 % of women become pregnant after one act of unprotected intercourse. ECPs are intended for one-time use or very occasional use. If a woman used ECPs multiple times during the year, her cumulative risk of pregnancy would be higher than if she consistently uses COC or another hormonal contraceptive, an IUD or even the condom.

c. ***Progestogen-only ECP.*** This regimen requires that one 0.75 mg levonorgestrel pill be taken within 72 hours of unprotected intercourse, followed by an additional pill 12 hours later. This type of pill is available for the purpose of EC (Postinor). Progestogen-only minipill can also be used instead, although this regimen is less convenient because of number of pills, twenty-five (each contains 0.03 mg levonorgestrel e.g. Microlut) that must be taken two times. The progestogen-only regimen is as effective as the combined pill regimen. In both types of ECP the treatment should be initiated as early as possible, hence the name the morning-after pill or postcoital pill. This should be initiated as early as possible and within 72 hours. Treatment efficacy declines with time.

Side-effects of ECPs

A key difference between the two ECP regimens is their side effect of causing nausea and vomiting. The combined-pill regimen causes nausea in 45 % of users and vomiting in approximately 20 % of users. In contrast, the progestogen-only regimen causes nausea in 15 % and vomiting in only 3 %. Some providers recommend that if a women vomits within two hours of taking ECPs, she should take a replacement dose. Other providers believe that this is not necessary, since the development of nausea and vomiting are indications that the drug has been absorbed. To reduce nausea and vomiting, some providers recommended prophylactic use of anti-nausea medication. Alternatively, the replacement pills may be placed in the vagina (from which they are effectively absorbed). Other side effects associated with both regimens include dizziness, fatigue, breast tenderness and headaches. These side effects generally do not last more than 24 hours. Generally, both regimens of ECPs do not cause break-through bleeding or delay in the onset of the subsequent bleeding; such a delay should raise the possibility of contraceptive failure.

There are no known short-term or long-term health risks associated with ECP use.

- There has been concern about combined regimen increasing the risk of thromboembolism due to its content of estrogen. Because the regimen is taken over a short time period, however, it does not cause changes in coagulation factors.
- Ectopic pregnancy following the Yuzpe regimen has been reported and a woman with special risk factor(s) for ectopic pregnancy is regarded to be a contraindication.
- There also is no evidence to suggest that either regimen cause birth defects in the event of method failure. A metanalysis of 12 studies found no association between intake of high-dose oral contraceptives (which are equivalent in dose and composition to combined regimen) during early pregnancy and fetal malformations.
- Both regimens also are safe for use while breastfeeding, causing no disruption of milk production or posing any risk to the breastfed infants.

2. Intrauterine contraceptive device as an emergency contraceptive

Insertion of an intrauterine contraceptive device is sometimes used as an emergency contraception, as an alternative to hormonal administration or if the women presents more than 72 hours after the unprotected intercourse; particularly if the woman plan a long-term contraception. IUD can effectively take place up to the expected time of implantation, i.e. up to 5-6 days after the unprotected intercourse.

3. RU 486-Mifepristone as an emergency contraceptive

Mifepristone is potent antiprogesterone that acts by competitive inhibition of progesterone effects. It has been used as an emergency contraceptive in a single dose of 600 mg given orally within 72 hours of unprotected intercourse. It proved to be highly effective

and had fewer side effects than Yuzpe regimen. However it frequently induced an earlier menstruation. There is a possibility of using Mifepristone in a much smaller dose of 50 mg as an emergency contraceptive. The drug acts by rendering the endometrium not suitable for nidation.

4. Danazol

The synthetic progestogen and androgen danazol can be used as an EC. This regimen consists of two doses of 400 mg each; the first is taken within 72 hours of the unprotected intercourse and the second 12 hours later. There are reports of efficacy of this approach.

Post-Ovulatory Methods of Fertility Regulation

In spite of overlap in the meanings, the term postovulatory methods should be distinct from emergency contraception. Postovulatory methods of fertility regulation are methods acting after ovulation through interfering with the process involved in fertilization of the ovum, transport and implantation of the embryo, or subsequent establishment of pregnancy. Thus, post-ovulatory approaches to fertility regulation include:

1. *Methods that are true contraceptives i.e. those that prevent fertilization and the establishment of pregnancy, as well as.*
2. *Method that cause abortion of the embryo.*

Wide use of post-ovulatory methods of contraception is hampered by the debate about the moment when pregnancy can be considered to have commenced: is it the time of fertilization, time of implantation or even the time when the fetus has gained viability. For certain legal, moral and ethical consideration interference aiming at intercepting the process of conception before establishment of implantation of the blastocyst can be considered as contraception and are more acceptable. On the other hand methods interfering with continuation of gestation after implantation is established are called contra gestation and are less acceptable in many social settings. Emergency contraceptives (as described above) can be considered as contraceptives, while measures to terminate pregnancy whatever early and by any method, whether medical or surgical should be classed as abortifecients. These methods are not acceptable with the laws in Egypt.

Postovulatory methods can include:

1. ***Emergency contraceptives*** (see under the heading).
2. ***Drugs repeatedly used after each intercourse (postcoital contraception).***
3. The most widely tested approach is giving a tablet containing 0.15 to 1 mg ***mifepristone*** taken within 3 hours after each intercourse. The approach had unacceptably high failure rate and caused menstrual disturbance. Daily administration of antiprogesterone like mifepristone during the early or late luteal phase on regular basis is still under trial.

4. ***Menstrual regulation*** (also known as endometrial aspiration menstrual extraction and menstrual aspiration): (see under abortion).

5. Induction of abortion

For details see under Abortion

a. Mechanical methods including (see abortion)

- Dilatation and evacuation.
- Vacuum aspiration.
- Manual vacuum aspiration (MVA).

b. Medical methods (see under abortion)

This include the use of drugs as

- Prostaglandins or their synthetic analogues (e.g sulprostone; carboprost and misoprostol).
- Mifepristone (Ru 486).
- A combination of Mifepristone and prostaglandin regiment. (most commonly utilized approach, so far).
- Epsilon, an inhibitor of 3 β hydroxysteroid dehydrogenase, (see under abortion), usually used in combination with a prostaglandin.
- Methotrexate plus misoprostol.

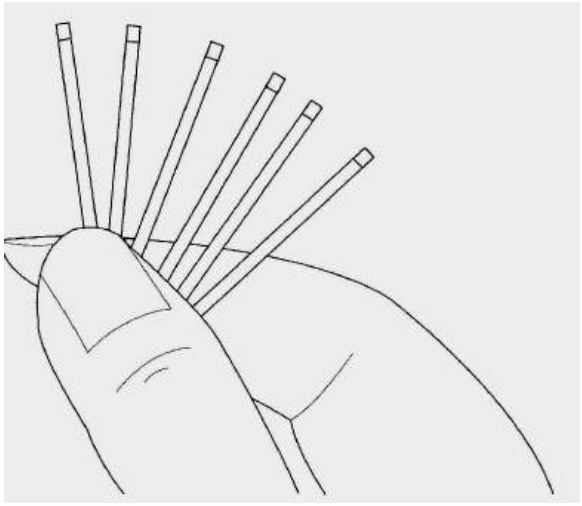
Norplant Contraceptive Implants

Contents:

- Evolution
- Pharmacology
- Effectiveness
- Mechanism of action
- Side effects- metabolic changes
- Advantages and disadvantages
- Eligibility criteria
- Procedural guidelines
- Newer implant systems

Norplant consists of six small (34 mm long and 2.4 mm in diameter) Silastic (an inert non-biodegradable elastic rubber) capsules, each containing 36 mg levonorgestrel, that is a total of 216 mg levonorgestrel in the six capsules. The capsules are inserted under the skin

under local anesthesia through a trocar (Figure 11). The six capsules conjointly release in the circulation amounts of levonorgestrel sufficient to produce highly reliable contraception for five years. At the end of this term, or upon the development of unacceptable side effects the capsules need to be removed. This is done by a minor surgical procedure under local anesthesia.

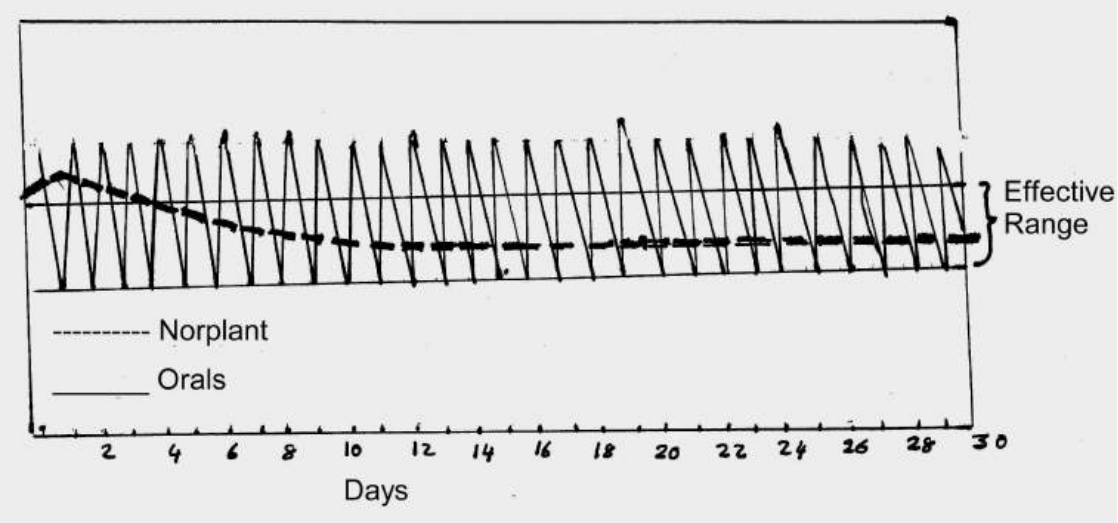


Contraception: Figure 11 Norplant Contraceptive Implants

Evolution of Norplant

Norplant has been developed starting from the 1960s by the Population Council, an international organization based in New York (which has developed a number of contraceptives, notably the T Cu 380 IUD and the levonorgestrel IUD). The development of Norplant was based on two principles:

1. The steroid levonorgestrel dissolves in and diffuse in the tissues from tubing made of the silicon elastomers, Silastic. This is a non-biodegradable, inert synthetic rubber that does not induce any tissue reaction.
2. The contained levonorgestrel is slowly released in the body in almost constant amounts that can produce effective contraception for duration of 5 years. The dose of the steroid daily delivered to the body is small, and almost equal to the dose-ingested daily in progestogen-only pills (minipill). However, The release of levonorgestrel from Norplant is not exhibiting the fluctuations that occur after oral administration, i.e. there are no peaks and nadirs. This is called the Zero-Order release (Figure 12). This even release of the contraceptive steroid enhances the efficacy of the small dose released in the body.



Contraception Figure 12: ***Zero-order release rate of the contraceptive achieved by Norplant as contrasted to delay spikes and nadirs occurring with oral administration.***

The population Council in 1966, first tested capsules providing a continuous release of different progestogens, when implanted subdermally. A further 20 years of clinical research were concerned with selecting the most suitable progestogen, determining the appropriate dose, assessing metabolic and pharmacological effects, evaluating efficacy, side effects, and acceptability, and elucidating the mechanism of action. Assiut University, Egypt has participated in some aspects of this international effort. The outcome of this effort is the formulation known as Norplant described above. The initial studies used " hard " tubing but current system uses " soft " tubing, which results in a greater daily release of levonorgestrel into the circulation, and is associated with lower failure (pregnancy) rates than the hard tubing.

After these prolonged clinical trials, Norplant has been registered in 60 countries including the USA and Egypt. The method has been used by some 6 million women worldwide. Although on clinical and scientific grounds, it is generally agreed that Norplant is a safe, effective long-term contraceptive, there has been lately controversy, particularly on the programmatic aspects of its wide-scale use (particularly in USA). The main concern has arisen about two aspects: 1) the possibility coercive use or continuation of use in spite of occurrence of side effects; that users with problems and those that have opted for discontinuation of the contraception for personal causes are pushed in continuing the use due to inaccessibility of removal service. The second concern is about the occasional difficulty in removal. These problems should be dealt with by certain programmatic provisions.

Pharmacology

Release of levonorgestrel into the circulation by physicochemical diffusion starts immediately after insertion of the capsule. *The contraceptive effect begins directly after insertion of the implants*. After an initial phase of high release of levonorgestrel, the release steadies 18 months after the insertion at about a daily rate of 30 ug which continues for 5 years. This daily does is < ¼th of the does provided by a low-dose combination oral contraceptive containing levonorgestrel, and equal to the daily does ingested in the progestogen-only pill containing this progestogen, the minipill. The even release of the does over the 24 hours (zero-order pharmacokinetic) contributes to the efficacy. This explains the higher efficacy of Norplant relative to POPs. This is in spite of the fact that*, the steroid load delivered to the body is minimal*.

After removal of the implants, levonorgestrel disappears from the circulation after few days, hence *the direct resumption of fertility and end of any menstrual bleeding disturbances upon removal* of the implants. This is in distinction from depot injectables whose effects can continue for some months after termination of use (see under POIC). This feature of immediate termination of effects upon removal of the non-biodegradable implants like Norplant contrasts with a number of biodegradable contraceptive implants which are currently under development. The merit of absence of the need for removal of these biodegradable implants is associated with the disadvantage of inability to directly terminate their effects.

Contraceptive effectiveness

Norplant is a highly effective long-term contraceptive. The cumulative pregnancy rate at the end of 5 years is approximately one per 100 women (table 5). This failure rate is comparable with the most effective female methods, including sterilization. Ectopic pregnancy rates are correspondingly low-0.3 per 1000 women-years.

So far, no harm or congenital anomalies have been reported in the rare pregnancies, which occurred during Norplant use.

Contraception Table 5: Pregnancy Rates according to years of Use

First Year	Second Year	Third Year	Fourth Year	Fifth Year
0.2%	**0.2%**	**0.9%**	**0.5%**	**1.1%**

Mechanism of action

The high efficacy results from the fact that levonorgestrel prevent pregnancy by at least four effects:

1. ***Inhibition of ovulation:*** The circulating levonorgestrel level is not high enough to suppress gonadotrophin release completely. Hence ovarian follicular development occurs irregularly, associated with intermittent peaks in circulating estradiol. However, levonorgestrel inhibits the positive feedback effects of these estradiole peaks on LH release. Consequently, ovulation is inhibited in about 50 % of cycles, as evidenced by absence of the luteal phase rise of progesterone (> 9 n mol /L). Inhibition of ovulation is more consistent during the first years of Norplant use. However ovulation may occur, particularly during the subsequent 3 years of use.
2. ***Luteal phase deficiency*** characterizes most of the presumed ovulatory events during Norplant use. This is evidenced by short-lived, modest elevations in progesterone during Norplant use.
3. ***Prevention of normal sperm transport*** through the female genital tract, particularly through the cervix. The cervical mucus in Norplant users is scanty, viscid and relatively less permeable to sperm in both *in vivo* and *in vitro* testing. This is an effect of the circulating levonorgestrel.
4. ***Inadequate development of secretary endometrium.*** This is an effect of both of inhibition of ovulation and of endogenous hormone plus the direct effect of levonorgestrel on the endometrium. On the rare occasions when fertilization might have occurred, the inadequate endometrial development will prevent implantation and hence normal embryonic development.

It is noteworthy that users of Norplant are *not* suffering from either hyperestrogenemia or hypoestrogenemia (the former could have exposed users to risks of endometrial hyperplasia, while the latter could have exposed them to the risk of osteoporosis and myocardial infarct). In fact, mean estradiol levels in Norplant users are very similar to those in women with regular ovulatory cycles. However; Norplant users exhibit irregular fluctuations of estradiol levels, but within the range normally found during the cycle. When estradiol levels fall, endometrial sloughing and uterine bleeding or spotting usually occurs. Because the peaks and troughs (nadirs) of estradiol levels in women using Norplant occur at irregular intervals, uterine bleeding also occurs irregularly in the majority of users. Follicular cystic development is occasionally observed during pelvic sonographic examination of Norplant users. These rarely exceed the diameter of 6 cm and are temporary.

Changes in Menstrual Pattern

The major side effect of Norplant is an irregular pattern of uterine bleeding. Changes in the timing, duration and volume of menstrual bleeding are common. In general, the flow is

light; heavy bleeding in women using Norplant is very uncommon. About half of women bleed fairly regularly at intervals of between 20 and 35 days; about 40 % have irregular menses with intervals outside this range and about 10 % are amenorrheic (defined as no bleeding for at least 3 months). Intermenstrual spotting or bleeding are likely to occur, particularly in early users. The menstrual pattern tends to improve with time of use. During the first year of Norplant use, about a quarter of the cycles are regular, but two-thirds are regular during the 5th years of use. Overall, the mean duration of bleeding per year declines steadily with time-from 54 days during first year to 44 days during fifth use. Consequently, the mean hemoglobin concentration tends to rise during Norplant year. This tendency for improvement of menstrual pattern stands in contrast with the tendency to increased incidence of amenorrhea in long-term users of progestogen-only injectables.

In the rare case of a pregnancy occurring in Norplant users, it is almost always in a woman with a recent history of regular cycles, i.e, she was probably ovulating normally. Hence, women who are amenorrheic or have infrequent episodes of vaginal bleeding after insertion of Norplant do not need monitoring for pregnancy with repeated pregnancy tests. It is noteworthy that women who have insertion of a new set of Norplant after removal of an expired set will not experience the early menstrual irregularities common during the early years of use of the second set.

Metabolic and Other Effects

- Routine biochemistry has shown that Norplant use does not significantly alter liver functions, renal function, and blood cortisol and thyroid function.
- Investigations of carbohydrate metabolism have revealed only minimal and inconsistent changes.
- Investigations of lipids and lipoproteins metabolism in Norplant have revealed a lowering of triglycerides, total cholesterol and LDL cholesterol, whereas HDL cholesterol was only slightly diminished or even increased. These results indicate that Norplant should not increase the risk of arterial atherosclerosis.
- No changes have been observed in the coagulation or fibrinolytic parameters. This indicates that Norplant should not increase the risk of venous thromboembolism.
- It is noteworthy that reliable epidemiological data are still lacking about rare cardiovascular risks on the arterial and venous side effects. A recently completed international study administered by WHO on post marketing surveillance of Norplant in a number of countries including Egypt, and which comprised 8000 Norplant users and comparison groups using IUD or sterilization, has demonstrated no significant excess of

myocardial infarction, stroke, venous thromboembolism, any malignant neoplastic disease in Norplant users relative to user of non-hormonal methods.

- About 30 % Norplant users have noted changes in body weight either weight gain or weight loss the former being more common.
- Headache is commonly complained of, but is usually mild and transient. However, headache is the second common reason for discontinuation after bleeding problems. Severe headache is exceptionally rare and should indicate removal of the capsules.
- Mood changes may occur particularly in the early months of use and include anxiety, nervousness, depression and diminished libido.
- Acne is a rare side effect.
- Longitudinal studies of bone mineral density in young women have shown an increase in bone mineral density after 1-2 year use of Norplant.
- The use of Norplant by breastfeeding mothers has been shown not to affect the growth or development of the breastfed infants.

Discontinuation of Norplant use

The usefulness of any contraceptive is measured not only by its efficacy in preventing pregnancy but also by the extent of continuation of use. In many settings, Norplant have shown a high continuation rate, better than those of some other temporary contraceptive like the COCs or POICs and comparable to the continuation rates of the second-generation IUDs (like T Cu 380). At the end of 5 years, about 25 % Norplant users will have requested removal of the implants because of bleeding problems. Another 15 % discontinue because of other medical problems, such as headache and weight gain. About 20 % of discontinue for the wish to become pregnant. This means that about 40 % of users are expected to continue using the method up to the end of its 5-year efficacy term. A recently reported big international study reported a higher 5-year continuation rate of Norplant 67 %; while the 5-year continuation of IUD in a comparison group was 65 percent. Through proper counseling (before insertion in particular) regarding the cause and nature of adverse effects, such as bleeding disturbances to be expected with Norplant reduction of discontinuation can be achieved. Norplant use requires “a service that cares”. Under no circumstance there should be any obstacle that prevents Norplant removal; directly on user’s demand.

Advantages of Norplant use

1. High efficacy.
2. Effective within 24 hours after insertion.
3. Long term, cost-effective.

4. Requires one decision on the part of prospective users. Nothing to remember is entailed, other than the time when the term of efficacy expires.
5. Not related to sexual act.
6. Can be used during breastfeeding. Norplant can be inserted 6 weeks after childbirth.
7. Suitable for women who have reasons to avoid using estrogen-containing contraceptives COCs.
8. Fertility returns almost immediately after the capsules are removed.
9. Helps prevent ectopic pregnancy.
10. Helps prevent iron deficiency anemia.
11. Helps prevent endometriosis.
12. May help prevent endometrial cancer.
13. May make sickle cell crises less frequent and less painful.
14. Insertion involves only minor pain of anesthesia needle.
15. Can be used by smokers.

Disadvantages of Norplant Use

1. Common side effects
   - Mainly menstrual bleeding disturbance.
   - Headache and mood changes.
   - Weight change.
2. Client cannot start or stop use on her own. Capsules must be inserted and removal by specially trained health care provider.
3. Difficulty in removal. This should be rare but can occur in 1 % of cases.
4. Does not protect from STDs. Recent data do not indicate any relation to change contracting HIV infection or progression of AIDS.

Eligibility

Norplant is suitable for women planning for a long term contraception, including

- Breastfeeding mothers starting from the 6th week postpartum or have recently aborted; directly after the abortion Norplant can be inserted.
- Any age.
- Any parity.
- Fat or thin.
- Smokers.
- Schistomiases.
- History of thrombosis.

- Headaches (except if severe and associated with focal neurological symptom).
- Benign breast disease.
- Varicose veins.
- Valvular heart disease.
- Pelvic inflammatory disease.
- History of ectopic pregnancy.
- Endometriosis.
- Fibroids.
- Gall bladder disease.
- Epilepsy.

Norplant can be used in presence of the following medical conditions if alternative contraceptives are not available or acceptable, the benefits outweigh the theoretical or proven risks:

- High blood pressure.
- Diabetes.
- Thyroid disease.
- Mild cirrhosis.
- Tuberculosis.

Norplant is better not be used in women with

- Current or history of ischemic hears disease.
- Current or history of stroke.
- Current or past breast cancer.
- Unexplained uterine bleeding until the cause is known.
- Severe headaches.
- Active hepatitis.
- Under treatment with rifampcin, phenytion.
- Suspected pregnancy.

Procedural Guidelines for Norplant

Due to the special implications of Norplant use which include: the long-term use, the need for minor surgical procedures for its insertion and removal, the frequency of disturbed menstruation during use, and the concern about the occurrence of coercive use, certain programmatic provisions are required in its wide-scale use. The quality of service provided is a major determinant of successful use of this method and of the subsequent degree of satisfaction of users. The Norplant services need to fulfill the following procedural guidelines:

1. *Adequate preuse counseling*

Norplant should be offered as one of all contraceptive options available to the prospective users. The merits and demerits of Norplant should be adequately mentioned in comparison with the other option available for the particular women. Among the merits that can be mentioned are the long-term, and high efficacy and the absence of worry about mistakes in use. On the demerits is the need for a minor procedure for insertion and removal and the high probablity of menstrual irregularity. The counseling should aim at enabling the woman (and her husband) to make an informed choice. In the Egyptian setting the implications, of menstrual irregularities for Muslims deserve special clarification (see under POICs)

2. Insertion procedure

a. When to start:

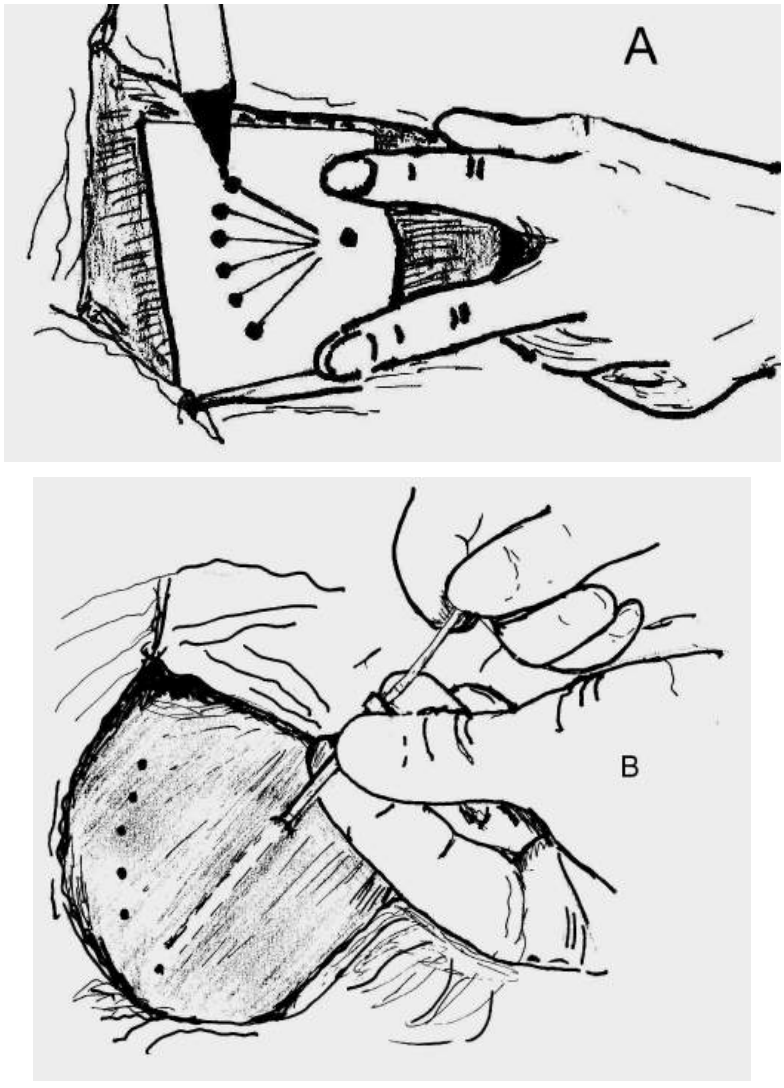
- During the first 7 days after menstrual bleeding starts.
- Later in the menstrual cycle when it is certain that the women has not already conceived.
- At the 6th week postpartum if the woman is breastfeeding.
- Immediately after childbirth if she is not breastfeeding.
- Immediately after abortion.
- Immediately on stopping other methods.

b. Steps of Insertion:

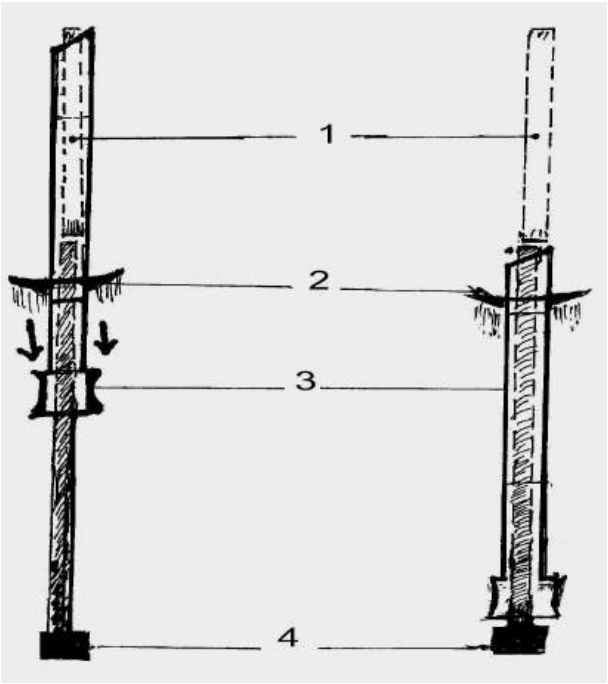
Learning Norplant implant insertion requires training and practice under supervision. The following principal steps need to be ensured:

1. Adequate asepsis. Sterilization of instrument, disinfection of hands of provider, and the skin of the upper arm of the subjects and proper drappings.
2. A small amount of a local anesthetic injected under the skin at the site of insertion; usually the inner aspect of the non-dominant upper arm (alternatively on the gluteal region).
3. A small scalpel incision (3 mm) in the skin on the inside of the upper arm.
4. The six capsules are inserted in a fan-shaped geometry that fans out from the site of the incision. A template (like that used in plastic surgery) can help to mark on the skin where the upper ends of the six capsules will be. When inserting the capsules, the provider lines up each capsule with one of the marks on the skin (Figure 13).

5. The capsule should be inserted superficially just under the skin. This is essential for their identification at the time of removal. Easy removal depends on careful insertion.
6. The capsules should be inserted by a withdrawal procedure (figure 14); the capsule should not be pushed out of the inserting trocar; the trocar is withdrawn from around the capsule. This will, at the end, ensure that the entire six capsules have their distal ends near the insertion site. One should avoid pushing the inserted capsule by its fellow next capsule.
7. After all 6 capsules are inserted; the incision is covered by an adhesive bandage, no need for stitching. The site of insertion is wrapped with gauze. Insertion takes 5 to 10 minutes. Slight bruising may occur.



Contraception: Figure 13 Norplant insertion; A. marking the position of the six implants with a template and a ball pen; B. Loading the first implant in the insertion canula.



Contraception: Figure 14 Insertion of Norplant capsule by withdrawal of the trocar.*1. The Norplant capsule; 2. the skin incision; 3. The trocar; 4. The plunger. While the plunger is fixed the trocar is moved out leaving the capsule under the skin. Note the trocar is withdrawn until the upper mark is just below the incision.*

Removal procedure

This is usually more difficult than insertion, and requires careful training. It entails the following principal steps.

1. Use the proper infection-prevention procedure.
2. The woman is given an injection of a small amount of a local anesthetetic agent. Injection of a big volume of this anesthetetic may make identification of the capsules difficult.
3. A small incision is made at about where the capsules were inserted.
4. By pushing each capsule through the skin, its distal end can be made to appear in the incision, from which it is pulled out with a fine artery forceps. This forceps may need to be pushed under the skin to get hold of the end of the capsule.
5. Easy removal depends upon proper insertion. Fibrosis does not occur around the capsules. They do not migrate away from the site of insertion. The capsule found away from the site of insertion had always been pushed away by a subsequent one at the time of insertion. Rarely, such an outlying capsule may require a second incision over its end.
6. An alternative technique for removal of Norplant capsule is the U-method of removal. The removal incision is made between the capsules which are then hooked out by a

special fine vasectomy forceps which encircle the middle part of the capsule, and pull it out bent in a U-shaped configuration.

7. The incision is covered by adhesive bandage and the site is wrapped by gauze.

Removal takes about 10 to 15 minutes and occasionally requires more proficiency than insertion. If difficulty is experienced, the removal procedure should be stopped, and the subject is referred to someone with more experience.

3. Follow-up and management of complaints

- Each woman should be given a durable card giving the date of insertion and the date when the 5-year term of Norplant expires.
- Mention to the user again the expected side-effects. In particular, she can expect changes in menstrual bleeding, spotting and amenorrhea.
- She can come to the clinic whenever, she develops any side effect. No particulars schedule is required, and no special physical is required. However, when she comes with any complaints, these need careful consideration. If after proper counseling she asks for removal, this should be immediately done for her. She should not be rescheduled for another visit. Removal service should be as easily available as the insertion service. The management of bleeding disturbance should follow the same lines detailed under POICs.
- The woman should be instructed to come to the clinic on the rare occasion of: suspecting pregnancy, having an acute abdominal pain or a bad headache.
- The clinical logbook should indicate the women who should have had removal because of end of term. The method has a long grace period, and no harm occur for the women if the use is extended for few months, other than the increased chance of failure of contraception.
- Insertion of a second set of Norplant can be immediately made at the time of removal of the first set.

Newer Implant Systems

❑ Norplant – 2(the rod implant system)

Due to difficulty in removal of the 6 capsule of the Norplant system, there have been trails to reduce the number of the implants used. Norplant-2 is the alternative which is most advanced on the line of production. The Population Council has produced norplant-2. It consists of two solid rods made of Silastic (or similar elastomere) in which levonorgestrel is dissolved, and the rod is covered with a thin film of silastic covering. The thinner covering

and different diffusion properties result in the two rods releasing nearly the same amount of the steroid and ensuring the same blood levels of levonorgestrel for the same duration of 5 years as in the original Norplant six capsules. Norplant-2 rods are slightly longer (4 cm) than Norplant capsules, and are inserted (with a different canula) but removed in the same way as the original Norplant. Because of advantages in manufacturing and in removal of the two rods in contrast to the six capsules, and equal efficacy and clinical performance, Norplant-2 is expected to replace soon the presently used Norplant system. Norplant-2 has been already approved in USA and Finland.

❑ Implanon

This is a one-rod system developed by Organon Pharmaceutical Company; The active progestogen is 3-Keto-desogestrel, and is an effective contraceptive for two years. It has already been approved in the UK and Indonesia.

❑ Uniplant

It is one capsule system containing the progestogen Nomegestrol acetate. It has been developed by the organization South-to-South Cooperation in Reproductive Health. Parts of phase II trials have been successfully completed in Assiut, Egypt. Besides high efficacy, comparable to that of Norplant, Uniplant has the special merits of easy insertion and removal, and the minimal effects upon various metabolic functions. A study in Assiut has demonstrated safety of use of uniplant during breastfeeding; when the use was initiated during the second postpartum month it did not interfere with growth, development and health of breastfed infants.

❑ Nestorone implant

The Population Council has developed a single-rod system that contains the progestogen Nestorone (ST 1435). It is intended for 2 years use. This progestogen has the special advantage of being not effectively absorbed from the intestines. Consequently it should be a safe contraceptive during breastfeeding; any amount of the progestogen secreted in the breast milk will not reach the systems of the breastfed infant. It can also have certain metabolic advantages over levonorgesterel releasing systes.

❑ Capronor

This is *a biodegradable* delivery system for levonorgestrel. This is still under development. Levonorgestrel is dissolved in a carrier material of poly-lactic- glycolic polymer which will control its release from the site of implantation ensuring an almost zero-order release over 12 months. This system has the merit of absence of the need for removal. However if side effects develop it will be difficult to remove it. Consequently, this system is not expected to gain wide acceptance.

Spermicides

Contents:

- Types and formulations
- Advantages and disadvantages

Until the modern types of contraception like hormonal methods, the IUDs, and sterilization have become available; spermicides were an important method of fertility control. Now the use of spermicides is limited because they are not very effective in preventing pregnancy. This is in spite of the fact that they are highly effective in killing or immobilizing sperm when tested *in vitro*. This is because, when applied in the vagina they do not disperse widely enough to deal with all the sperm in the vagina. Spermicides are more commonly used to enhance efficacy of other barrier methods like the diaphragm or condom. They may be occasionally used alone, but they are not reliably effective. Another aspect of use of spermicides is their possible effect in preventing transmission of sexually transmitted infections. Presently, there is a great interest in developing and evaluating spermicides that can not only prevent pregnancy, but can also kill and reduce the chance of infection with bacteria, chlamydia and viruses particularly HIV.

Types and Formulations of Spermicides

Spermicides preparations consists of two components:

- a sperm-killing chemical.
- a base or carrier which is responsible for dispersing the chemical in the vagina over the cervix, and holding it in place for some time.

The *sperm-killing ingredient* in many products is nonoxynol-9, a potent surfactant that kills sperm cell by destroying their cell membrane. It is the active ingredient in many vaginal suppositories (like Contra-Seed available in the Egyptian market), Jellies, foam tables and films. Other surfactant spermicides include benzalkonium chloride, Octoxynol, menfegol. The latter is the spermicide in the foaming vaginal suppository called Neosampoon (available in Egypt). Spermicides that use enzyme inhibition like A-gen 53 has been used.

***Spermicides can be carried in*:**

- Suppositories or tablets, which can have either a wax or water-soluble base. They should be inserted high in the vagina at least 15 minutes before intercourse to allow time for dissolution and dispersion of the spermicide.

- Foam tablets usually contain sodium bicarbonate and an acid and once it gets wet; carbon dioxide is released. This produces a foam that carries the spermicide to the greater part of the vagina. The foam contributes to contraception by reducing contact between semen and the cervix. The foam tablet should by inserted few minutes and no later than one hour before intercourse.
- Foam aerosols. Ready made foam can be injected into the vagina from a pressure can through a pliable nozzle that can be inserted high in the vagina.
- Jellies usually have a water-soluble base such as gelatin, which liquefies rapidly at body temperature, allowing the active spermicide to spread throughout the vagina. It should be inserted high in the vagina.
- Creams have an emulsified fat base, which is insoluble in water. They tend to remain where they are put, and do not spread wide in the vagina. They are suitable for use in conjunction with barrier methods.
- Thin water-soluble films containing the spermicide: e.g. contraceptive or C-films, 5 cm in diameter. The film is folded in half and inserted with dry fingers near the cervix. This film dissolves releasing the spermicide.

How to use spermicides:

- They are commonly used to enhance the efficacy of barrier methods, or can be used on its own.
- The woman inserts the spermicide in her vagina before each act of sexual intercourse.
- They are applied 15 minutes before and no later than one hour before intercourse.
- She should not douche the vagina for at least 6 hours after intercourse.

Effectiveness of spermicides

The effectiveness is highly influenced by the degree of motivation of the couple, the care exercised in their application and the education they received. The typical effectiveness when used alone in the family planning clinics varied widely ranging from 3 to over 20 pregnancies per 100 woman-years. Therefore, the effectiveness is far from perfect, but they are better than nothing.

Effect on STDs transmission:

Spermicides prevent STD infection by inactivating bacterial and viral pathogens through disrupting bacterial cell membranes and viral envelopes. When tested *in vitro* they are highly effective, but when tested in vivo they confer a moderate protection.

The protection is enhanced when spermicides are used in conjunction with barriers. Such combination reduces the incidence of infection with gonorrhea, chlamydia, trichomonas and bacterial vaginosis. They also reduce the incidence of PIDs. They have been also shown

to reduce the risk of cervical cancer (which have been shown to be dependant on certain viral infections). It is not yet certain whether spermicides protect against HIV *in vivo*.

❑ Advantages of spermicides

- Enhance the effectiveness of barrier methods.
- A woman controlled method.
- No systemic side effects.
- Not requiring a daily action.
- Not interfering with breastfeeding.
- Can be used with little practice.
- May increase vaginal lubrication.
- Help in preventing some STDs and conditions caused by STDs-PID, ectopic pregnancy, infertility, and possibly cervical carcinoma.

❑ Disadvantages of spermicides

- Not very reliably effective. Effectiveness requires care and consistency in use.
- Not suitable for women in whom pregnancy is especially dangerous.
- May cause irritation to the woman or her partner, and may cause local allergic reaction.
- May increase the chance of urinary tract infection.
- May be messy and objectionable from the partner.
- Melting types must be placed in the vagina 15 minutes before intercourse and not more than one hour.
- Some types may melt in hot weather.
- Foaming tablets-may cause warm sensation.
- Entails manipulating the genitalia that may be objectionable for some women.

Barrier methods

Contents:

A barrier method of contraception prevents spermatozoa from reaching the upper genital tract. The most important method of this type is the male *condom.* Methods inserted in the vagina include the *diaphragms, sponges, cervical cap,* and recently the *female condom*. A spermicide is usually used with the vaginal barriers and these enhance their effectiveness. However, the use of a spermicide in conjunction with the condom has not been proven to enhance the effectiveness of the condom.

Male condom

The pre-Islamic Arabs used to have intercourse with enslaved women from behind their underwear to avoid them getting pregnant. In Roman times animal bladders were used for protection against venereal disease rather than as a contraceptives.

Modern condom is generally made of latex, a product of the rubber tree. They are manufactured in a thin, stretchable film made by two stage dipping process on a glass mould. It is dried by heating and rolled off the glass mould before being dusted with talc. The condoms are subjected to a number of quality controls including testing for tensile strength. The condoms are then lubricated and packed, ready rolled, in a foil wrapper. Latex condom may deteriorate on long storage particularly in hot weather. The latex condoms available have a thickness ranging between 0.03 and 0.05 mm. This is a thickness that ensures resistance to bursting under stresses of sexual intercourse together with least interference with sensations. The condom length generally ranges from 16 to 22 cm, the flat width varioes 4.9 to 6.5 cm. Some condoms have a teat end to contain the ejaculate. They are available in different colors.

Plastic condoms are less commonly used. They are made of the synthetic plastic polyurethane (PUR). They have the advantages of being thinner 0.025 mm and therefore transmit sensation and heat better than latex condom. Plastic stores for indefinite period, it has better lubricity, and plastic condom is easier to manufacture. However, it may break at the side seam. i.e. it may be less reliable. Plastic condom cost more but might be reusable. All these merits and demerits are still in the process of evaluation and improvement.

Skin condoms made of the caecum of young lambs, are rarely available. It is claimed to be better in conducting sensation in intercourse. It is expensive and therefore rarely used. Skin condoms may be less efficient in preventing transmission of viral STDs.

Use of the condom:

The condom is a good contraceptive for a steady relation between motivated couples having occasional intercourse. It can also be used in conjunction with periodic abstinence

being used during the fertile phase of the cycle. It is best suiting an unplanned sexual intercourse. However, interest in the condom has been recently emphasized to prevent transmission of STDs. Latex condoms, correctly and consistently used, effectively reduce the risk of transmission of STDs, including the human immunodeficiency virus (HIV). " The day of the condom has returned "; around the world, an estimated 50 million couples use the condom as a method of contraception (may be along with another contraceptive), and there are indication that its use is rising. This is the only presently available method to slow down the enlargement of the pandemic of AIDS. The popularity of the condom ranges widely in different countries between 10 % of contraceptive couples (as in Japan) to less than 1 %, which may be the level of utilization in Egypt.

Mechanism of action

Condoms placed over the erect penis act as barrier methods, preventing sperm from entering the vagina. Some condoms are coated with spermicide, but it has not been proven that this effectively increases the efficacy of the condoms particularly in reducing the incidences of condom break.

Effectiveness

The condom is moderately effective in preventing pregnancy when employed in the typical use (use effectiveness)-resulting in average failure rate of 12 pregnancies per 100 women in the first year of use. The consistency and care in use evidently diminishes the failure rate. When consistently and correctly used it results in only3 pregnancies per 100 women in the first year of use. The failure usually results from breaking of the condom during intercourse or slipping off the penis before it is withdrawn.

The condom efficacy in protecting women against HIV transmission has been variously estimated between complete prevention and reducing the rate of infection of the undiseased partner to one-sixth of the rate of nonusers. Condom also effectively reduces the chance of infection by other STDs like gonorrhea and chlamydial infection, the relative risk of infection varied in different studies between 0.0 to 0.51.

Advantages and Disadvantages

Advantages

- Safe. No side hormonal effect.
- A reasonably effective method of contraception if used correctly.

- Can be used in an unexpected sexual intercourse, e.g. unexpected return of the husband.
- Can be used to cover a period of uncertain efficacy of another contraception, e.g., missing two or more COC pills on a row, early days of use of POPs, or removal of the IUD during a fertile period and until another reliable method can be initiated.
- Offer an occasional contraception with no daily upkeep.
- Encourages male participation in contraception.
- Can be used shortly after childbirth.
- Can be used without seeing a medical provider.
- Prevents STDs, including HIV.
- Helps protect against PID, infertility and, may be, cervical cancer.

Disadvantages:

- May decrease sensation, making sex less enjoyable for either partner.
- Not suitable for men who cannot maintain erection.
- Couple must take the time to put the condom on the erect penis.
- Supply of condoms must be kept ready.
- Not always reliable. There is a possibility that the condom may slip off, or break during sexual intercourse.
- Latex may cause itching for either partner who is allergic to rubber or to the lubricant on some brands of condoms.
- Condoms can deteriorate on long storage (years after date of production) particularly in hot, humid weather, or upon exposure to sum.

Instruction to users:

1. A new condom for each act of intercourse.
2. Put the condom on the erect penis before the penis touches the vagina.
3. Hold the condom so that the rolled rim is facing up. Place the condom on the tip of the penis, and then unroll the condom all the way to the base of the penis. Leave 1 ½ cm of empty space at the tip. The condom should unroll easily, if not it has been damaged; use another one
4. Wait until the vagina is well lubricated, because a condom tears if the vagina is dry. If extra lubrication is needed, use water, saliva, K-Y jelly, or spermicidal foam or cream. Don't use oils or Vaseline-they damage the condom.
5. After intercourse, withdraw the penis immediately (before the erection softens), holding on the rim of the condom to prevent spilling.

6. Check the condom for tears before throwing it way. If the condom has torn, quickly insert spermicidal foam or jell into the vagina. It is better to consult with the physician; an emergency contraceptive can be used. (See under EC)
7. Store the condom in a cool dry place; a bedside cupboard is reasonable. Immediately dispense with the used condom in the toilets, or team buried or burnt.

Diaphragm

The diaphragm is a dome-shaped rubber cup with a flexible rim. It is inserted into the vagina before intercourse so that the posterior part of the rim rests in the posterior fornix and its anterior part fits snugly behind the pubic bone, with the dome covering the cervix. Correctly placed condom will separate the posterior vagina, where semen is usually deposited, from the cervix. A spermicidal jelly or cream should be placed in the dome side that will face the cervix before the diaphragm is placed in the vagina.

Diaphragms made of rubber were introduced in 1880s and has its widest use in Holland hence the name *Dutch Cap*. The type most widely available now has a malleable spring-loaded rim. When the rim is folded it assume an arc form that allows its easy insertion. When the rim is left to unfold it fits in the posterior fornix and the anterior rim is then manipulated to rest behind the pubic bone. The cervix uteri can be felt through the dome. It is reusable. After each use it is checked for holes then washed in soap and water, dried and dusted with talc and stored.

Diaphragms are available in a rage of sizes 60 to 85 mm, corresponding to the rim diameter in millimeters. The correct size is chosen by fitting trails by the health provider. The provider will teach the users on method of application and should check her ability on correct placement.

Effectiveness of diaphragm

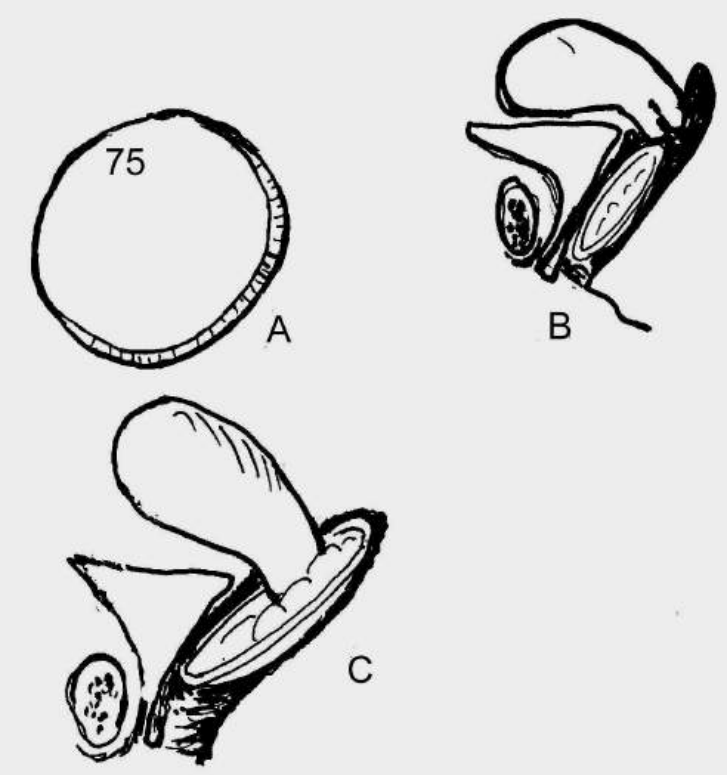
Like all barrier methods, factors other than inherent method effectiveness are extremely important in determining success with the diaphragm. Such factors include:

- Inherent fertility of the couple.
- Frequency of intercourse.
- Ability of the users to master proper use.
- Degree of motivation of the couple.
- Care and time given by the provider in choosing the proper method, instructing on correct use and discussing the possible pitfalls.

When used with spermicides the effectiveness in the "usual" typical use of the diaphragm is in the region of 15 % i.e. 15 pregnancies per 100 woman-years. Among perfect user the effectiveness can be as high as 3 %.

The efficacy of diaphragm (along with spermicide) in preventing STD transmission, and in preventing their consequences like PID and cervical cancer is much less certain than the protection given by the condom.

Instruction on use of diaphragm



Contraception Figure 15: Contraception by the vaginal Diaphragm. *A. the diaphragm itself 75 mm; B. The diaphragm is incorrectly placed; c. the diaphragm is correctly placed with the upper rim in the posterior fornix and the lower rim ± 3 cm above the introitus.*

1. The woman holds the diaphragm with the dome down like a cup.
2. She squeezes about a tablespoon of spermicidal cream or jelly into the cup of the diaphragm and smear the rim with the spermicide.
3. She presses the middle part of the rim together, with the dome side towards her palm, pushes the diaphragm into the vagina as far as it goes.
4. With the index finger, she ensures that the posterior part of the rim gets behind the cervix, and then moves the anterior rim to behind the pubis. Through the dome of the diaphragm, she should feel the cervix like the tip of the nose.

5. For each additional act of intercourse, she uses a fresh application of spermicidal jelly or cream in the vagina, but *without* removing the diaphragm.
6. The woman leaves the diaphragm in place for *at least 6 hours* after the intercourse. She does not leave the diaphragm in for more than 24 hours. Doing so might increase the risk of toxic shock syndrome.

   Toxic shock syndrome (TSS) is a rare but serious illness caused by anaphylaxis to bacterial toxins absorbed from the vagina. TSS has been observed in users of vaginal tampons used to contain menstrual flow. A few cases have been reported in diaphragm and cervical cap users. The longer a diaphragm or cap is left in place, the more the bacteria can grow. Symptoms are sudden high fever, body rash like sunburn, vomiting, diarrhea, dizziness, sore throat and muscle aches, tachycardia and hypotension. Treatment with antibiotics, intravenous fluids and corticosteroid is very effective.
7. She gently hooks out the lower rim of the diaphragm for removal.
8. She washes the diaphragm, and dries it in air; powder it and keep in a cool place.

Vaginal Contraceptive Sponge

It is small, pillow-shaped polyurethane sponge that contains 1 gram of nonoxynol-9 spermicide. It has a concave dimple on one side, which it is intended to fit over the cervix and decrease the chance of dislodgment during intercourse. The other side of the sponge has a woven polyester loop to facilitate removal. The sponge is available in one size. It is moistened with tap water prior to use and is inserted deep in the vagina. Once in place, the sponge provides Protection for up to 24 hours. After use it is discarded, is not intended for repeated use.

First year failure rates reported for sponge ranged between 15 and 25 per 100 woman year. This is too high to allow a wide scale use.

Cervical Cap

The cervical cap is a cup-shaped rubber cup that fits over the cervix and is held in place, at least partially, by suction between its firm, flexible rim and cervix. Recently a cap intended for continuous use incorporate a one-way valve that allows escape of mucus an menses. However, caps are more difficult to apply than diaphragm and have been shown to have a high failure rate.

Female Condom

A female condom has been recently approved for marketing in the US. It consist of a soft, loose fitting tubular sheath and two flexible polyurethane rings at its ends. One ring is

positioned inside the vagina at the closed blind end of the sheath, and serves as an insertion mechanism and internal anchor. The outer ring forms the external edge of the device and remains outside the vagina after insertion, protecting the vulva and the base of the penis during intercourse. The man's penis goes into the sheath. It is intended for one use and does not require fitting by health care provider.

Compared with the male condom, the female condom offer an advantage in that it can be inserted prior to beginning sexual activity and left in place for a longer time period after ejaculation. Because the female condom also covers the external genitalia, it should offer greater protection against the transfer of certain STD organisms, particularly genital herpes and papilloma virus. Being made of polyurethrane, the female condom is less likely to rupture than the latex male condom. The female condom is a woman-controlled method to protect against pregnancy and STDs.

Effectiveness is similar to male condoms and other barrier methods-As commonly used (typical effectiveness) is 20 %, when perfectly used 5 %.

Natural Methods of Contraception

Contents:

- Abstinence
- Coitus interrupts
- Periodic abstinence
- Lactational amenorrhea method (LAM)

These approaches depend on utilization of knowledge about natural bodily changes (physiology) to avoid the occurrence of pregnancy (contraception) without the use of any medication or appliance.

They comprise the following methods

- Abstinence,
- Coitus Interrupts = Withdrawal,
- Periodic abstinence, and
- Lactainal Ammenorrhea Method LAM.

Abstinence

Historically, sexual abstinence has probably been the single most important factor in curtailing human fertility. In Man sexual intercourse has not only been determined by instinct

but also by certain personal and social factors. Marriage has been the most important amongst the latter factors. Extramarital relations have undoubtedly been made safer, and encouraged by availability of modern time contraceptives, which are accessible and reliable.

At the personal level, abstinence is most unnatural. Even utilizing all the range of methods of sexual expression, short of penis-in vagina intercourse are not humanly satisfactory, but can occasionally be utilized by certain couples. Certain types of abstinence have been and are being widely used in many communities and these include:

1. Extramarital abstinence as determined by religions and social norms can avoid many pregnancies, which are usually unwanted and high-risk. Delaying the age of marriage may have a demographic impact besides its health and social merits (see under Health Rationale of Family Planning). After the worldwide pandemic of AIDS and other STDs, extramarital abstinence has never looked better.
2. Lactional abstinence (abstinence from sexual intercourse) is practiced in certain communities. However, it is not required by Islamic and Christian doctrines. Islam has clearly permitted sexual intercourse during lactation.
3. Terminal abstinence. This is a curious, socially determined, practice in certain Sub-Saharan African communities wherewith a women is not socially acceptable to have sexual intercourse (to get pregnant) after getting her first grandchild!!

Coitus Interrupts

Coitus interrupts, or male withdrawal, is very old, widespread, and at times effective method of contraception. The historical origins of the method dates back to the beginning of Man. The book of Genesis describes that Onan (Kabeil in Arabic) son of Adam have spilled his seed upon the ground to avoid impregnating his brother's wife. Later, Jewish and Christian teachings proscribed the practice. Islam, however, has allowed the practice for the indication of contraceptive. It has been widely used practice in many countries including Egypt until the more reliable modern contraceptive methods have become available. Coitus interrupts is believed to be responsible for the onset of demographic transition from high to low fertility.

A couple using the withdrawal method have sexual intercourse until ejaculation is impending, at which time he withdraws his penis from vagina. Ejaculation should occur completely away from the vagina and the external genitalia of the female partner. There are two reasons for failure of withdrawal method:

1. Lack of self-control, the man may feel the urge to achieve deeper penetration at the time of impending orgasm, so may not withdraw in sufficient time to prevent semen from being deposited on the his wife's external genitalia.

2. Some pre-ejaculatory fluid (called in Arabic Mazei) can escape at any time before ejaculation. This fluid contains sperm; a drop can contain millions of sperm. This fluid contains more sperm after a recent ejaculation; the likelihood of failure due to release of this pre-ejaculatory fluid increases with the occurrence of multiple orgasms within a short span of time.

Advantages and disadvantages

As a method of contraception, coitus interrupts, requires no devices, involves no chemicals, and is available at no cost. However it has a high failure rate. Among typical users (not specially selected for a study) the failure rate is 20 % during the first year of use. In perfect users who are highly motivated and careful the failure rate is about 5 % during the first year of use. It has the other disadvantage of interruption of the excitement at the plateau phase of sexual response cycle that may diminish the pleasure of a couple. Another disadvantage is that the method is not under control of the woman.

Couples utilizing coitus interrupts who dislike shifting to other more reliable methods should on no account be discouraged from using it (after receiving counseling about other available options) , it is better than nothing.

Periodic Abstinence or Fertility Awareness-based Methods

Fertility awareness is a method or combination of methods of preventing pregnancy (or planning it) by identifying the fertile days of the menstrual cycle.

Fertility awareness methods depend upon teaching the women how to know when the fertile time of her menstrual cycle starts and when it ends (i.e. the time during which she can get pregnant).

A woman can use several ways to tell when her fertile time begins and ends:

1. *Calendar calculations methods*
2. *Basal body temperature (BBT).*
3. *Cervical mucus change, Billings' method.*
4. *Feeling of the cervix.*
5. *A woman may use combination of the above.* To tell when the fertile time starts, she can use calendar calculations and cervical secretions. To tell when the fertile time ends, she can use BBT, cervical secretions and calendar calculation: The use of the combination of approaches is *called Symptothermal or multiple-index method.*

The couple avoids pregnancy by changing their sexual behavior during fertile days. They can:

- Abstain from vaginal intercourse completely during this period. This practice is called periodic abstinence and Natural Family Planning (NFP). This is the method acceptable to the Catholic Church.
- Use withdrawal during the fertile period.
- Use barrier methods like condoms, diaphragm plus spermicide, or spermicide alone during this period.

Calendar Calculation Method

Worldwide, the calendar calculation method is the oldest and most widely used of fertility awareness methods. *The physiological basis of the method is that:*

1. Ovulation occurs 14 days before menses. The variation in the length of the menstrual cycle between women, and from one cycle to the other in the same women, is on the expense of the length of the preovulatory (follicular) phase. It is not widely appreciate that the length of the normal menstrual cycle tends to vary from a cycle to another within usually $\pm$ 4 days and from one woman to the other within a range of 21 and 35 days.
2. The ovum can be fertilized as late as 24 hours after ovulation and sperm can live up to 8 days in a woman's body.

How to calculate the day of start and the day of end of fertile period.

- Before relying on this method, the woman records the number of days in each menstrual cycle for at least 6 cycles. The first day of menstrual bleeding is always counted as the beginning of the cycle and the day before the day of start of the subsequent menstruation as the last day of cycle.
- The woman subtracts 18 days from the length of her shortest recorded cycle. This tells her the estimated *first day* of her fertile time. Then she subtracts 11 days from the length of her longest recorded cycle. This tells her the *last day* of her fertile time.

Examples:

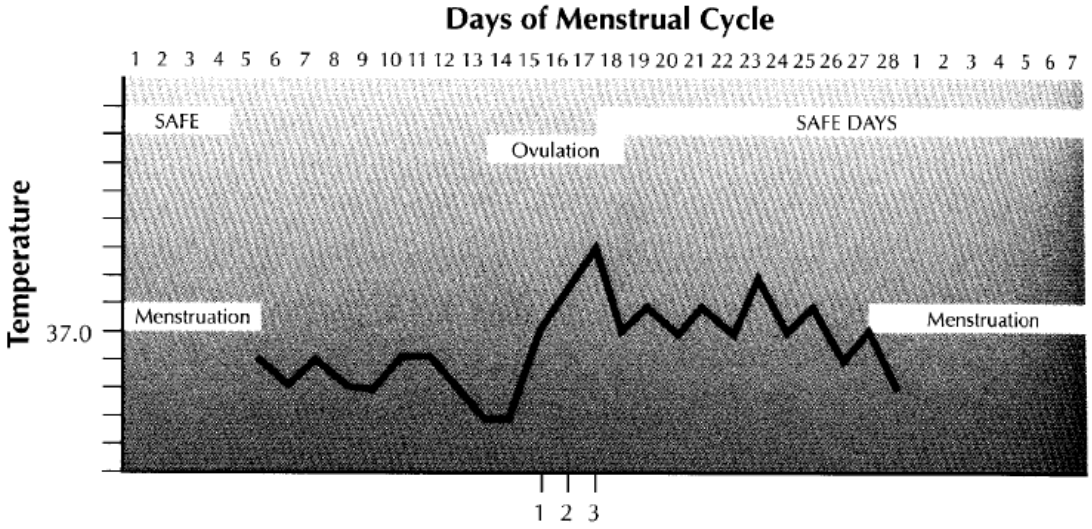
1. If her recorded cycles vary in length from 26 to 30 days
   - 26-18 = 8. She starts avoiding unprotected sexual intercourse on the 8 th day of her subsequent cycles.
   - 30-11 = 19. She can have unprotected sex again from the 20 th day of her cycles. This means that she must avoid unprotected sex from 8 through day 19 of the cycle. This means avoiding unprotected sex for 12 consecutive days each month.

2. When the woman has a greater variability in the length of the cycle the calendar method become more restrictive, e.g.. if her recorded cycles vary in length from 26 to 34. She has to avoid unprotected sex from day 8 through day 23 of her cycles. This means avoiding unprotected sex for 16 days. This may prove too restrictive for such couples to practice periodic abstinence. This couple may use in addition to calendar calculation other approaches of fertility awareness to identify the end of the fertile phase e.g. BBT or cervical mucus method i.e. a multiple index approach. This allows the couple more days of unprotected sex.

Basal Body Temperature (Rhythm) Method

The rise in basal body temperature indicates that ovulation has occurred but does not predict it. It is due to the thermogenic effect of the progesterone produced by the corpus luteum. The temperature *may* drop slightly about 12 to 24 hours before ovulation. After ovulation, the temperature rises 0.2 ° Celsius to 0.5 ° Celsius (Figure 16 FPM 484). A true postovulatory temperature rise lasts about 10 days. Because body temperature response to many stimuli, including illness, stress, and disturbed sleep, the interpretation of the temperature pattern requires cautious judgment. Some women do not exhibit any rise at all.

A woman using temperature chart must consider herself fertile from the beginning of her cycle until her temperature has been elevated for 3 consecutive days.



Contraception Figure 16: Biphasic basal body temperature chart

Basal body temperature (BBT) to identify the end of the fertile period:

- The woman must take her body temperature in the same way, orally, rectally, or vaginally, at the same time each morning before she gets out of bed. She must know how

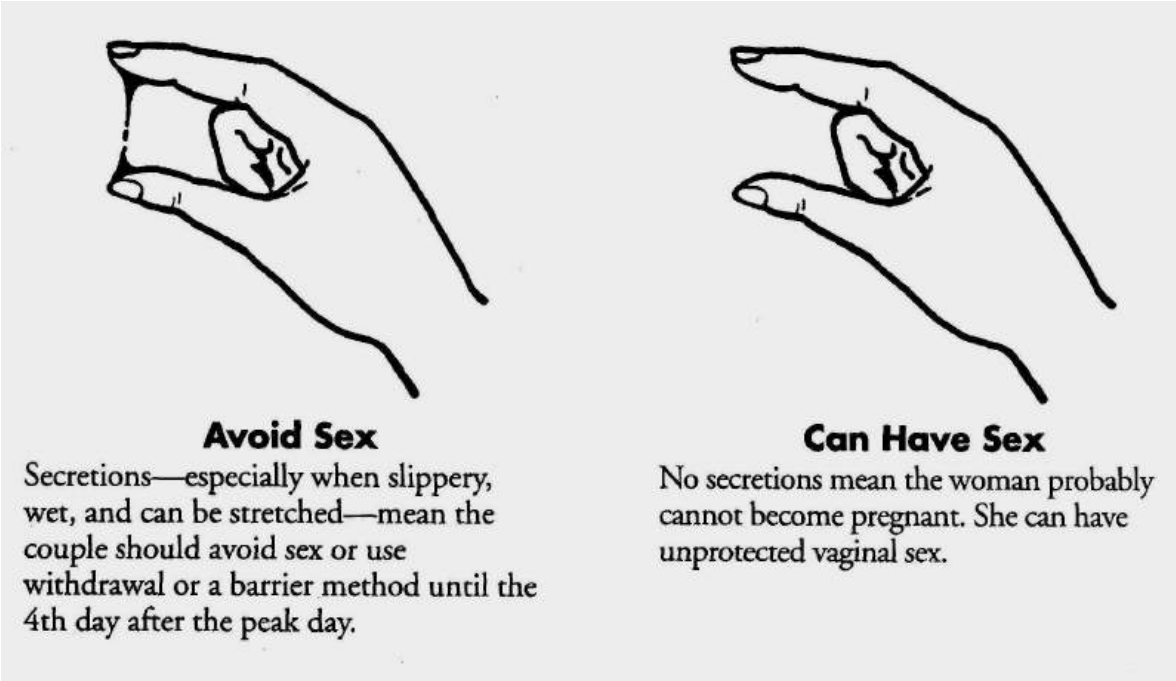
to read the thermometer and must record her temperature on a special graph (provided to her).

- The woman's temperature rises 0.2° to 0.5° Celsius around the time of ovulation (about midway through the menstrual cycle).
- The couple avoids sexual intercourse, use a barrier method, or use withdrawal from the first day of menstruation until the woman's temperature has risen above her regular temperature and stayed up for 3 consecutive clays.
- After this, the couple can have unprotected sexual intercourse during the subsequent 10 to 12 days until her next menstrual bleeding period begins.

Cervical Mucus Method

Cervical mucus changes periodically during the ovulatory menstrual cycle. After menses and before ovulation, the discharge is scant or absent with a whitish or yellowish tint. As ovulation nears and under the effect of preovulatory estrogen rises, the mucus becomes more clear and abundant with a slippery texture. The mucus present at the vaginal introits becomes stretchy so that a drop placed between the thumb and forefinger can be stretched to 6 centimeters or longer (Figure 17). After ovulation the mucus becomes again scant and loses elasticity and stretchability or it disappears altogether. In general, ***ovulation occurs one day after the abundant, clear, elastic, stretchy mucus disappears from the vaginal introits.***

Women can learn to recognize these changes that occur around time of ovulation to identify the fertile period. This technique is known as *Billings method of natural family planning.*



Contraception (Figure 17): Billings's method of natural family planning.

How to use cervical mucus method

- The woman is taught to check for any cervical secretions. She may feel wetness at the opening of her vagina or see secretions on her finger, underpant, or tissue paper. She should know that the nature of the mucus on the vulva or in the lower vagina can be changed by douching, vaginal infections, semen, contraceptive foams and jellies, lubricants, and sexual arousal.
- After menses stops, the woman may have several days with no secretion. Sex is usually considered safe during this time. However, the couple does not have unprotected intercourse if she is unsure whether there is secretion.
- As soon as she notices any secretions, the couple avoids unprotected sexual intercourse.
- The secretions have a peak day, when they are most slippery stretchy and wet. The couple continues avoiding unprotected sexual intercourse until 4 days after the peak day. By this time the secretion has become sticky, pasty or thick, or the woman has no secretion at all. The couple can have unprotected sex until menstrual bleeding begins again.

Feeling of the cervix

This is seldom used alone, and can be used in conjunction with the Mucus Method. As the fertile time begins, the opening of the cervix feels softer, opens slightly, and is moist. Apart from this time, the opening is firmer and closed.

Multiple Index method: Symptothermal method

To tell when the fertile time starts; she can use calendar calculations and cervical mucus. The couple starts avoiding unprotected sex when the woman senses cervical secretion. To tell when the fertile time ends, she can use BBT, cervical secretions. The couple keeps avoiding unprotected sex until both the fourth day after peak cervical secretion and the third full day after the rise in BBT has passed. This approach is evidently more reliable and may indicate the end of the fertile period one or two days earlier than what it is predicted by calendar calculation. Other signs and symptom of ovulation include abdominal pain, cervical changes, and breast tenderness. However, these manifestations should not be relied upon alone.

❑ *Effectiveness of various approaches to periodic abstinence*

Effectiveness varies more than for any other family planning method. As commonly used (typical effectiveness) various approaches of periodic abstinence are only somewhat effective;

20 pregnancies per 100 woman in the first year of use. Consistent users who are strongly motivated and carefully instructed (perfect effectiveness) can have lower pregnancy rates:

- BBT: 1 pregnancy per 100 woman in first year of use (when intercourse take place only after ovulation and before next menstrual period.
- Cervical secretions: 3 pregnancies per 100 woman in the first year.
- Calendar: 9 pregnancies per 100 woman in first year.

The use of do-it yourself tests to detect the ovulatory LH peak in urine is being evaluated as an approach of identifying the fertile period.

Advantages and Disadvantages of Periodic Abstinence Methods

Advantages

1. No side effects.
2. No cost.
3. Acceptable to some religious groups-notably Catholic Christian who do not accept all or most of other methods.
4. Can be used by most couples if they are committed to it.
5. Can be used to help the occurrence of planned pregnancy.

Disadvantages

1. Lower efficacy relative to many other methods.
2. Requires long periods without vaginal intercourse. The method interferes with the spontaneousneess of sexual relations.
3. Takes 2 or 3 cycles to learn to identify fertile period accurately using the cervical mucus and BBT, and longer observation for six cycles to reach the proper calculation of the calendar method.
4. Require commitment of the both the husband and wife.
5. It is difficult to use in women with irregular menstruation cycles or who are breastfeeding.
6. Require reasonably educated couples.

Eligibility

The methods are not suitable for:

- Women nearing the menopause, because of increased frequency of anovulatory cycles.
- Early married couples.
- Women with irregular menstrual cycles.

- Women under treatment, which interfere with the physiology of the menstrual cycle.
- Breastfeeding mothers.
- Adolescent women.

Lactational Amenorrhea Method (LAM)

Contents

- Evolution of the method
- Effectiveness
- Advantages ad disadvantages
- Alternative contraceptive methods suitable for breast feeding mother.

Evolution of the " Method"

Lactation has played and is plying a major role in prolonging the child spacing interval worldwide. In many parts of the developing world, breastfeeding has greater impact in promoting child spacing than any other contraceptive methods. This influence of breastfeeding on fertility varies from culture to culture. It is most apparent in poor, rural areas. Mothers of the African Kung hunter-gatherers, a tribe in South-East Africa, feed their babies on demand for 3 years or more by carrying them in a pouch hanging to their chest all throughout the day and night time. Consequently, they have a long child spacing. Breastfeeding is initiated by more than 90 % of women in Egypt, Nigeria, Bangladesh, India and Pakistan, and at 6 months' postpartum over three fourths of women are still breastfeeding their babies.

In the last half of the 20th century there has been a trend of decline in the prevalence and duration of breastfeeding. This trend has been caused by increasing urbanization; the employment of women in jobs which make on-demand breastfeeding difficult; and the marketing of bottle-feeding with prepared formula of " humanized " milk. Formula feeding has become common in industrialized countries and the trend is spreading to many poor countries. This is unfortunate since the mother milk is the best nutrient to the infant, and it is the safest food from the point of absence of the possibility of contamination. In addition, breastfeeding helps to confere a good deal of contraception resulting in good birth spacing. If, for example, the breastfeeding patterns in Bangladesh were to decline to levels prevailing in the US, child mortality in that country would double.

The 1980s and 1990s has witnessed revival in interest in lactation. The health benefits of breastfeeding have been reemphasized both on the part of the infant and the mother, and the effects of breastfeeding on the fertility of the mother has been reevaluated both in developed and developing country settings. The latter revaluation has culminated in the Bellagio consensus statement as regard the contraceptive effect of lactation (1989). In Bellagio (in North Italy) a group of scientists and health workers from different parts of the world, including the author, have agreed on a statement indicating that exclusive or almost exclusive breastfeeding during the first 6 postpartum months is attended by a very low chance of conception, of less than 2 % provided the menstruation has not been resumed. This contraceptive effect of lactation which is comparable to use effectiveness of most modern temporary contraceptives requires three provisions: 1) exclusive or almost exclusive breastfeeding, 2) lactational amenorrhea, and 3) the first 6 postpartum months. Loss of one or more of these three provisions results in a rise of the chance of conception, and necessitates the use of another contraceptive (which does not interfere with lactation). This scientific information resulted in characterization of the lactation Amenorrhea Method (LAM) as a possible contraceptive approach available to breastfeeding mothers during the first 6 postpartum months. Moreover, it has also become apparent that extending the period of efficacy to 9 months may be possible, provided the amenorrhea persists and breast milk remains the main source of nutrition of the infant.

Mechanism of the contraceptive effect of breastfeeding

1. ***Lactational amenorrhea:*** During the first months postpartum when the infant is mostly dependant on his mother's milk, the intense stimulation of the mother's nipple by suckling initiates a reflex arc resulting in excessive secretion of prolactin which is associated with suppression of secretion of gonadotrphins (see under reproductive Physiology). This results in suppression of ovarian function and amenorrhea. The chance of ovulation preceding the resumption of menstruation is very low during the first 6 months of lactational amenorrhea (< 2 %). The longer the duration of breastfeeding, which is usually associated with a decline of suckling stimuli that results from introduction of supplementary feeding, is attended with higher chances of ovulation preceding the first menstrual bleeding.
2. ***Anovulatory menstruation*:** After resumption of menstruation during breastfeeding, the cycles are usually irregular, longer or shorter than normal and frequently anovulatory.

3. ***Luteal-phases insufficiency***: Even when ovulation occurs there is high incidence of luteal phase deficiency as evidenced by modest and short rises of progesterone during luteal phases.

It is not clear how nipple stimulation results in these changes in the function of the hypothalmo-pituitary-ovarian axis. It is not simply secondary to hyperprolactinemia. It seems that a common neurotransmitter(s) changes in the hypothalamus causes a drop in dopamine (the prolactin inhibiting factor) function and depression of formation and release of GnRH.

Two different breastfeeding practices have been proven to be equally efficient in suppression of the hypothalamo-pituitary ovarian axis: The first is the practice prevailing in developing poor communities in which there are many breastfeeding episodes > 12 or 16 each lasting for few minutes; the second is the practice in developed countries consisting of few suckling episodes, $\pm$ 6, each lasting for > 10 minutes. With both styles of breastfeeding, nighttime breastfeeding remains important to preserve the adequacy of milk flow and the antifertility effect of breastfeeding.

Effectiveness of LAM

The lactational amenorrhea method is the use of breastfeeding as a temporary method of family planning. LAM is very effective when correctly and consistently used-0.5 pregnancies per 100 women in the first 6 months after childbirth (the Assiut findings). As commonly used in different settings, LAM has an effectiveness of $\pm$ 2 % i.e. 2pregnancies per 100 women in the first 6 months after childbirth (1 in every 50).

Correct and consistent use means that The following three criteria are all needed:

1. The baby gets at least 85 % if his or her feeding as breast milk, and the mother breastfeed often; the interval between breastfeeds not exceeding 4-6 hours.
2. The mother's menstrual period has not returned. It has to be remembered that some of the actively breastfeeding mother (15-20 %) have an episode of bleeding during the first 6-8 weeks postpartum and that this bleeding is followed by lactational amenorrhea. This episode of bleeding (frequently called in our culture as the 40-day bleeding) is not to be considered a resumption of menstruation, and.
3. The baby is less than 6 months old.

If any of these three conditions is lost, the woman should use another method for effective family planning-one that does not interfere with breastfeeding (see later).

Advantages and Disadvantages

Advantages:

1. Highly effective during the first 6 months postpartum.
2. Can be used immediately after childbirth.
3. No cost.
4. No supplies or procedures needed.
5. No side effect.
6. Encourages the best breastfeeding patterns: Breastfeeding have important health benefits for the baby and mother.
   - Provides the healthiest food for the baby. Exclusive breastfeeding ensures optimal feeding of the infant during the first 6 months of his life. It needs some supplements after the 6th month of the infant age. In poor communities breast milk remains the more nourishing than all alternative feedings even after this time. The supplements in these settings are usually made of poorly nourishing fluids like rice water, and diluted Cow's milk.
   - Breast milk is available at low cost to the baby.
   - Protects the baby from life-threatening diarrhea, resulting from contamination of other types of feeding.
   - Helps to protect the baby from life-threatening diseases such as measles and pneumonia by passing the mother's immunoglobulins to the baby.
   - Helps to develop close relationship between mother and baby (Bondage).
   - Counseling for LAM encourages starting a follow-on method at the proper time.
   - Other methods of contraceptives can be initiated if desired at anytime during correct use of LAM without waiting for having a menstrual period e.g., insertion of an IUD or starting on a progestogen-only method.

Disadvantages

1. Frequent breastfeeding may be inconvenient or difficult for some women, especially working mothers.
2. Effectiveness after 6 months is not certain.
3. The mother may neglect starting the use of more reliable contraceptive method after expiry of one of the requirements of LAM method. One of these requirements may expire at a time not suitable for the woman to go to the clinic to initiate another method. Because of this possibility, users of LAM should not be discouraged to initiate other long-term contraceptive methods like the IUD, if they choose that, even before the expiry of the terms of LAM.

4. No protection against STDs including HIV/AIDS.
5. If the mother has HIV infection, there is a small chance that breast milk will pass HIV virus to the baby.

Alternative contraceptive methods suitable for breastfeeding mother:

- **The IUD** is the best contraceptive method available for breastfeeding mother. It is commonly initiated around the 6th week postpartum. Immediate postpartum or postabortion IUD insertion is possible (see under IUD). Insertion of the IUD in a woman who has been breastfeeding for a long time should be done with care in order to avoid perforating the uterus during insertion. The uterus can become atrophic, hyperinvoluted and thin-walled as result of prolonged suppression of ovarian hormones during lactation.
- **All progestogen-only contraceptives** including, injectable, minipill and Norplant. These have been shown not to interfere with the quantity and quality of breast milk or to have any bad effect on the growth, development or health of breastfed infants. New implant systems and vaginal rings releasing progestogens or progesterone are under development and evaluation (see later).
- **Tubal ligation:** after proper counseling.
- **Barrier methods and spermicides.**
- **Fertility awareness methods** have occasionally been advised to use during breastfeeding. A woman who has already been experienced in using the cervical mucus method can be able to recognize the return of wetness to her external genitalia.
- **Combined oral contraceptive method** (low-dose types) has occasionally been considered suitable for use after the 6 month postpartum i.e. after establishment of milk flow. However, if the woman is keen to preserve her breastfeeding, low dose COCs, in the opinion of the author, will not be suitable because of their negative effects on the quantity and quality of breast milk, even after 6 months of lactation.

Sterilization

Contents:

- Female sterilization

  Interval sterilization

  Minilaparotomy

  Laparoscopic sterilization

  Effectiveness

Complications

- Vasectomy

Techniques

Complications

Introductory remarks:

- Sterilization is a permanent method of contraception, which can be done to the female or the male by interrupting of the continuity of the genital tract at certain critical sites; the fallopian tube or the vas deferens. Sterilization is commonly described as surgical contraception or voluntary surgical contraception (VSC). These latter nominations by avoiding the use of an unpopular name, sterilization might improve acceptability of the procedure. This is not, in any way, an attempt to disguise the nature of the medical intervention.
- The need for a permanent contraceptive method arises because of disparity between the limited number of children any couple affords or like to have, and the long years of fecundability. Healthy women are fertile until about the age of 50; healthy men are fertile essentially throughout life. Because many couples have all the children they want, or afford to have, by the time when the wife is 30 to 35 years old, there are many years when couples need effective protection against unwanted pregnancy.
- Sterilization is the most effective contraceptive method for either the man or the woman, and is also one of the safest and most economical methods.
- Surgical sterilization, both male and female has become the most widely used contraceptive method in the world; the number of users is expected to reach 250 million by the year 2000. The demand on the operation varies from one country to another, and is influenced by social, religious, legal and economical variables. It is also influenced by the availability of other contraceptive options. The percentage of women protected from pregnancy by male or female sterilization varies between 39 % in China, 28 % in the United States and < 1 %, as it is the case in Egypt (where all sterilization are only for the female).
- Vasectomy (male sterilization) is much simpler, safer, and less expensive than female sterilization, although it is usually less popular in most countries. The reasons for this disparity are numerous: 1) The concern (unjustified) of men about anything which may interfere with their more positive role in sexual intercourse. 2) Women has for long, carried the responsibility of contraception. 3) Women face the end of the reproductive career sooner, by middle age when they go in the menopause. Other cultural factors contribute to this difference.

- The widespread use of sterilization demand care in prior adequate counseling that obviate regret of the decision in later life.

Counseling on sterilization

Medical counseling has special importance in sterilization. ***The following guidelines should be observed:***

1. Medical counseling is the procedure to help the client to make the best choice between different approaches to therapy.
2. It is based on offering the service receiver all the information about all therapeutic approaches available to her or him to achieve their particular goal(s). The advantages and disadvantages of each option should be clearly given in a simple language, and discussed with the client.
3. No coercion should exercised in choice of sterilization.
4. The service provider should not impose his own attitude and opinions on the couple.
5. The demographic aspects should not influence the particular contraceptive method chosen for the couple. The provider-receiver interaction is a person to person process; the provider should respect the particular needs of the couple.
6. Permanency of sterilization should be reemphasized. Reversal of sterilization should be presented as a major, expensive surgical interference of no guaranteed success.
7. It should be always carried in the mind of both the service provider and receivers that one cannot always properly judge his or her long-term future needs. Changing social conditions, like loss of a child or divorce and another marriage are possibilities that may result in regretting sterilization.
8. A written consent should be signed (or thumbed) by the receiver. It should contain all relevant information. In certain countries (like in Egypt) the consent of the spouse is also needed.
9. Studies have shown that proper counseling diminishes the incidence of regret of sterilization.

Female sterilization

Sterilization for women involves blocking the fallopian tubes to prevent meeting between the ovum and sperm. To achieve this a number of methods for blocking the tubes, and a number of approaches to reach the tubes are used.

Blocking the tubes can be accomplished by ligation, ligation and removal of a segment of the tube, electro coagulation, application of clips or an occluding a ring to a

segment of the tube; or blocking the lumen by injecting in it of a sclerosing material. The methods used should ensure: 1) freedom of side effect, 2) least likelihood of recanalization, and 3) the best chance of reversal, would sterilization be regretted in the future.

The fallopian tube can be approached 1) during a formal laporotomy (as during cesarean section or any other laporotomy), 2) via a minilaparotomy, 3) laparoscopy, 4) culdoscopy or posterior colpotomy. 5) Injection of sclerosing material done via the uterus.

The timing of female sterilization whether pregnancy-related or not (the latter occasion is called ***interval sterilization***), is important in deciding the surgical approach and the technique of occluding the tubes. However, sterilization should always preceded by adequate counseling and should not be imposed upon the patient at a time when she yield to pressure to terminate her fertility, e.g., after having a specially difficult obstetric experience. Sterilization should not be an extra reason for the patient to be submitted to a laporotomy, e.g. cesarean delivery. It should never be a penalty imposed during induction of abortion.

Postpartum and Postabortion Sterilization

1. Sterilization in conjunction with cesarean section

This does not entail additional morbidly. The tubes are occluded by one of the following techniques (figure 18):

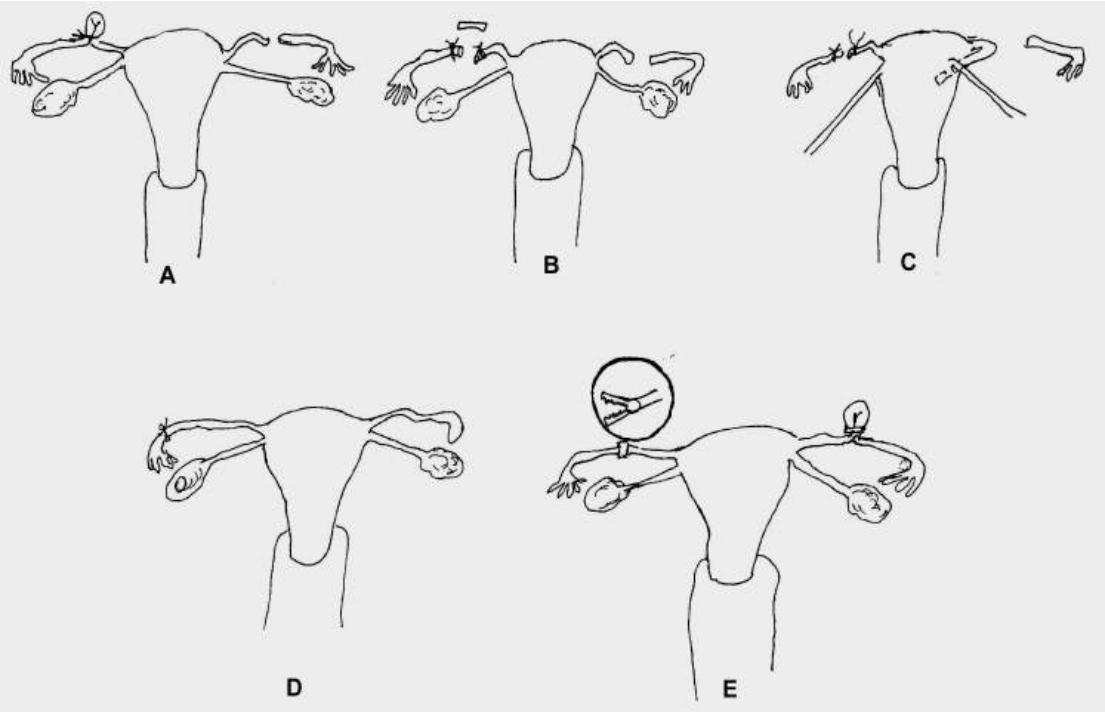
a. *Pomeroy technique* is the most widely used one. A loop of the midportion of the tube is ligated by *plain catgut* and is then excised. After the catgut dissolves the two cut edges will recede apart making recanalization least possible. Retention of the abdominal ostia ensures that ova become trapped in the occluded lateral part. This method has the advantage of avoiding troublesome hemorrhage and needs a limited access to the tubes. Pomerory technique is used in the post-cesarean, post postpartum, minilaparatomy and posterior colpotomy approaches. It lends a reasonable chance for reversal due to limited tissue destruction.

b. *Pritchard (Parkland) Technique*: This is the technique is most commonly used. It avoids the approximation of the cut ends and preserves more of the tubel length than the Pomeroy's technique. The mesosalpinx is pierced in an avascular area by one-Zero chromic catgut. The thread is used to ligate the tube at two points 2 cm apart and the intervening segment is excised.

c. *Irving Technique*: The uterine end of the tube after cutting is bent and buried under the peritoneum on the front of the uterus. This ensures the least chance of recanalization, but increases the morbidity of the procedure, and diminishes any chance for future reversal.

d. *Fimbriectomy:* removes more tissue, has been associated with higher failure rate and is less reversible. The fimbrial end is sometimes more accessible in limited access approach as in posterior colpotomy.

The post-cesarean section sterilization should carry no added morbidity but brisk bleeding from engorged postpartum vessels should by avoided by gentle handling of the tubes.



Contraception Figure 18: Tubal sterilization techniques*. A. Pomeroy, right hand-side after healing; B. Pritchard (Parkland), right-hand side after healing; C. Irving, the right-hand side after healing;D. Fimbrectomy, right-hand side after healing; E. Laparoscopic techniques, Filschi clip on the left side silastic Yoon's ring on the right side.*

2. Postpartum sterilization by subumbilical minilaparotomy

The immediate postpartum period (within 48 hours of delivery) is the most common time for female sterilization in many countries. This is largely because of ease of surgery, lower costs, and more efficient use of health resources. The procedure can be completed under local anesthesia and does not usually prolong hospital stay.

Procedure: Immediately after delivery, the uterus and tubes are high in the abdomen and can be approached through a small 1.5 to 3 cm middle-line incision. Local anesthesia with light sedation and or analgesia is frequently sufficient. The procedure is done in the dorsal position. The tubes are usually easy to reach by tilting the uterus to one and the other side. The Pomeroy or Pritchard technique can be easily used. The small incision in the peritoneum can be left to heal spontaneously. The skin can be closed by one or two subcutical buried stitches of two-zero Dixon.

If the procedure cannot be performed within few days after childbirth, it is better to wait until 6 weeks postpartum when minilap is done as an interval sterilization.

It needs to be reemphasized that postpartum sterilization should not be imposed on the patient by the distress of the situation of a difficult delivery; and a written consent should be obtained from both partners.

3. Postabortion sterilization

Tubal occlusion may be performed immediately after a first trimester abortion by either suprapubic minilaparotomy, or laparoscopy (see below) approaches. After a second-trimester abortion it is better to defer the sterilization until the uterus has sufficiently involuted, i.e. is done as an interval sterilization. When a postabortion sterilization is done, care should be exercised in handling the thickened, edematous, and more vascular tube. Tubal occlusion is accomplished by Pritchard or Pomeroy technique via a suprapubic minilaparatomy. When laporoscopic procedure is used the clip method is more favorable than the ring or band technique. In the latter technique the tube may tear during application of the ring due to changes mentioned above.

4. Interval sterilization

This is done by either the suprapubic minilaparotomy or the laparoscopic approach. Other approaches are less popular.

a. Suprapubic minilaparotomy

Suprapubic minilaparotomy is performed as an interval operation 4 or more weeks after delivery when the uterus is fully involuted. The technique involves a small (2 to 5 cm in length) just above the pubic hairline.

Eligibility:

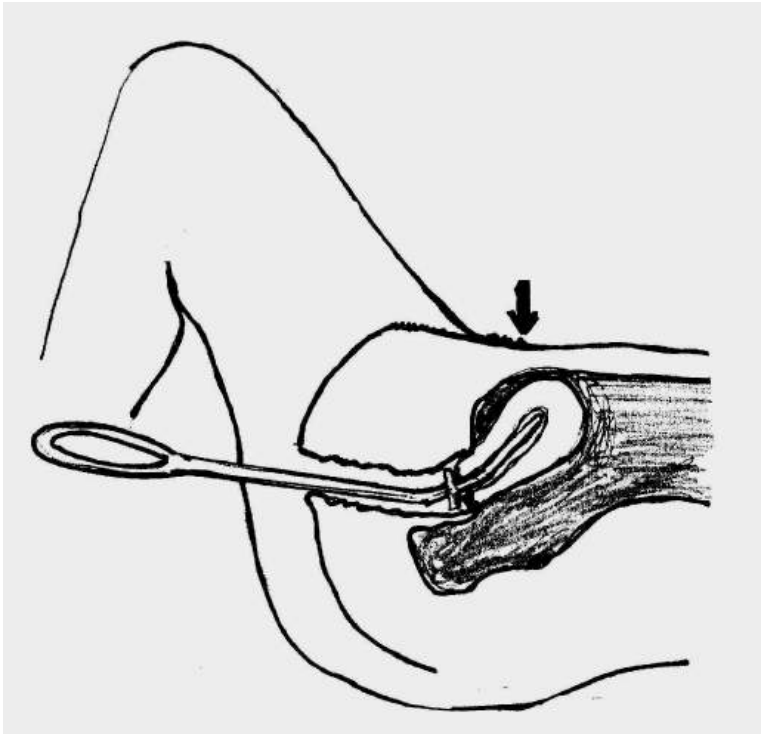
1. Sterilization should follow upon careful counseling of the couple; all available alternatives should be considered with the subject including male sterilization.
2. The following condition should contraindicate the operation.
   - Previous abdominal or pelvic surgery.
   - Diabetes mellitus unless mild and controlled.
   - Bleeding problem.
   - Pelvic inflammatory disease.
   - Fixed retroversion of the uterus.

- Pelvic mass.
- Marked obesity.

Procedure:

1. The procedure can be done under local anesthesia backed up by sedation given orally or intravenously. The site of the operation is infiltrated by anesthetic, layer by layer. Apprehensive women need general anesthesia. Careful aseptic technique should be observed.
2. The bladder is emptied by voiding immediately before the operation or, else by catheterization.
3. The woman is put in the lithotomy position.
4. Suprapubic hair is cut if not already removed.
5. A small (2-5 cm in length) transverse incision is made in the skin just above the hairline or suprapubic skin crease. If the incision is made too high it will be difficult to bring the uterus to the incision, and if is made too low there will be a risk of bladder injury. The anterior rectus sheath is incised transversely. The recti are separated and the peritoneum is entered by a transverse small incision.
6. The uterus is raised to the incision by a dually angled special uterine elevator with a cervical shoulder or stopper (Figure 19).
7. Intrapritonineal manipulation should be gentle in order to diminish the pain. The tubes are identified and a tubal hook similar to the Babcock forceps is used to lift the tube in the incision. The fimbria must be identified to ensure that the structure is the tube and not the round ligament.
8. The Pomeroy or Pritchard technique is used for occluding the tube; the clip or the silicone ring can alternatively be used.
9. The wound is closed in layers. There is growing evidence that it is unnecessary to suture the peritoneum since small peritoneal defects will heal without adhesion. The skin wound is sutured by subcuticular two zero Dixon.
10. The wound is dressed. No need for antibiotics. The woman is usually discharged on the same day.

***Possible complications*:** wound infection, uterine perforation by the elevator, bladder injury, tearing or bleeding from the mesosalpinx, and rarely intestinal injury. Complications usually occur in less than 1 % of cases.



Contraception Figure 19: ***metal uterine elevator used in minilap sterilization. The arrow indicates the level of the incision.***

b. Laparoscopic sterilization:

The laparoscopic approach is used to occlude the tube by electrocoagulation or by application of a clip or a silastic ring (band). Such procedures require special laparoscopic instruments and adequate training on their performance. The laparoscopic approaches are to be used in fully equipped, high volume centers.

Procedure:

1. Laparoscopic sterilization can be performed using local anesthesia backed up by sedation. General anesthesia is required for apprehensive women; this requires endotracheal intubation and controlled ventilation. The choice of the woman should be respected
2. Aseptic technique should be ensured. The woman is put in the lithotomy position and the bladder is evacuated if not emptied by voiding immediately before the procedure.
3. A uterine manipulator or elevator is fixed to the uterus.
4. Pneumoperitoneum is induced: A small incision in the lower edge of the vagina. While firmly lifting the anterior abdominal wall, a *Veress needle* is inserted tangetionally in the direction of the pelvis (away from major vessels on the back of the abdominal cavity). The Veress needle has a spring loaded blunt plunger that is released once the peritoneal cavity is entered thus pushing viscera away from the needle tip. To obviate the possibility of injecting the gas into an extraperitoneal

space, into the omentum or a punctured viscus, the Veress needle is connected to a flowing gas insufflator; the pressure in the flow-meter will drop once the tip of the needle gets into the peritoneal cavity and should not exceed 10 mm Hg(or 0 level if an automatic insufflator is connected). The patient is put in the Trendeleberg position and 2 to 3 liter of gas (carbon Dioxide or Nitrous oxide) is insufflated. The pressure in the abdomen should remain low during the whole insufflation time. With the woman in the Trendelenberg position intestines move away from the pelvis that is filled with the gas.

5. The needle is withdrawn and the trocar in a canula is inserted, again in backward and downward direction. The insertion should be made tangentionally. The trocar is removed and replaced by the scope. By utilization of fiber optics the scope transmit a strong light (without heat) to illuminate the peritoneal cavity, and transmit back the images from the peritoneal cavity. The scope in sterilization-instruments contains in a separate channel the operating instrument like the diathermy forceps or the ring or clip applicator. In other systems these are introduced through a second puncture. The second trocar is inserted under direct visualization of the back of the abdominal wall from the inside via the scope, in order to obviate injury of vessels by the second trocar.

Variations from this description include " open laparoscopy " during which the peritoneal cavity is opened under vision by making an incision like the subumbilical minilaparotomy. The cannula connected to the gas insufflator is then placed and stabilized by a purse-string suture. Thereafter, the canula is used for insertion of the laparoscopy. This technique is used whenever there is a possibility of adhesion of viscera to the abdominal wall. It avoids the blind entry of the sharp Veress needle and the trocar into the abdomen, which may puncture a viscus.

6. Occlusion techniques comprise:

a. *Diathermy coagulation* utilizing monopolar or bipolar instrument. The latter carries less risk of electric burn to the abdominal wall and viscera; the current only passes between the two jaws of the coagulating forceps. The latter can contain an inbuilt cutting scissors. This approach has a small risk of failure due to reconlalization of tubal lumen. It has a relatively lower chance of reversibility because of destruction of a long segment of the tube by diathermy. Although diathermy burn is rare, it is possible.

b. A spring-loaded plastic clip can be applied to the narrow isthmic portion of each tube. It requires a special applicator (figure 18). The spring clip consists of two plastic teethed jaws that are hinged at one end by a small metal pin. After application to the tube, a

stainless steel spring is pushed over the jaws to hold them closed over the tube. The clip destroys only one mm length of the tube.

c. A silastic ring (band), the Yoon's or Falope ring is applied around a knuckle of the midportion of the tube (Figure 18). The knuckle is not resected. The ring applicator consists of two concentric cylinders; the inner is telescoping in the outer. Within the inner cylinder is a forceps for grasping, elevating a knuckle of the tube into the inner cylinder. The silastic ring is stretched around the lower end of the inner cylinder by the means of a special conical ring loader. The outer cylinder slide over the inner one, moving down the silastic ring onto the tubal knuckle. Necrosis occurs in the tubal knuckle, the damaged part is 3 mm long.

The last two techniques require special instrument for application " the laprocator " and require special training for its use. In fact they are easy to learn. Care is also needed in maintaining the system and checking integrity of all its parts before starting the procedure. Both technique produce less damage of the tube and should enhance the prospects of reversibility due to minimal tubal damage. There is however, a very small chance of recanalization, resulting in tubal or uterine pregnancy.

7. After careful inspection of the pelvic viscera, the pneumoperitoreneum is completely evacuated. The patient can be discharged in the same day.

Complications. Although complications from laparoscopy are not more common than from minilaparotomy, some are more serious. These include:

a. Anesthesia related complications can be aggravated by gas filled abdomen and the Trendelenberg tilt.

b. Uterine perforation by the elevator-is usually managed conservatively.

c. Injury of blood vessel.

d. Bowel burns can occur from electrocoagulation. The bipolar diathermy carrier less risk of burns than the uniplor. In the latter condition a laporotomy is needed.

e. Tearing the tube can occur during application of the Falope ring resulting in bleeding from the mesosalpinx. The condition can be managed by application of a ring on both sides of the tear.

C. Vaginal approach-Sterilization through culdoscopy or colpotomy

The fallopian tube can be reached through an incision in the posterior fornix of the vagina, i.e. posterior colpotomy; or through an operating scope inserted in the cul-de-sac, culdoscopy. Posterior colpotomy approach is particularly easy if there is an element of prolapse, and in thin women with lax vagina. The tube is delivered in the incision and is

occluded, usually utilizing fimbriectomy or better pomeroy's technique if possible. The approach needs a surgeon with some training in vaginal surgery. The vaginal approach has lost favor after the advent of minilaparatomy and improvement of laparoscopic surgery.

D. Transcervical sterilization methods

These are still in the stage of development, and aim at obliterating the lumen of the tube by utilizing electrocoagulation, laser, cryosurgery, and injection of sclerosing substance or plugs. The uterine ostium is reached from the inside of the uterus either aided by VUSG, or hysteroscopy and is occasionally blindly canulated by utilizing special instruments. Various agents like quinacrine or phenol pellets are injected into the tube. The delivery systems are still being perfected.

E. Hysterectomy

Hysterectomy, whether performed through the vaginal or abdominal approach, carriers a much higher risk of morbidity and mortality than other sterilization procedures. Therefore, it is not performed for contraceptive purposes alone, but for a gynecologic disease that justifies removal of the uterus.

Effectiveness of sterilization

A sterilization failure rate associated with standard occlusion techniques is very low: 0.05 pregnancies per 100 women-years (one in every 2000 women). Sterilization failure rate do not include women who have already conceived at the time of sterilization (when the operation is done late in the menstrual cycle). Fewer failures occur in the subsequent years. The failures are markedly influenced by the surgical skill of the provider. Certain occlusion techniques have a slightly higher failure rates e.g. ligation without removal of part of the oviduct or fimbriectomy.

Long-term complications and consequences

a. ***Ectopic pregnancy*:** Ectopic pregnancy should be ruled out any time a woman shows signs of pregnancy following tubal sterilization. Recanalization of the tube can occur if the two ends remain together; or alternatively the ectopic results from formation of a tuboperitoneal fistulae.

b. ***Abnormal menstrual pattern*:** Abnormal menstrual pattern in the form of polymenorrhea or polymenorrhagia have been described after tubal sterilization, and is commonly associated with pelvic pain or weight gain. This has occasionally been named as post-tubal ligation syndrome. However, the cause and effect relationship has not been confirmed in properly conducted trials. Abnormal menstrual pattern can be part of perimenopusal ovarian

dysfunction. Tubal occlusion has not been shown to produce definite changes in the levels of relevant hormones.

c. ***Regretting sterilization***

Reports on the incidence of regretting having had sterilization have given various estimates, ranging from 0 to 12 %. The incidence depends primarily on what is the type of regret; this can range from occasional expression of dissatisfaction to psychological disturbance or request for reversal. Regret may depend upon change of the social conditions like divorce and another remarriage, or loss of a child. It has been shown that regret is commoner when the procedure has been done in young age or with a small number of children who does not comprise both sexes. Loss of fecundability may disturb the fine family balance between husband and wife in an unstable marriage. Even if no more children are desired the loss of the potential of fertility may prove disturbing. Social pressure, particularly from immediate relatives can prove disturbing, particularly in communities which put great value to big family. The rule of 120 has been suggested, requiring that the product of multiplying the age the subject by the number of her living children be at least 120. However, this is not always required, personal reason that makes women with lower " product " request sterilization.

Reversal of Female Sterilization

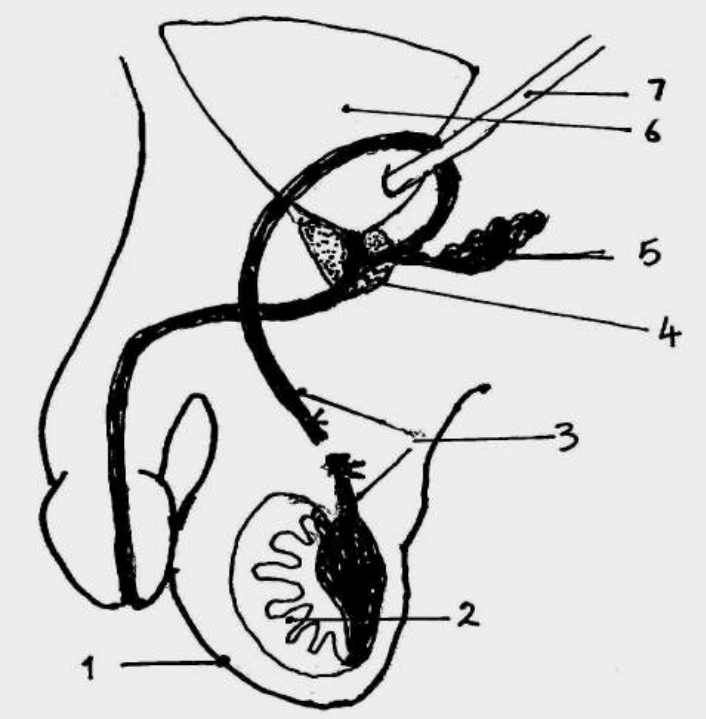
Sterilization should be considered permanent, but even with responsible and careful counseling some women may request reversal. However, it needs to be emphasized in the pre-sterilization counseling, and again when request at reversal is made that reversal requires major surgery and special expertise, is usually expensive, and its success cannot be guaranteed. Special conditions make success of reversal less likely: mainly the amount of damage of the tubes, and the age of the patient.

The success rate of reversal depends upon the technique used for tubal occlusion. The best chance follow the clip method where only 1 cm of the tube is damaged. The second most reversible is the ring or band method that destroys 3 cm of the tube. The Pomeroy and Pitchard techniques come third. Electrocoagulation produces the greatest damage of a good segment of the tube. Given the best surgical care and the proper choice of cases, the success rate of reversal of tubal sterilization ranges from 40 to 80 %. These success rates are achieved through the use of microsurgical techniques by a specially trained surgeon.

For women who are poor candidates for reversal surgery, IVF and ET is an option. However, success rate are generally in the region of 30 % and the procedure may be too expensive for some couples.

Male Sterilization-Vasectomy

Male sterilization is an operative procedure that entails blockage of the vas deferens in both sides (figure 20). Relative to tubal sterilization of the female, vasectomy is much simpler; safer, does not require specialized skill; it can be done by a general practitioner; usually as an outpatient procedure; and in about 20 minutes. Vasectomy is also less expensive. It has the disadvantage of not being immediately effective, until all sperm in the genital tract have been exhausted. This generally requires about 20 ejaculations to achieve this, in which another male or female contraceptive should be used. Vasectomy is not free of side effects, including hemorrhage causing hematoma formation and infection. Vasectomy in certain cultures, and for a certain couples is less acceptable than female sterilization. Reversal, particularly after long-standing vasectomy may be less successful than reversal of tubal sterilization.



Contraception: Figure 20: Vasectomy.*1. scrotum; 2. testicles; 3. closed vas deferens;4. prostate; 5. seminal vesicle; 6. urinary bladder; 7. ureter.*

Technique of vasectomy:

1. Proper counseling is as essential as it is for female sterilization.
2. The scrotal hair should be removed beforehand or clipped at the time of surgery. The area is washed with soap and water. An effective antiseptic painting of the skin is made and the area is draped. Sterile approach should be always observed.

3. The vas deferens is identified and anchored to the skin by atraumatic forceps. The operation is usually done through two small 2 cm incisions.
4. One percent lignocaine, without epinephrine, is infiltrated into the area to be incised and then deeply in the perivasal tissue. The skin and muscle covering the vas are incised. Alternatively, a single midline incision can be used through which the two vasa deferentia are delivered in it.
5. The vas is isolated, lifted into the incision and is divided. The cut ends are fulgurated to a depth of 1 cm in each direction by inserting a needle electrode, or hot-wire cautary into the lumen. A fascial barrier may be created between the ends by drawing the sheath over one end and suturing it.
6. The skin incision has one or two stitches, and is covered.
7. The man receives instruction of rest for 2 days avoiding vigorous exercise, to come after 7 days for follow up and removal of the stitches. He is usually given analgesic tables. He should come if has severe pain or a swelling of his scrotum.
8. If his wife is not using a contraceptive the man is given twenty condoms to use in intercourse before his operation can be relied upon for contraception.

No-scalpel vasectomy

This producer employs two special instruments. A special atraumatic ring tipped forceps is used to encircle and firmly steady the vas without penetrating the skin. A sharp tipped curved artery-like forceps is used to puncture and stretch a small opening in the skin and vasal sheath. The vas is occluded in the same way as described above. The no-scalple technique was developed in china and helps to reduce anxiety about vasectomy, and is claimed to be associated with less complication.

Complications

a. Immediate complication are rare and minimized by training:

1. Bleeding and hematoma formation. These are managed by scrotal support, analgesic or ice application. Large painful or infected hematoma is incised for drainage.
2. Infection should be minimized by aseptic technique.
3. Sperm granuloma. This occurs as a result of leakage of sperm from the occluded end resulting in the formation of a tender nodule, which usually needs excision.

b. Long term effects

1. About one half to two thirds of men will develop sperm antibodies following vasectomy. However, there is no evidence of any pathological complication arising from this condition. It reduces the chance of reversibility.

2. Earlier reports of a possible link between vasectomy and carcinoma of the testis or prostate have not been confirmed by more recent and careful epidemiological studies.

Reversal of vasectomy

Microsurgery is required, and the results in the form of pregnancy cannot be guaranteed. Sperm appearance in the ejaculate can be achieved in a good percentage of such treated patients (20 to 80 %). However, the success of reversal of vasectomy in the form of causing pregnancy is expected in a lower percentage depending upon variables such as the duration since vasectomy, presence of sperm antibodies, the age of the wife, and the length segment of the vas that has been damaged in the vasectomy.

Attempts to develop a plug, valve, or simple reversible vasectomy have not been successful, so far.

New Contraceptives being developed: Contraceptives in the pipeline

Contents:

Increasing the options the couple can use for contraception can ensure client satisfaction and better utilization of contraceptives

A. Contraceptives for men

The presently available fertility regulation methods for men are limited, including only withdrawal, condoms and vasectomy. The extent of participation of men in family

planning is also limited. The international Conference on Population and Development (ICPD) in Cairo, 1994, called on the governments and organizations to " increase the participation and sharing of responsibility of men in the actual practice of family planning ". This will entail enlarging on utilization on what is available and improving upon condom manufacturing and improving vas occlusion methods. Newer methods need also to be developed:

1. Better condoms and better availability: (see under Condoms)

2. Vas occlusion (Vasectomy)

Research on vas occlusion has recently focused on a) the long term safety of vasectomy, and b) new devices or procedures that may be simpler to perform and may increase the chance of successful reversal:

a. ***Safety of vasectomy***. Overall, vasectomy has been shown to be a safe contraception. Earlier reports of a possible link between vasectomy and cancers of the testis and prostate have not been confirmed by more recent and careful epidemiological research.

b. ***New techniques for vas occlusion***

1. The non-scalpel method (see under male sterilization).
2. Percutaneous intravasal injection of sclerosing agents like quinacrine, phenol has been shown to be successful in occluding the vas but does not increase the chance of reversibility.
3. Percutaneous injection of polyurethrane elastomers or silicon which when harden will form a vasal plug. This approach can contribute to improved reversibility.

3. Hormonal Contraceptives for men

a. *Testosterone only injectables*: 200 mg of testosterone enanthate if injected weekly-induced azospermia in more than half of subjects tested within 12 weeks, which persisted thereafter for 12 months and have proven reversible after discontinuation. Some men failed to reach azospermia. The long-term effect of testosterone administration on the risk of prostatic cancer needs further evaluation. More convenient methods of hormone deliveries including implants are being tested.

b. *Progestogen-androgen combination*. The progestogens suppress testicular function, including production of azospermia and hypotestorongenemia. For the latter, the androgen components are given for replacement.

c. *Gn RH agonists /antagonists-androgen combinations*. The agonist or antagonist suppresses testicular function while the androgen is added for replacement purpose. The peptide and the androgen can be delivered by separate implant systems. The potent synthetic androgen MENT (an analogue of testosterone) is being tested for the purpose.

MENT is not reduced in the body to the 5 dihydrotestosterone equivalent. Therefore, MENT is expected to replace anabolic and sexual function of testosterone without stimulating the prostatic tissue; i.e. carrying less risk of testicular, and prostatic neoplasia.

4. Agents acting directly on spermatogenesis

Gossypol, isolated from cottonseed, was discovered by Chinese to produce azoospermia in men. Clinical trials have shown that Gossypol is highly effective but have two disadvantages: a) reversibility is not 100 % (25 % of users remained azoospermic after discontinuation), and b) it produces hypokalemia in some users. Research on gossypol has therefore, been discontinued. Other plant derivatives have been tested for the purpose without success.

5. Contraceptive Vaccines for men (see under can contraceptive vaccines).

B. New COCs: Newer progestogens (See under COCs).

C. New IUD: Frameless IUD, LNG-IUD (See above).

D. New injectables: Monthly CIC (See this section).

E. New Implants (See under Norplant).

F. New delivery systems for hormonal contraceptives for women

1. Vaginal pills

The daily vaginal administration of the combined oral contraceptive have been shown to be highly effective in producing contraceptive effect comparable to that of oral administration. The contraceptive steroids are effectively absorbed from the vagina into the general circulation.

Multicenter trial (that included Assiut) has confirmed that the vaginal pill administered, with the 21 days on and 7 days off schedule, is equally effective as the oral pill. The vaginal pill users less commonly complained of the symptoms like nausea vomiting and headache than oral users. The vaginal pill has the same disadvantage of the need to make a daily decision to use the contraceptive. They may increase complaint of vaginal discharge in users.

2. Contraceptive Vaginal rings (CVRs):

Contraceptive Vaginal rings is a promising approach for long-term contraception. The outstanding merit of CVRs is that the use of the ring is under the sole control of the woman; she can discontinue the use without the need for a service provider to remove a device like with the IUD or implants. Two basic research findings have contributed to the development of the CVRs: The first was that the vagina is a suitable portal for administration of drugs including contraceptive steroids. The second was that certain silicone polymers like Silastic (used in Norplant) could absorb and slowly release a number of steroids. The steroids are contained in pliable rings made of this polymer. The rings are torus-shaped. The ring needs only to be retained in the vagina, and does not need to placed in a special position in the vagina. The external diameter of CVRs ranges between 50 and 75 mm and therefore does not exert pressure on the vaginal wall. They do not act as a barrier contraceptive. The contraceptive steroids are contained either in the whole thickness of the ring, only in its core or in a subsurface layer of the ring cutsectional diameter.

The rings act by systemic effects of steroids absorbed from the vagina. Two types of CVRs are being developed: The first, are **progestogen-only rings (POCVRs)** which produce effects similar to the minipill, progestogen only injectables, and Norplant. The second type is **combination rings (CCVRs)** that contain an estrogen and progestogen with effects similar to the combined pills, or the monthly injectables. The POCVRs are worn by the woman continuously throughout their period of effectiveness. CCVRs are generally worn for three weeks on and one week off schedule, allowing for 7-day intermissions during which the woman can have a menstruation-like bleeding. The woman can remove the ring during sexual intercourse, if its presence bothers the husband. The contained steroids are usually sufficient for a period of effectiveness ranging from 3 to 12 months. The ring is washed with tap water every now and then (e.g. weekly). Therefore, CVRs are long-term contraceptive methods under the sole control of the woman.

a. Progestogen-only-rings (POCVR)

POCVRs comprise the following types:

1. *Levonorgestrel ring* is the most advanced in development (by WHO). This ring releases approximately 20 ug of levonorgestrel daily over 90 days. It has been shown to be reasonably effective; with a contraceptive effectiveness comparable to the progestogen-only pill. Its use results in the same menstrual disturbances observed during use of the minipill. Some woman with lax vaginal introitus complains of frequent expulsions.

2. *Progesterone ring:* A ring releasing approximately 10 mg of the native progesterone daily for a period of 90 days has been tested for use by lactating mothers in a number of centers (including Assiut). It showed reasonable effectiveness and acceptability in these women. However, their effectiveness is not very sure in non-lactating women. Using the natural progesterone as a contraceptive for the nursing mother offers a special merit of safety, since any amount of the steroid secreted in the mother's milk will not be effectively absorbed from the gut of the breastfed infant obviating any theoretical concern about any future effect of steroid ingestion on the child. The main problem with this ring will be the difficulty on deciding when contraceptive effect of breastfeeding has waned to the extent insufficient to support the effectiveness of ring, the progesterone ring is not reliable contraceptive for non-lactating women.

3. *Nestorone (ST 1435) ring:* Nestorone is a synthetic derivative of progesterone with a particular attractiveness resulting of its high potency and less pronounced effects on serum lipids relative to the nor-testoserone progestogens. The Population Council (New York) is evaluating a CVR that releases nestorone over a period of effectiveness of 12 months. This ring will have a special advantage for use during breastfeeding, sine like progesterone; nestorone is not effectively absorbed from the infant's gut. Nestorone ring will be a better alternative to the progesterone ring since its contraceptive efficacy will continue after deterioration of the contraceptive effect of breastfeeding.

b. Combination Rings (CCVRs)

Rings containing both an estrogen and progestogen are intended for intermittent use, three weeks on and one week out during the period of utility of the ring (3-12 months). They will produce better bleeding pattern than POVCRs and hence, will be more appealing to certain users. The vaginal administration of the two steroids ensures better bioavailability and has allowed the use of lesser steroid load. This is due to bypassing the hepatic destruction at entry the body, as it is the case with oral administration, and to having a zero-order pharmacokinetic. A number of CCVRs are being tested, including:

a. *3-keto-desogestrel / ethinyl estradiol ring* (Organon, Holland). Rings releasing 3-keto-desogestrel in a daily dose of ranging from 75 to 150 ug. (the oral equivalent COC, Marvelone delivers a daily dose of 150 ug of desogestrel), together with 15 ug of ethinyl estradiol (the oral pill delivers 30 ug daily). Each ring is intended for use for 3 months (3 cycles). The active metabolite the progestogen in the body, desogestrel has been shown to have less impact on serum lipids than levonorgestrel, a merit of safety (see under COCs)

b. *Levonorgestrel / estradiol (E2) rings:* has been discontinued due unfavorable lipogram.

c. *Norethindrone acetate / ethinyl estradiol ring* is being developed by the Population Council. The rings deliver norethndrone acetate in daily doses that are ranging from 0.65 to 1 mg, and a daily dose of ethinyl estradiol ranging from 20 to 30 ug. The rings are intended for one-year (12 cycles) use. The rings have shown good cycling pattern and minimal effects on the lipogram.

d. *Nestorone (ST 1435) / EE ring* is being developed by the Population Council. This ring has been shown to produce consistent inhibition of ovulation, and minimal effects on the lipograms.

Advantages and Disadvantages of CVR

Advantages:

1. Long-term effect.
2. Being under control of the user; she can discontinue the method whenever she decides, without the need for a medical intervention (like in removal of implants)
3. CVRs are not coitus related.
4. With combination rings, the removal of the ring (to allow for a withdrawal bleed) can be delayed until it is convenient for the women to have a period. The user can decide when she will have her menstruation.
5. The vaginal administration has allowed the use of certain contraceptive steroids, which are not biologically active when administered orally like estradiol, progesterone, and nestorone.
6. Administration of certain steroids by the vaginal rings, e.g. progesterone and nestorone, has special advantage in the use by breastfeeding women (see above).
7. Vaginal administration of steroid by the vaginal ring ensures a zero-order pharmacokinetic and avoids the hepatic first-pass. This allows the use of lesser steroid load without loss of high effectiveness.
8. Lower dose of steroids administered daily will produce less impact on biochemical functions of the body e.g. effect on the lipogram; hemostasis and carbohydrate metabolism.
9. Avoidance of oral route diminishes the incidence of symptoms of nausea and epigastric discomfort through an element of suggestion.

Disadvantages

1. Some women may experience frequent expulsion of the ring.

2. Increase in the incidence of vaginal symptoms like discharge irritation, and discomfort during intercourse. The ring can be removed during intercourse, but should not remain out for more 3 hours.
3. Certain rings, notably the levonorgestrel ring has been rarely associated with the development of erythematous patches in the vagina. These have been noticed at the site of possible contact. Their nature is most probably a combination of atrophy plus increased congestion. This problem will result in effort to increase the flexibility (pliability) of the ring, but it has already delayed the introduction of CVR to public use.

Considering the information presently available it can be concluded that a number of contraceptive vaginal rings will be soon available for general use.

G. Contraceptive Vaccines

Development of vaccines that can interfere with reproduction is an attractive idea, which is presently receiving great scientific interest. In the development of a contraceptive vaccine, the events or processes in reproduction accessible to immune intervention must first be defined, and then specific antigenic molecule(s) identified that when neutralized by vaccination antifertility effects will results. With the advent of recombinant DNA technology, the antigens could be readily produced, purified, and evaluated.

Crucial antigens that may be neutralized through immunization include:

- Chorionic gonadotrophins.
- Pituitary gonadotrophins.
- Hypothalamic Gn RH.
- Sperm antigens.
- Zona pellucida antigens.
- Gonadal steroids.

The development of vaccine is a complex process since:

1. Some of these specific molecules are not strongly antigenic e.g. Gn RH, and steroids; and their antigenic property needs to be enhanced by coupling them to stronger antigenic molecules (e.g. bacterial component like diphtheria or tetanus toxoid)
2. The immunization is usually transient; delivery system for repeat booster administrations must be developed. The hope that a single vaccination could result in infertility is usually impossible. Repeat boosters or continuous delivery system of the antigen e.g. through microspheres are being attempted.

3. The variability of response to the vaccine must be minimal.
4. There is a need for the vaccines not interfering with biological functions e.g. sexual performance or menstruation.
5. Return of fertility must be ensured for temporary vaccination.

These difficulties show that a lot of work is still needed before we can have an effective and safe antifertility vaccine. The most thoroughly studied vaccine are those that elicit antibodies to human chorionic gonadotraphin or its β subunit, this can interfere with establishment of implantation. Therefore, it can be considered as an abortificent.

H. Antiprogesterones or Antiprogestins

Progesterone is essential for normal reproductive function: 1) It regulate development of ovarian follicles and the process of ovulation. 2) It facilitates the transport of the fertilized egg through the fallopian tube. 3) It causes the formation of secretary endometrium, which is required for implantation, and nourishment of early conceptus. 4) During pregnancy, it keeps the uterus in a quiescent state that is essential for normal development of the embryo/fetus. Because progesterone plays such key functions in the reproductive process, any approach that prevent this hormone from acting on its target cells in the reproductive organs will have contragestational or contraceptive effects.

In general, prevention of physiological effects of progesterone effects can be achieved by: a) by inhibiting the biosynthesis of progesterone, either i) directly at the level of progesterone-producing cells through the use of steroid enzyme inhibitors e.g. 3β-hydroxysteroid dehydrogenase (3β- HSD) inhibitors such as epostane and similar drugs, or ii) indirectly through preventing trophic hormone from stimulating progesterone producing cells by the use of anti hCG vaccine. b) Another approach for producing progesterone withdrawal is interfering with progesterone action at target organ level through the use of progesterone receptor blockers, which are called antiprogesterone or antiprogestins. This latter approach has been the most advanced, and a number of products are now available and widely tested.

The antiprogestin most widely used for the purpose is mifepristone (Ru 486). It is a steroid, which has a bulky substituent at C 11 position. It is acting through competitive inhibition; by binding to the specific progesterone receptor in target cells; mifepristone "shams " these receptors, preventing them from binding to the natural hormone.

Mifepristone has been most widely used for induction of early abortion i.e. termination of early pregnancy. The drug induces uterine contractions and increases myometrial reactivity to ecbolics like prostaglandins, and their analogues. The success of this

combination is highest in early pregnancy termination. The usual dose of mifepristone is a single oral dose of 600 mg. This is usually followed by either intramuscular injection of the prostaglandin sulprostene, vaginal administration of a pessary of Gemeprost or oral administration of misoprostol. The success rate of such combinations in inducing early pregnancy abortion (within 6 weeks of the date of last menstruation is generally higher than 95 %. The failures include persisting pregnancy in less than 2 % of cases, incomplete expulsion in 3 %. The " abortion pill " has stirred great enthusiasm in countries where induced abortion is legal, and consequently a good deal of societal reaction.

Apart from in induction of abortion mifepristone can be used in other ways which are still under evaluation:

1. As an emergency contraceptive (see above).
2. Luteal, once-a-month contraception. Administration of an antiprogestin during the mid-to-le luteal phase of the menstrual cycle causes endometriolysis and vaginal withdrawal bleeding 1 to 3 days later.
3. Early luteal phases administration can interfere with implantation of the fertilized ovum.

E. Inhibins and Contraception

Inhibins are a family of protein hormones produced by the testis and ovaries with a specific function of inhibiting the production of FSH (and not LH). It can therefore, control the functions of folliculogenensis and spermatogenis without interfering with LH functions, e.g. estradiol or testosterone secretion. The hormone has been separated, and synthesized utilizing recombinant DNA technology and has an RIA for its measurement. It is a promising molecule for contraception in both the male and female. The pharmacological action of inhibins needs more clarification, and a delivery system is under development.

Contraceptive for Family planning

Contents:

- Counseling on contraception
- Family planning for special stages of life, and special conditions
  a. *Newly married couples*
  b. *premenopausal women*
  c. *Breastfeeding Mothers*
  d. *Postabortive*

e. *Smokers*
f. *Certain diseased conditions*
g. *Interaction with other drugs*

The family is the most working type of human cooperative unions. If left to nature such union can result in a big number of children, more than the married couple can afford, or like to have. Given the limited physiological capabilities to produce healthy offspring, and the limited resources to support children, a certain degree of planning needs to exercised on the family formation. This involves, among others, the following measures of planning.

- Choosing the age at which a man or a woman starts the family.
- Limiting the size of the family, and.
- Spacing of births.

Given the limited economical resource a country can have, family planning has become one of the solutions to ensure a balance between resources and numbers. Amongst other solutions, family planning seems to be the easiest one, which may also give the earliest demographic effect. Therefore, many countries have initiated special family planning programmes.

Given the limited resources the world have and inequity of distribution of such resources between countries, there has been an organized international interest in family planning to limit population growth. The national programmes are supported by international effort and donor agencies. This has also resulted in organizing international effort to develop better contraceptives and more effective family planning programmes.

Given the different and intricate aspects of human reproduction there has been a tendency to enlarge from family planning programmes to ***reproductive health programmes***. Such latter programmes give equal attention to sexual and material health besides fertility health including management of infertility and contraception. Moreover, reproductive health has become a goal in itself, and there has been enlargement to encompass all health issues related to the female sex; ***woman's health***.

Where the medical service team stands in all this? This team is in the very center, delivering the services, but the contribution of other actors is required for the completion of the job. These include the demographer, social workers and special activist groups, the advocates of woman health. The members of medical profession should attend primarily to their " medical " roles, giving space and working in harmony with other parties. However being responsible member of the society, the medical service providers have an ***advocacy role***. They need be advocates of improving the women (and family) status and measures that contribute to her (and her family) well-being.

Contraception and Family planning

The use of the various contraceptives helps individual couple to achieve their aspiration in the family structure. The big variety of contraceptive methods presently available allows fulfilling these aims for the majority of couples. The members of medical professions help the couple to choose between the available contraceptive methods through carefully conducted *medical counseling*, and thereafter offer the service and deal with any consequent side effects.

Counseling on contraception

Through counseling, health providers help clients make their own decision about reproductive health and family planning. Counseling is an interactive process between providers and receiver of service ending in the client taking her or his own decision. It has been repeatedly shown that good counseling result in better client satisfaction, promote acceptability, help tolerance of side-effects of treatment, and ensure longer continuation of the contraceptive use.

Principle of good counseling

1. **Respect of the receivers**: Speaking the language of the clients; crossing any social gap between provider and receiver is essential for success in provision of medical services. This should start by respecting the clients; and not just showing them respect. The provider should be true in all what is said, and needs to be open and simple in putting facts about the treatment proposed. The provider should respect all concerns and discuss all questions the receiver may have. Confidentiality should be assured about any information obtained during the process of counseling.
2. **Interactive counseling**. The provider should listen to, learns from, and responds to clients. Therefore the provider encourages clients to talk and ask questions.
3. **Provision of information** This takes the form of a discussion about all available methods of treatment (contraception) suitable for the particular needs of the individual client e.g., be it a long-term, or a short-term use, and suitable for her or his stage of life, and the nature of sexual relation practiced. The advantage and disadvantage of each option should be clearly given; no side effect is concealed or lessened. The information should be given in the language the receiver can understand. Information pamphlet may be given to the client during the waiting time; these can be the basis of the discussion. The receiver should not be drowned in too much information (information overload) that may make taking a decision hard.

4. **Allowing-as far as possible-the service receiver to take the decision:** The provider helps client make their own informed choices, and the provider respects these choices. Most new clients already have a family planning method in mind. Good counseling starts with this method. Then, in the course of counseling, the provider checks whether the client knows all the advantage and disadvantages of this choice. Alternative methods are then discussed and compared with the method in mind. If there is no medical reason against the latter method, the client should have the method she or he wants. This is the process of making informed choice. When clients get the methods they want, they use them longer, and more effectively, and are more ready to bear with their side effects.
5. **Written consent is required for methods of treatment that carry a major problems or a serious decision** e.g. methods entailing operative interference or permanent effect, this is mainly applying to sterilization.
6. **All details about the use of the method of treatment (contraception)** : These should be provided through the discussion, helped by models or posters or pamphlets. The provider should check whether the client has understood how to use the method. She can be given a reminder of a specific important dates e.g. date of the next injectable, the expiry of the effect of an implant, or a certain important follow-up visit.
7. **At the end, after providing the service, the client should be made feel welcomed to come to the family planning center whenever she has any problem or concern.**

Steps in Counseling New Client

Deciding on a family planning method and using it involves a step-by-step process. To help remembering the basic six steps have been suggested and put together in the word **GATHER:**

a. **G** Greet client, and gain her confidence.

b. **A** Ask the client if she has a particular method of contraception in mind; and the reason(s) of this choice; and about her past contraceptive experience if any.

c. **T** Tell the client about choices available to her and the merits and demerits of each, putting emphasis on the method(s) she prefers.

d. **H** Help client make an informed choice (see above).

e. **E** Explain fully how to use the chosen method. Encourage her to ask questions and ensure she has understood well the method of use.

f. **R** Return visit should be welcomed, and indicated to the user if a timed visit is required e.g. having the following injection.

Family planning for special stages of life, and special conditions

a. Contraception for the newly married couples

This is a period of frequent sexual intercourse with a great deal of spontaneousness. The uterus may not be completely developed; and under special circumstances, there can be an increased risk of STDs. There is usually a concern about potential fertility, which has not yet put to test.

Among the various options available for temporary contraception the following are the better choices:

1. **Low-dose COCs:** This is usually the best choice. COCs is started during the month preceding marriage. Concern about any effect on future fertility should be dispelled; the use of these pills for any duration of time do not delay the occurrence of pregnancy once their use is discontinued. Any such delay would depend upon the original fertility index of the couple. The high effectiveness and the regularity of menstruation are advantage in this situation. The main disadvantage is the absence of protection from STDs if the possibility exists. The need to take a daily action can be another disadvantage. The COC may be used to delay the menstruation for some days to avoid menstruation on the day of wedding.
2. **Condom** is a possible option. It has the advantage of protection against STDs. However, its possible interference with sexual pleasure is the main disadvantage. Use failure is higher in young couples because of higher frequency of condom break or slipping.
3. For women who have a special contraindication for use COCs due to their estrogen content e.g. smoking woman above 40 years of age, hypertensive or diabetic a **progestogen-only contraceptives** can be used. Norplant is a good choice if long-term contraception is desired. Its high effectiveness, and the long-term effect and the absence of the need to take a daily decision are the advantage. Immediate resumption of fertility after Norplant discontinuation is another advantage. The disadvantages are the need for a minor surgical procedure for insertion and removal of Norplant, the visibility of Norplant implants, and the menstrual disruptions. Progestogen-only-pills (minipill) can be used if only short-term deferment of pregnancy is planned; they can discontinue at any time. However, the need to make a daily decision of taking the pill, and at the same time of the day is a disadvantage; besides the menstrual disruption they cause. The progestogen-only injectable may not be a suitable alternative because of time lag of return of fertility after discontinuation of injectable

besides the high frequency of menstrual disruption. The monthly injectables are good choice.

4. **The IUD** is not a suitable option for the nulliparous recently married woman. In such women, the bleeding, pain, and spontaneous expulsion are commoner. These complications may be related to the smaller size of the uterus and higher frequency of intercourse. Transmission of STDs is more likely in these couples and there is higher likelihood of PID.
5. ***Periodic abstinence*** interferes with spontaneousness of sexual intercourse and usually result in higher failure rate.

b. Contraception in the premenopause

In general, the use of contraceptives during the 15 years preceding the menopause has to take in consideration the following three issues:

1. Women are less fecund, but still pregnancy can occur.
2. Pregnancy in this period has special risks, and certain social and psychological implications that make it an unwelcome occurrence. There is an increase of maternal mortality; four times as high in the fifth decade of life as compared to the third one. Spontaneous abortion rates doubles between these two decades. Prenatal mortality doubles. These rates are usually compounded by high parity common in this age group. The risk of chromosomal anomalies in the fetus is increased with age. Psychologically, a workingwoman, or one who is having grown-up children may not be ready to the personal and social implications of an extra child. Induction of abortion is frequently resorted to in these situations.
3. The uses of certain contraceptives in women above the age of 40 may carry certain risks that should be taken in consideration. This has been particularly associated with COCs. However, recent data indicated that the use of low-dose COCs carry no special risk to women above the age of 35 year (and up to age of menopause) provided they are not having any risk factor for cardiovascular disease, like smoking or hypertension.
4. The premenopasual years have special symptoms and conditions, like vasomotor symptoms and dysfunctional uterine bleeding; and it will be advantageous if these conditions are attended to along with contraception.

Contraceptive options for premenopausal women:

1. **Sterilization:** After the age of 35 year, male or female sterilization is a good option if the desired family size has been achieved. The incidence of regretting sterilization in these women should be low.

2. **Intrauterine contraceptive device:** The long-term effect of the second generation copper IUD, like T Cu 380 A nicely suits the need of women above 35 years. The high efficacy coupled with reduced fecundity in this age group may allow extending the term of such IUD beyond the ten years and until the menopause is established, reducing the need for IUD replacement. This can reduce the chance of developing pelvic inflammatory disease, which is particularly higher in the first 20 days following the insertion. The main problem with the IUD in this age group is that it will accentuate the already increased probability of uterine bleeding. In this age group, a policy of liberal removal in case of bleeding is advisable. This will avoid delay in diagnosis of organic causes of bleeding. The levonorgestrel IUD (LNG-IUD) combines high efficacy with reduction of menstrual bleeding. The latter effect is due to a local effect of levonorgestrel in suppressing endometrial growth.
3. **Combined oral contraceptive pills:** Since early use of COC their association with increased risk of cardiovascular disease of thrombotic nature has been suggested. On the arterial side there was a suggestion of an association with myocardial infarction and cerebral stroke, and on the venous side with venous thrombosis and embolism. These associations were observed in women above the age of 35 or 40 years. However more recent and more carefully conducted epidemiological studies have shown that users of low-dose COC stand no increased risk of these arterial disease regardless of their age, provided that they are not having risk factor for this disease like smoking hypertension or diabetes mellitus. There is a slight increase in the risk of thromboembolism that is not related to middle age (see under COCs). The low dose pill can be safely used by women aged more than 35 years and up to the age of menopause.

   Low-dose COCs in this age group have the special advantages of 1) high efficacy, 2) ensuring regular menstruation, 3) relief of climacteric symptoms occasionally complained of by middle aged women, 4) improving vaginal dryness and sexual performance, 5) reduce the incidence of dysfunctional uterine bleeding, 6) protection against epithelial ovarian and endometrial cancer. These are besides the other non-contraceptive health benefits common to all ages, like reducing the incidence of premenstrual syndrome, dysmenorrhea, anemia, symptomatizing endometriosis, fibroid, functional ovarian cysts, endometrial and ovarian cancer.
4. **Progestogen-only contraceptives:** Women at increased risk of developing cardiovascular diseases on using COC e.g. smokers and hypertensives can use any of the progestogen-only-contraceptive including the minipill, injectables and Norplant. However, they have the disadvantage of causing irregular menstrual pattern that may raise concern about organic causes for such bleeding.

5. **Barrier methods and periodic abstinence** can be used by couples that have been successfully using them for some years. The condom may not be suitable for a male partner of declining potency. The mucus method become less " readable " because of irregularity in menstrual cycles and the more frequent occurrence of anovulatory cycles.

When to stop using contraceptive in middle aged women.

Women above the age of 45 years are traditionally considered menopausal after having 1 year of amenorrhea. However, some 10 % of these women may have an occasional menstruation and may be ovulation thereafter. Therefore, it is advisable that women continue to use contraception up to 2 years after their last menstruation. A woman using hormonal contraceptives can stop using them at age of 52 years, and then use some barrier method and continue using them until she has had two years of amenorrhea, or until she has shown the postmenopausal high levels of FSH characteristic of menopause in two assays 6 months apart.

c. Contraception for Breastfeeding Mothers

Traditionally, in Egypt breastfeeding continue for long time. More than 90 % of Egyptian initially breastfeed their children. Islam *encourages* breastfeeding for two years. Given the high total fertility of Egyptian women (about 4), particularly in rural areas, a high percentage of the clients of family planning clinics are expected to be breastfeeding. About 50 % of the clientele of the Assiut University Family Planning Clinic are breastfeeding.

Contraception during breastfeeding ensures a good interval between births and effectively contributes to family size limitation (see later under Health rationale of family planning).

Contraceptive suitable for use of breastfeeding mother should ideally have the following features:

1. Not interfering with the initiation of lactation.
2. Not changing the quantity and quality of breast milk; and thus not negatively interfering with the growth, development and health of the breastfed infants.
3. Hormonal contraceptive suitable for breastfeeding mother should be minimally secreted in the breast milk; and whenever secreted in the milk, the contraceptive or their metabolites are better if not effectively absorbed from the gastrointestinal tract of the child. In fact most steroid contraceptives are secreted in very small amounts in the breast milk and do reach the infant. Ideally, preference should be given to use of hormone, which are not absorbed from the gut of the infant. This will ensure absence of any systemic effects of ingested compounds, and guarantee absence of any future

effect on the offspring in future life. Although no such effect have been yet proven; the proof needs prolonged follow-up of big number of offspring in later life.

Contraceptive options for breastfeeding mothers:

1. **Lactational amenorrhea method (LAM):** Lactational has long been recognized as a way of diminishing the fertility and spacing births. However, at the individual level the contraceptive effect of breastfeeding varies according to: 1) its duration, 2) the frequency and duration of breastfeeding episodes, 3) the vigor of infant suckling, 4) the extent of supplementation breastfeeding by complementary feeds (fluid, semisolid or solid), 5) and the resumption of menstruation. The Bellagio (a town in Northern Italy) consensus statement represents an attempt to quantify the contraceptive effect of breastfeeding: The consensus is an agreement of a number of investigators working on populations from different developing and developed countries upon a statement that says that " if a woman is exclusively (or almost exclusively) breastfeeding, and whose menstruation has not been resumed, her chances of getting pregnant is less than 2 % during the first six months after the childbirth". This effectiveness is comparable to the typical effectiveness of many contraceptives. This specific scientific finding has allowed the introduction of lactational Amenorrhea Method (LAM) for contraception. LAM requires all the three criteria: 1) exclusive or almost exclusive breastfeeding, 2) lactational amenorrhea; 3) and during the first 6 months postpartum. The method, which is in reality is an advice, has been field tested in a number of settings (including Assiut) and proven highly effective and reasonably usable by a good percentage of breastfeeding mothers. It carries no cost and has the added merit of encouraging active breastfeeding that have important health benefits to the infants in comparison to artificial feeding. The expiry of any of the above three conditions should indicate the use of other contraceptive, thereafter, the contraceptive effect of breastfeeding becomes less sure. The mother should then be started on methods that will not interfere with lactation. The initial use of LAM after childbirth may encourage women to use long-term methods after expiry of the LAM criteria.

   LAM should be viewed as a quantitation of the " limitations " of the contraceptive effect of breastfeeding; it limits the woman's intention to continue relying upon contraceptive effect of breastfeeding. There are two main disadvantage for use of LAM: 1) The extent of use (utility) of the method can be limited particularly for working women who spend a good time outside their homes and away from their infant. 2) The condition of LAM may expire any time; at times when it is not suitable for the woman to initiate alternative methods. Consequently, women who are willing to initiate another suitable alternative method, before expiry of LAM criteria should not discouraged from doing so.

2. **Intrauterine contraceptive device:** The IUD is the most suitable contraceptive during breastfeeding; it has no effect on breastfeeding. It combines high effectiveness to long-term effect. Usually the IUD is inserted 4 to 6 weeks after delivery. If it is to be inserted later, the provider should be reasonably certain that the woman has not already conceived, e.g. inserting the IUD shortly after a period. The presence of the three terms of efficacy of LAM can reasonably ensure absence of this possibility. Insertion of the IUD in a woman who is having long-term amenorrhea should be done with special care to avoid perforation of a hyperinvoluted uterus. Women vary markedly in the extent of this involution. Some women who have been breastfeeding for a long time have a uterus with compromised length and thin myometrium.

   The IUD can be inserted immediately postpartum (within 48 hours after birth), (see under postpartum IUD).
3. **Progestogen-only-contraceptives**: the progestogen only pills, injectables and Norplant (and Uniplant) can be safely used by breastfeeding mothers. Their use does not interfere with the quantity or quality of breast milk, or the growth, development and health of breastfed infants. The LNG-IUD is presumed to be equally safe. Progestogen-only contraceptives can be initiated 4 to 6 weeks postpartum. The safety of earlier initiation has not be documented; theoretically this may interfere with initiation of lactation or involution of the uterus. The menstrual irregularities associated with progestogen-only-contraceptive are better tolerated during lactation.
4. **Low-dose COCs:** It is sometimes prescribed to breastfeeding after the 6 th month postpartum i.e. after establishment of lactation and beginning of supplementation. However, women keen to preserve the function of breastfeeding for a long time should better avoid low-dose combination pills during lactation because of the negative effect of the contained estrogen on the quantity and quality of breast milk.
5. **The condom and other barrier methods**: They can be safely used during breastfeeding, if more reliable methods are not acceptable.
6. **Periodic abstinence**: generally not suitable for breastfeeding women because of irregularity of menstruation and ovulation.
7. **Sterilization (male and female)**: is a good option if the desired family size has been achieved. Tubal sterilization can be done shortly postpartum (within 7 days) by subumbilical minilaporotomy. If this opportunity is missed it should be deferred to 4 to 6 weeks (or later) postpartum when it is done by one of the " interval " operations utilizing suprapubic minilaportomy or lapaporoscopic approach. Sterilization should follow proper counseling; the distress of the memory of difficult delivery should not influence this decision of having permanent contraception.

d. Postabortion contraception

1. The time of abortion is a good opportunity for counseling about and initiating contraceptive use. The couple may opt for a period of rest after the disappointing experience, and may need some time to recover from the blood loss attending the abortion. Had the aborted pregnancy been unwanted, the women is receptive to counseling about contraceptive, this is particularly so if the abortion was induced. Ovulation may precede the first menses after an abortion, particularly when it was a first-trimester abortion.
2. Induction of abortion should not be relied upon as a method of contraception. Its hazards are high, and can be serious. This is particularly so with induction of abortion, done for unwanted pregnancy, and under suboptimal circumstances. Provision of health care for unsafe abortion is now rightfully receiving more attention.
3. Provisions for safe abortion services comprises the following: 1) use of proper medical and surgical techniques for induction of abortion (within the Law and Norms of the society. 2) Improving care of complicated abortion. These form a big sector of emergency admissions to hospital, 3) counseling of women about contraception, and initiating suitable methods.
4. All hormonal contraceptive and the IUD can be initiated immediately after a first trimester abortion. This is provided that the abortion is complete. Inserting the IUD carries no increased morbidity provided there is no evidence of sepsis.
5. After a second trimester abortion no particular risk attends immediate initiation of any contraceptive, except for the IUD. The immediate insertion of the IUD may carry an increased risk of spontaneous expulsion and infection and insertion is frequently deferred until the uterus is well involuted (± two weeks latter). In the latter situation condoms or other barrier method can be used until the IUD is inserted. With exercise of adequate aseptic approach and special inserting technique, immediate postpartum IUD insertion can be as safe as interval insertions.
6. Sterilization is an option, but this should follow a careful and responsible counseling. Sterilization should never be a condition for giving pregnancy termination service.

e. Smokers and contraceptives

Smoking particularly when heavy (> 20 cigarettes / day) increase the likelihood of development of cardiovascular complication (myocardial infarction, stroke and VTE) on using combined oral contraceptives. This is particularly in women above the age of 35. The benefit frequently outweighs the risk in light smokers, younger than 35 years.

There is no increased risk of use of all progestogen-only contraceptive by smokers. The IUD and all other non-hormonal methods can be used.

f. Contraception in certain diseased conditions

It should be always considered that women with certain disease are in particular need for contraception because of high risk of pregnancy; the benefit-risk should be weighed.

- ***Essential hypertension***
  - The IUD is the best option; and all non-hormonal contraceptive can be used as well.
  - Women with marked hypertension (≥ 180/110) are better avoiding COCs, because of enhanced risk of developing cardiovascular complication and of increasing the hypertension. This does not apply to pre-eclampsia, this is usually a disease of primigravidae, and is rarely followed by persistence of hypertension.
  - Women with mild or moderate hypertension can use low dose COCs if other options are not acceptable.
  - Progestogen-only contraceptive are relatively safer than COCs in women with hypertension in case the use of IUD is not acceptable.
  - Any hypertensive woman using hormonal contraception needs to have her blood pressure measured every 3-6 months.
- ***Diabetes mellitus***
  - The IUDs can be safely used by all diabetics. There is no increased risk of PID as originally, and theoretically feared.
  - COCs are better avoided by patients with a long-standing diabetes (> 20 years) because of enhanced risk of cardiovascular diseases. The risk is higher when there are renal, neurological and retinal complications. Short-term diabetics can usually use low-dose COCs safely, the benefits outweigh the risks. The dose of insulin or oral anti-diabetics may need some adjustment.
  - Progestogen-only-method may be used if other non-hormonal contraceptives are not acceptable.
  - Because of special risks of pregnancy, sterilization should be considered in women who have attained the desired family size.

- ***Current or history of ischemic heart disease or stroke***
  - Such women should avoid using the hormonal contraceptive available particularly, COCs.
  - The progestogen-only methods are less risky, but better avoided.
  - The IUD, barrier method and sterilization are better options.

- ***Deep venous thrombosis (DVT) Pulmonary Embolism***
  - History of, or current condition should contraindicate the use of COCs.
  - Progestogen-only-contraceptive can be safely used; it is the estrogen which enhances thrombotic tendency.
  - All non-hormonal methods can be used.
  - Varicose veins, unless marked, should not contraindicate the use of COCs.
- ***Valvular heart disease***
  - The women can use an IUD. Prophylactic antibiotics are advised after the insertion for prevention of endocarditis, unless the woman is not already receiving long-acting penicillin.
  - Barrier methods carry no risk other than the higher possibility of contraceptive failure.
  - Low dose COCs can be used in women with uncomplicated valvular heart disease. Patients with atrial fibrillation, history of subacute bacterial endocarditis or pulmonary hypertension should avoid COC.
  - Progestogen-only contraceptives can be safely used.
  - Sterilization should be considered in women who have completed the desired family size. The risk of the disease is enhanced with age, due to the prolonged strain put on the myocardium.
- ***Biliary disease***
  - Women with symptomatic or treated biliary disease better avoid estrogen-containing contraceptive, but can use progestogen-only methods. Non-hormonal method are suitable.
- ***Fibroid uterus***
  - Women with current fibroids or who have had myomectomy can use all hormonal methods. The best of them is the low dose COCs. They can ensure regular menstruation and reduction in the amount of menstrual blood loss. Progestogen-only methods are also usable but they can cause menstrual irregularity which may raise suspicion of being caused by the fibroids, and can lead to a decision of hysterectomy.
  - IUD can be used unless there is a fibroid encroaching on uterine cavity (as shown by USG or HSG). The progestogen-releasing IUS may have the special advantage reducing blood less during menstruation. This can be used if the uterine cavity is no distorted.
- ***For other disease refer to individual contraceptives.***

g. Interaction with other drugs

(see under COCs)

Health Rationale of Family Planning

Contents:

The world Health Organization has defined Health as " a state of optimal physical, mental, and social well-being; and not merely the absence of disease and infirmity ". This definition recognizes the broader need of families to be provided with nutrition, clothing, and education for their children, as well as protect mothers, and children from risks that can be associated, with the sexual relation, pregnancy, and childbirth. Three parties are involved in Family Health, the mother, the father and children. **Family planning has plays major roles in family health including the following aspects:**

1. Family planning reduces maternal mortality

The World Health Organization (WHO) defines maternal mortality "as the death of women during pregnancy or within 42 days after pregnancy, irrespective of the duration or the site of pregnancy, from any cause related or aggravated by the pregnancy or its management ". Maternal death results from *direct* or *indirect* causes.

- ***Direct causes:*** *The most important five causes of maternal mortality are:*
  1. *Hemorrhage* is the leading cause of maternal death. During pregnancy and delivery the woman is particularly liable to loose blood. This results from placental separation or from trauma to the birth canal, including rupture uterus and trauma resulting from unsafely induced abortion.

2. *Sepsis* can develop after delivery or abortion, particularly induced abortion. Infection is likely to occur when products of pregnancy remain in the uterus and when unclean hands, instruments or other objects carry infection into the genital tract.
3. *Pregnancy induced hypertension* including eclampsia.
4. *Obstructed labor* resulting from failure to recognize mechanical difficulties and mismanagement of these difficulties.
5. *Complication of unsafe abortion.*

- ***Indirect causes*** of maternal death include maternal diseases not specific to pregnancy, however their presence aggravates the risks of pregnancy. Anemia is the most important among these diseases. An anemic woman is five times more likely to die of pregnancy-related causes (particularly hemorrhage) than a woman who is not anemic. Anemia is very common in Egypt; more than 50 % of women attending antenatal care are anemic. This is due to nutritional deficiency and parasitic diseases.

  Rheumatic heart disease is prevalent in women of the childbearing age and carries high risk during pregnancy in Egypt. Other infectious diseases e.g. viral hepatitis or endocrine disorders mainly diabetes aggravate obstetric risks.

The maternal mortality is evaluated by a number of indices.

1. *Maternal mortality ratio* = maternal deaths per 100,000 live births. It is a ratio and not a rate. The maternal mortality ratio varies much between developed and developing countries, and is a good index of development of a society. It can be as low as 10 per 100,000, as in the UK Or Japan and North America; or as high as 1020 per 100,000 as in some parts of Africa. The official figures of Egypt is about 150 per 100,000 live birth, but this may be an underestimation, due to misclassification of maternal death as deaths from other reasons. In upper Egypt the real figure can be as high as 400/100.000, or even more in rural areas.
2. *Maternal mortality rate* = maternal deaths per 100,000 women aged 15-49 per year. This is the true maternal mortality rate, although less often cited than the ratio. The rate is important because it measures the impact of maternal death on the population of women as a whole, not just on pregnant women. This rate is affected by two factors:
   - The risk of death among pregnant women.
   - The proportion of women who become pregnant each year. Consequently, the maternal mortality rate can be lowered by either

making childbearing safer or by reducing the fertility rate of the population.

3. *Lifetime Risk of Maternal Death:* The lifetime risk of maternal mortality accumulates together the risk of dying in repeated pregnancies and deliveries over the woman's reproductive lifetime. This is different from the infant mortality, to which each person is exposed only once. The lifetime risk of maternal death is the most eloquent estimation of the risk of death a woman in a particular community faces in her " typical " reproductive career. It is a multiplication of the maternal mortality ratio by the ***total fertility*** of the population (the average number of pregnancies a woman goes through in her reproductive life in this community), e.g. if the maternal mortality in a country is 500 per 100,000, the lifetime risk of maternal death is 1 in 200 if the total fertility is one; 1 in 100 if the total fertility is 2; and 1 in 25 if the total fertility is 4. The lifetime risk varies between developed and developing countries much more markedly than the maternal mortality ratio; the lifetime risk is as low as 1 in 3,700 in North America and as high as 1 in 12 as in some parts of Africa; it is can be as high 1 in 25 in some parts of Egypt.
4. *Proportion of maternal mortality to all deaths among women of reproductive age.* This is a less sensitive index of the magnitude of the maternal mortality than the lifetime risk in different countries. This is because wherever the maternal mortality is high, so will be is the deaths from many other causes e.g. infectious diseases. However, pregnancy related complications cause a high percentage of death of women in the reproductive age; maternal mortality causes one-quarter to one-half of deaths among women of reproductive age in some developing countries while the maternal death contributes to only 1 % in the USA. This comparison reflects the especially poor care women receive during their pregnancy and delivery in developing countries.
5. *Reproductive mortality rate:* There is a tendency nowadays to include maternal mortality in Reproductive Mortality, which include besides maternal deaths, deaths due sexually transmitted diseases and death due to side effects of contraceptive methods.

Family planning and maternal mortality

More than 99 % of world wide maternal mortalities occur in developing countries. In these countries, each year, an estimated 585.000 women die from complications of pregnancy, childbirth and abortion; about one death every minute. Nearly all of these deaths

are preventable. One of the effective ways (among others) of reducing this death toll is family planning which will diminish the number of times the woman will face risks of maternity (life-time risk) through the limitation of the number of pregnancies the woman goes through. With proper timing of pregnancy, they will occur when the woman is most physically, psychological and socially prepared, thus reducing the numbers and severity of pregnancy related complications, including those of induced abortion. Frequent pregnancies prolonged lactation, heavy work and shortage of adequate feeding produce a continuous cumulative " nutritional drain " on women; their bodies do not have time to replenish stores of vital nutrients. As a result, they are less able to combat hemorrhage, infections and other complications associated with pregnancy, abortion and delivery or the everyday exposure to illness.

A better impact of family planning on maternity risk is achieved when family planning services are linked to other family health services, like antenatal, intranatal, postnatal and infant and childcare. This is a logical continuum that also ensures better and more effective utilization of these services. *This has led to the evolution of the concept of " reproductive or woman health " as a better strategy than delivering of each of the above health components separately.* Recently woman's health has become the goal in itself rather a mean to achieve other goals like limiting population growth.

Family planning reduces the demand on induction of abortion and the incidence of unsafe abortion. Serious complication can arise from the latter; in the form of loss of life or much morbidity.

2. Family planning Reduces Maternal Morbidity

Women who survive pregnancy/delivery complications may suffer chronic health problems, which compromise the quality of their life. These include anemia, pelvic inflammatory disease, chronic pelvic pain, secondary infertility and genital prolapse. Serious infirmities like urinary or rectal fistulae, hysterectomy for rupture uterus and infertility can also result from complicated deliveries. Little is known about the prevalence of maternal morbidity in developing countries; estimates have ranged from ratios of 16 to 100 episodes of illness or disability for each maternal death.

3. Family Planning obviates the risks of high-parity

The lifetime maternal risk is not a simple multiplication of risks in individual pregnancy. The perinatal and maternal risk estimates go in a U-shaped curve. They are relatively high in the first pregnancy, and drop in subsequent pregnancies until the fifth, when they start to rise again and reach dangerous levels with the 7^{th} delivery and plus.

High order pregnancy is attended with special risks. The women are designated as " grand multiparae " that is equivalent to the "dangerous multiparae". These special risks of high parity include increased incidence of the following complications:

***A. Druing pregnancy*:**

- Anemia becomes commoner and severer. This includes both iron deficiency anemia and megaloblastic anemia of pregnancy.
- Severe bone softening and deformation of the pelvis to the extent of *osteomalacia* have become extremely rare in modern practice. However, less marked forms of pelvic deformation can result from calcium and vitamin D deficiency resulting from frequent and unspaced pregnancies and lactations, coupled with untritional deficiency and lack of exposure to sun. Bone depletion results in chronic bone aches, and minor pelvic deformities that may escape clinical notice, and result in an unexpected dystocia in grand multiparae.
- Increased incidence of essential hypertension and maturity onset diabetes.
- Increased incidence of placental abruption

B. During labor:

The four determinants of the outcome of labor can be at fault in a grand multipara; (faults in the passage, passenger, forces of labor and attendant of labor).

- The *bony passage,* the pelvis can get deformed due to some degree of bone softening.
- The *passenger*, the fetus, can be at fault. There is progressive increase in the fetal weight (macrosomia) with increasing parity. Due to pendulous abdomen, and uterine laxity, abnormal lie or presentations (face and brow) are commoner in a grand multipara.
- The uterine *forces* can be at a serious type of fault due to the rapid development and stretching of the lower uterine segment. The percentage of fibrous tissue in the uterine wall increases with high parity, and this is on the expense of muscle tissue. This results in diminished stretchability of the uterine wall, and makes spontaneous rupture uterus more likely to occur; the incidence of this serious complication is concentrated in grand multiparae.
- The *attendant,* the doctor; midwife-TBA, can be the source of the trouble by dealing with the grand multipara with false sense of security resulting from a history of repeatedly having normal vaginal deliveries. Moreover, due to the various causes of dystocia mentioned above, there is increased resort to operative delivery, which are frequently done as an emergency, and with inadequate facilities resulting in higher rates of morbidity and mortality to both the mother

and the fetus. Improving emergency obstetric care can effectively reduce maternal mortality, and morbidity; and improve fetal outcome.

4. Family planning obviates risks of pregnancy in elderly women

In women above the age of 40 there is a sharp increase of risk of pregnancy:

- The maternal mortality rate during the fifth decade is four times as high compared to the third.
- Spontaneous abortion rates double between the same two decades reaching 26 % in the 40-49 year age group.
- Perinatal mortality rates double as maternal age doubles.
- These risks are also compounded with the risks of the usually associated high parity.
- The risks of chromosomal anomalies in the fetus increase with age.
- Pregnancy in this age is frequently unwelcomed from social, psychological and health points of view, and there is a more frequent resort to induction of abortion which carries its own risks.

5. Family planning may prevent risks of pregnancy in adolescents

Adolescent pregnancy is an important problem in countries where there can be premarital sexual relation; which is diminished by use of contraceptive. Teenagers are not psychologically or physical prepared for pregnancy even within marriage bond. Their reproductive system might have not reached maturity, and the pelvis is not fully developed. There is increased rates of abortion, preterm labor, toxemia of pregnancy and dystocia in adolescent pregnancy and infant and child mortality. There is also increased perinatal infant and child mortality. In Egypt where girls are put to marriage at young age (the laws require a minimal age of 16 years old), most of the risks of young -age maternity apply. About 10% of all pregnancies occur in adolescent according to latest survey.

6. Family planning ensures proper childspacing (good inter-pregnancy intervals).

a. ***Birth spacing gives the mother time to replenish her resources, nutritional and otherwise.***

b. ***Birth spacing appears to have the greatest impact on child survival***. The increased mortality rates affect both the child before and after short interval between pregnancies. On the average, babies born less than 2 years after their

next oldest brother or sister are twice as likely to die as babies relative to those born after a 2 year interval. The explanations of this increased mortality are, 1) depletion of maternal nutritional resources by close repetition of pregnancy and lactation, before time is allowed to replenish the mother's nutritional resources; the child environment begins before birth. 2) Closely spaced siblings compete for food and maternal care. The older child may be weaned too soon if the mother becomes pregnant again, often depriving this child of the best affordable and safest nutrient, the mother's milk. In rural Egypt the ill health of the older child is ascribed to " "envy " to the newer brother or sister for getting the mothers attention.

7. Children in small families have better survival chances

There is an increase in perinatal mortality rate (fetal deaths in the last 2 months of pregnancy, and infant deaths in the first week of life per 1000 live births) with increased birth order, and is quadrupled for women having their fifth order or higher delivery. Birth order affects the nutritional status of a child. The third, fourth and subsequent children are likely to eat fewer calories and proteins, thus makes them more susceptible to illness, including fatal diseased conditions like Kwashiorkor syndrome. The latter word had its origin in local language in Ghana and means " the child displaced from the breast soon " because the mother gets pregnant again.

Family planning also can diminish the numbers of children born to elderly or very young mothers that have increased perinatal mortality. There is higher incidence of chromosomal anomalies in the infants born to elderly mothers.

8. Noncontraceptive benefits of contraceptive methods

- By using condoms a woman may protect herself (and her partner) against sexually transmitted disease, including AIDS, pelvic inflammatory disease, and cervical dysplasia or cancer.
- Oral contraceptives have been shown to have a protective effect against ovarian and endometrial cancer.
- Oral contraceptives have been shown to have a protective effect against fibroid, benign breast disease, endometriosis, dysfunctional uterine bleeding, dysmenorrhea functional ovarian cysts, premenstrual tension syndrome and anemia.
- The couple will enjoy more relaxed sexual relations by removing the warry about the occurrence of pregnancy.

9. Avoiding unwanted pregnancy diminishes the problem of unsafe abortion.

A good proportion of induced abortion occurs of unwanted pregnancy. Estimates of the exact proportion are difficult to make and vary from one society to the other. In societies where law does not allow abortion service, or they are not readily available in the health service system, induction of abortion is done under unfavorable circumstances, and is likely to be completed i.e. " unsafe abortion ". These complications are serious and can entail loss of life. The proportion of maternal mortality due abortion is estimated to be around 13 % worldwide (50, 000 to 100,000 women deaths annually) but varies from one country to another. It can amount to one fourth of maternal mortality. In some communities a good number of such deaths and much higher number of sublethal morbidities can be avoided by effective and properly utilized family planning programmes through avoiding unplanned pregnancies.

The time of offering abortion service, whether at the time induction of abortion (where it is allowed) or the time treatment of complications is a good opportunity for counseling about, or initiating family planning methods (see above).

10. Social and psychological benefits of family planning

- Allows the couple to have the desired number of children they are willing and afford to have.
- Allows the couple, particularly the women to observe and develop their career. A small family will allow the mother to be gainfully employed.
- A smaller family puts fewer burdens on the father, and gives him more time to develop his career and enjoy life.

Demographic aspects of Family Planning;
Medical Professions and Demography

The population of the world reached six billions during 1999. It is currently growing at the rate of 1.74 % per year, this growth results in the addition of about 89 million people every year, or 244 thousand people every day or 10 thousand people every hour. Half of the current population of the world is below the age of marriage, which means that we are already committed to continuing rapid expansion of human numbers until well into the twenty-first century.

Given the limited resources of food and well being the world is presently having, or perceived to have in the foreseeable future, the population problem has attained great importance worldwide. With the unequal distribution of the resources between nations, the problem has special importance for poorer countries. The population of Egypt has exceeded 65 million and is projected to exceed 100 million by the year 2020. The population problem have aspect other than the absolute numbers, including mainly, age structure, distribution over the country, and the extent of crowding. These latter three aspects are especially relevant to Egypt. The percentage of the population below the age of 20 (usually dependable on the older people for income raising) is more than 30 %. There is escalating tendency for urbanization of the population and marked crowdness of the population in a narrow inhabited part of the country. The impact of the population problem on the environment has gained great interest in the last 20 years.

Fertility is only one of the determinants of population. The population of a country or a governrate or a city can change in only three ways: through births, deaths, or migration. Many of the issues involved in the population problem are beyond the scope of the work (not of the interests) of the members of the medical team. Their work is by nature personalized; the members of these professions helps individuals achieve their perceived health goals; and not to decide these goals for them. The aim of the subsequent discussion is to help medical practitioners to understand how the use of contraception and its effectiveness can influence the aggregate level of fertility in a population. The discussion is not meant to be an " introduction to Demography ". The

aim is just a trial to help medical and family planning practitioners to understand the meaning of terms they frequently meet in their readings and work, and to sensitize them to the demographic impact of their work. It is a sort of limited **GLOSSARY.** Interested reader is referred to specialized texts.

- **Rates:** the number of events (e.g. birth, death, or contraceptive use) divided by the average number of persons exposed to the risk of the event in a year. It is better to use as the denominators the number of person-years lived rather than the whole population.
- **Crude death rate (CDR)** in a population = the number of deaths each year divided by the average population in this year.
- **Crude birth rate (CBR)** = the number of births each year divided by the average population in this year.
- **Crude rate of Natural Increase (CNIR)** = the difference between the CBR and CDR. this is given as a percentage.
- **Crude growth rate (CGR)** is equal to CNIR if the effect of migration is negligible. Otherwise the CGR equals to the sum of CBR plus the crude rate of in-migration minus the sum of CDR and the crude rate of out-migration.
- **Doubling Time of the population:** The CGRs are usually exponential (compounded).

  The doubling time (T) = the length of time it will take a population to double. If a population is growing at a rate of r % per year, then it will double in approximately T = 69.3/r years (69.3 is the natural logarithm). It is evident that the higher the CGR the shorter is the doubling time.
- **Malthus:** The economist Thomas Malthus had reached two hundred years ago, to the dismal prediction that the world population growth would soon outstrip food supply. He reached this conclusion by arguing that if population growth continued unchecked, it would increase in a geometric sequence (1,2,4,8,16,32,64,128,….) while food supply could only grow in an arithmetic sequence 1,2,3,4,5,6,7,8, …..). Under such conditions, the ratio of food to population diminishes rapidly. He proposed this as an argument for the need to curb population growth. Fortunately, the Malthus predication has not become true. He failed to predict the improvement in food production technology (he could not have dreamt of biotechnology revolution) and the widespread acceptance of effective contraception in many societies. Had the world expenditure on wars be diverted to food production, the Malthus predication would have been too pessimistic. However, the predication

holds true for poor nations growing at rates exceeding the rate of growth of their national income, this result in a meager income per-capita.

- **Age specific population growth rates**

  Crude rates, as those given above do not take in consideration the age distribution of the population; e.g. the birth rate in women aged 20 to 24 is much higher than that for women aged 45-49 years, and vice versa for death rate (but the extent of difference in CBRs is not equal to the difference in CDR). The crude rates can often hide more than reveal because of these influences of age structure of the population. Therefore, demographers prefer to calculate age-specific rates. These can be given for each year of age, or for each of the commonly utilized 5 years periods (15-19, 20-24, ….45-49). But, this can result in too many figures to consider; hence there is a need to combine together the age specific rates into a single fertility (or mortality) rate.

- **Total fertility:** Age-specific fertility (average number of children born to women) are calculated for each year, or for each group of 7 typical five year groups of the woman's fertile age. (15-19, 20-24, ……. 45-49). Then these rate are added together to give the total fertility rate (TFR). This is the number of births that the typical woman in this locality would have if she experienced the fertility rates prevailing at every age, and lived through the end of childbearing ages. The figure for Egypt is 3.5 and the present time.

- **Life expectancy:** This is calculated by the life table approach utilizing actuarial statistical procedures. A life table is constructed showing the number of people who are still living up to each birthday out of a particular number born at a particular date. Suppose we started to observe 1000 births in the year 1970. Then we record the number who have their first birthday (still living) in 1971, their second birthday in 1972, and so forth. These numbers are used for the denominator in calculating the incidence of death rate at each successive year or groups of years. We can also calculate how many person-years were lived between birth and a certain cut-off date e.g. age of one, two, five years. ……) If we add up all years lived and divide by the number who were born, we get the average number of years lived, longevity, or the expectation of life, for example of children that survived until their first birthday; or of individuals who have reached the age of 40. This life-table approach is widely used to find the rate of incidence of complications (events) in contraceptive users (see above).

- **Population Momentum**

  The current population and its age structure contain a momentum, just as a moving car does. This momentum occurs because the number of persons already born will reproduce before they die. Utilizing figures as age specific fertility rate, life expectancy one can predict the population growth. It has to be remembered that these figures are present-time figures and may change in the future if drastic changes occur in its components. The estimates give the population trend i.e. the change in population should birth and mortality rates remain the same.

- **Contraceptive prevalence** simply refers to the percentage of women in the fertile phase of their lives who or whose partner are using contraception in general, or who are using a particular method of contraception. The percentage of these women who desire to have no more children and the percentage who desire postponing further pregnancy can help to decide the unmet needs for family planning. This gives the rationale for development, organization and, enlarging upon existing family planning services.

- **Years of protection:** This term is sometimes used to roughly estimate the extent of use multiplied by the " typical " duration of use. The number of initiators of each method of contraception is multiplied by the average or " typical " duration of continuation of use of the method in this community e.g. 6 months for COCs and 2 or 3 years for the IUD, 3 years for Norplant and so on. These figures are used to evaluate the effectiveness of family planning programmes in a certain community**.**

- **Determinants of Population growth**

  The population growth in a country is determined by factors influencing fertility, mortality, and in and out-migration.

  Determinants of fertility:

  a. Age at menarche and menopause.
  b. Age at marriage.
  c. Proportion married.
  d. Prevalence of infertility.
  e. Birth interval length.
  f. Prevalence of breastfeeding.
  g. Contraceptive prevalence and effectiveness of family planning programmes.

  Determinant of mortality

At the population level, mortality is mainly influenced by infectious diseases in developing countries. In developed countries, causes of death are mainly concentrated around degenerative diseases. In developing country infant and child mortality contribute for the highest percentage of mortality. Poor nutrition and unfavorable environment contribute to the high prevalence and mortality of infectious diseases in these age groups. This high child mortality greatly influences the life expectancy of the population. Control of diarrheal, infectious and parasitic disease can effectively raise the expectation of life

Determinants of Migration are mainly economic, social and political and include "pull and push " factors. Within a country significant migration can occur like rural to urban migration, and can result in population problem in big cities and certain slum sectors.

Some Demographic Figures for Egypt

- Population (in 1996) = 61, 45, 2382
  Proportion < 6 years = 15.1 %
  Proportion < 15 years = 35 %
  Proportion > 60 years = 5.1

- Crude Birth rate = 27.8 per 1000

- Population growth rate (1996) = 2.1 %
- Total Fertility rate = 3.6 for each woman; the whole country figure
  Total fertility rate for Urban Women = 3: 0
  Total Fertility rate for Rural Women = 4.2
  for rural Upper Egypt = 5.2

- Pregnancies in adolescents = 10 % of married women.
- Contraceptive use rate = 47.8 % of women in reproductive age
  In lower Egypt 55.4 %
  In Upper Egypt 31.4 %

Chapter 29

CLINICAL EVALUATION OF A GYNECOLOGICAL CASE

Contents

Introduction

Clinical evaluation aims at reaching a *diagnosis* of the diseased condition(s) causing the *complaint(s).* It also aims at elucidation of the *etiology* of these conditions and their possible *complications.* It needs be remembered that the diseased condition(s) can be in the *body* or in the *mind.* Many of gynecological complaints have psychological background. It is difficult to decide where the body stops and the *psyche* begins. The mix between the two may be more intricate in the case of the female. The influence of the environment is also important. *Social influences* can determine complaints, e.g. dyspareunia or chronic pelvic pain or reproductive tract infections. The evolving roles of the woman in the society have had its impact on the health of the body and psyche of the female e.g. delayed marriage and greater need for family planning. The woman should never be looked upon as a simple container of the uterus and ovaries.

Two additional aspects need be taken in consideration in gynecological assessment in our community. The first is the *social norms* and restrictions. All effort should be made to ensure equal easiness and acceptance of males as well as females service providers. The other is the *economical aspect* of health care of the women. In spite of all societal efforts, women, in poorer community are still given a more limited budget for their health care relative to males, including male children. A good clinician should be sensitive to the cost of the service, whether it is in the form of investigation or therapy.

The *ethical aspects* in gynecological and obstetric are increasingly characterized and emphasized (see the special chapter on ethics).

The clinical evaluation comprises history taking, examination and investigation. It entails from the service provider not only ***knowledge*** but also ***skills*** and ***attitudes***.

A. History taking:

▪ General considerations

Clinical interrogation: Clinical interrogation differs from other types of interviews in the following:

1. *Giving the patient all the chance to express her complaint(s) in her own way.* A good physician is a good listener. The patient should be encouraged to give her story in the chronological order and in the order of the relevance to her. The progress of the diseased condition and all the manifestations are thus known, and the relative severities of the problems are heard. Many patients are coming to the clinics to exteriorize their problems

and concerns. They will get great (may be complete) relief from having in the doctor a considerate and sympathizing ear. A truthful explanation of the problem is of great help.

2. Only after hearing the story in the patient's style, the physician should start *posing questions*. These aim at filling gaps in the story and therefore need be deferred until the whole story has been volunteered. The questions should be worded not to imply a certain answer e.g. how is your menstruation, urination, etc. They better not be answerable by yes or no; some patients are habitual "yes" sayers. Sometimes one needs to ascertain that the problem is present now, and has started with the diseased conditions.
3. The four *unoposed questions:* By the end of the clinical interrogation, the physician should have satisfactory answers to the following four questions without posing them to the patient:
   - *Why is this patient coming?* This may not be clear from the patient's story and may be confused amongst the many details. The patient may be shy to mention it, when for example, her real problem is related to a sensitive sexual problem; pelvic pain may be mentioned instead of dyspareunia or vaginal dryness instead of frigidity. A woman with a number of living children may be shy to mention that she is coming for infertility. Failure to address the real problem (even if not mentioned) is a failure of the physician.
   - Why is this patient coming *now*? The complaint of the patient might have been longstanding; what are the new developments that prompted her to come now?
   - Why is she *coming to a gynecologist* instead of going to an internist or a general surgeon for a complaint common to the two specialties e.g. pain in the right iliac region, loss of weight, urinary troubles,. ...etc?
   - Why is she coming to me as a person? This may point to unsatisfactory performance of collogue who has already seen her, I can avoid. The physician should start from where other colleague(s) has ended. He should carefully read notes or letters given by previous physician in charge. All the previous prescriptions should be considered with great care.

"Possibilities" approach: The clinical history should address the possibilities that may be causing the complaint aiming at their rating in the order of probability (odds) and importance. For each clinical complaint the physician should have a list of possibilities. A good clinician should have a comprehensive list of possibilities for each complaint, and should have them listed in the "computer" of his mind in the order of their likelihood (incidence) and importance. A poor physician may miss an important possibility or may go to

rarities instead of the near or common things, e.g. from appendicitis and to Grohn's disease for causing pain in the right iliac fossa.

The proper possibility rating (deciding on the odds) depends on having for each diseased entity a group of salient features (i.e. important symptoms, signs and tests). Again these features need not only be comprehensive but also prioritized in this "computer" in the mind of the physician. A poor physician requires rare features of a disease while neglecting important ones. Part of the clinical training is achieved by setting the computer and being trained to change the odds with presence or absence of salient features.

▪ Items in the history

1. *Personal data including:*

- Name and address
- *Marital Status:* duration of marriage: If there has been more than one marriage, the duration of each should be recorded, as well as the duration during which she was single in between. The duration of consummation of marriage should be ascertained.
- *Parity:* This is a two-figure summary of the obstetric history (as will be taken later). The first figure gives the number of previous deliveries and the second the number of previous abortions with a plus sign in between. A para 2+1 is the woman who had 2 previous deliveries and one abortion. In Gynecology cases this represents a sort of a title to the individual like the title doctor or professor on the business card; it greatly colors and influences how the individual is considered.
- Patient's work and her husband's work
- *Special habit(s):* In order not to miss later, this item entered here; e.g. whether she is a cigarette smoker. Smoking can influence a number of diseases.

2. *Complaint(s):*

This should be recorded in the patient's words. Clinical terms may be used like amenorrhea for absence of menses, so long as they are not including a diagnosis or adding or subtracting significance from the patient's complaint. A complaint of something protruding from the vulva should not be recorded as uterine prolapse and vice versa.

There can be more than one complaint; these are entered in the patient's priority of mentioning. The duration of the complaint should be asked for if not volunteered by the patient. If this seems to be too long, the patient may be asked for any recent development.

3. *Menstrual history:*

Before going into the history of present disease it will be, in OB/GYN cases, beneficial to have the menstrual and obstetric histories. Many of the gynecological complaints are about or related to the menstrual function and/or past obstetric performance. The menstrual history starts by a description of her *basic menstrual function* before the present disease. It begins with her age at the *menarche*, or menopause (if postmenopausal). Then the usual *length of the cycle* is recorded. The cycle begins with the beginning of a menstruation and ends by the beginning of the subsequent one. A common mistake is to record the interval between the two bleeding episode as the length of the cycle. A month-to-month variability of plus/minus four days is not to be taken as an irregularity. The duration of the period can also vary from one cycle to the other with a plus/minus of one or two days. The menstrual cycle may be recorded as a fraction; the numerator is the days of the period, and the denominator the days of the cycle. The amount of menstrual flow is usually consistent for a woman and can be judged by the number of sanitary pads the subject needs to use. Pain is a common association with menstruation *dysmenorrhea* should be recorded. It is usually primary and tolerable; new development of pain or recent increased severity or duration should be recorded.

Then the patient is asked about any recent or present change in the menstrual function. This is better detailed with the present history if the patient is presenting for menstrual problem. After that the menstrual history ends by recording the date of the first day in the last menstrual period.

4. *Obstetric History:*

This compromises the following items:

- *Previous pregnancies including number of previous normal pregnancies (NP),* which are uneventful pregnancies and the number of *previous abnormal pregnancies (AP)* followed by specification of the abnormalities. Specific complications of pregnancy e.g. antepartum hemorrhage and hypertensive toxemia of pregnancy come before nonspecific complications of pregnancy e.g. rheumatic heart disease and diabetes mellitus. Details of this item are usually required in Obstetrical cases.
- *Previous deliveries* including number of previous *normal deliveries (ND)* which are the deliveries having all the following features of being term deliveries, with vertex presentation, completed spontaneously i.e. without operative interference, within 24 hours, without maternal or fetal complications or retained placenta and /or postpartum hemorrhage and resulting in live-born healthy baby. Number of *abnormal deliveries (AD)* which deviated in one or more of the previously mentioned specifications. This is followed by specification of the abnormalities in labor like preterm labor, face

presentation, prolonged labor, forceps delivery, perineal laceration (episiotomy does not qualify delivery as abnormal), postpartum hemorrhage or delivery of asphyxiated fetus.

- *History of any puerperal morbidity* in any of the previous puerperiums, e.g. puerperal pyrexia or venous thrombosis.
- *Number of living children,* followed by number of living males. The latter point is important in our culture particularly in rural areas. No living males (or even few of them) may explain concern about infertility. Previous child loss should be reported including the age at which the loss has happened and the cause. The latter point is particularly important in early (within the first postnatal week) death, since this can suggest complication of labor as birth trauma, asphyxia neonatorum, or respiratory distress syndrome (RDS).
- *Date of last delivery*
- *Number of previous abortions (Ab)* and the week of pregnancy at which the abortion occurred. History of induced abortion and any following complication(s) should be detailed.
- *Date of last abortion*
- *Breastfeeding experience:* The usual duration of breastfeeding and whether she is presently breastfeeding.

NB: Sometimes the obstetric history is given pregnancy by pregnancy to include more details about particular events.

5. *Contraceptive history*

- The *types* of contraceptives that have been used.
- Any *complication(s)* that resulted from their use.
- The *presently used contraceptive* and when this use has been initiated.
- Any impact of this use on her complaint is detailed in the present history.
- More details will be required during counseling for contraception.

6. *Present history*

This is the history of the presenting disease. *This is an analysis of the patient's complaint in the light of the possibilities aiming to reach a provisional diagnosis.* It starts by hearing the story of the complaint(s) as volunteered by the patient before posing questions. Sometime, the physician needs to keep the patient in the story of the present disease. The questions will serve to complete gaps in a forming picture. The history will indicate certain points on which stress is put during clinical examination. Routine questions should be kept to the end of the

history and may need to include urinary and gastrointestinal symptoms. Sexual history is usually but not always needed.

The present history should comprise besides deciding on the possibilities, consideration of *etiological factors* for the relevant possibility e.g. sexually transmitted disease, postabortal and puerperal infection. The history is incomplete without considering the *complications* of the relevant possibility, e.g. urinary tract complications and strophic ulceration in case of genital prolapse.

It has to be emphasized that many diseased conditions are diagnosed from the history e.g. ectopic pregnancy and other types of acute abdomen, pelvic inflammatory disease, and endometriosis. The author has kept telling this story hundreds of times. It is that of a novice in the reception room (RR) who, in the early hours of the morning, received a patient with acute right lower abdominal pain. Keen to do more appendectomies for training purposes, he rushed to the diagnosis of acute appendicitis. Happily he took phone permission from his senior to do appendectomy. The patient on the table looked very obese, and therefore he gave her a big Mc Burney incision that entailed some muscle cutting. When he reached the peritoneum he discovered much blood. He ran to the telephone to tell his senior. The latter happened to be too lazy to come at this time, so he advised the young man to leave the right-sided oblique incision and do the proper right paramedian exploratory incision. When this was done, the poor surgeon was overwhelmed by the severity of the bleeding which he considered to be coming from above. The across telephone advice was to enlarge the exploratory incision upward in order to explore the spleen for rupture, an accident which is common in our part of the world because of bilharziasis. He enlarged the incision up to the costal margin but was unable to be sure that the bleeding was not coming from the spleen; there were too many of intestinal loops. Now the advice was to make a transverse incision toward the left lumbar region. He found the spleen intact. The next advice was to enlarge the incision down and look to the tubes where he discovered a spurting artery on a ruptured tubal pregnancy. The price of not hearing the history of the patient was a disfigured abdomen and bad incisional hernias, and immense stress of the coronary circulation of the poor young man.

Examples of history taking in common gynecological problems:

Pain: The following points should be ascertained:

- The exact location.
- Severity.
- Type: spasmodic colicky, stabbing, piercing, bursting, aching. These descriptions have suggestion of intestinal, ureteric, or ruptured or torted viscous or an inflammatory nature.

- The radiation of the pain: radiation to epigastrium suggests intestinal pain, to the inner thighs suggests genital origin and to the loin ureteric origin.
- Bilaterality of the pain suggests urinary origin or tuboovarian involvement. Exacerbation with defecation suggests rectal irritation by something pressing like pelvic abscess or hematocele.
- Associated or following symptoms, Nausea and vomiting, constipation may suggest appendicitis. Lower urinary tract irritation suggests urinary origin. Bleeding may suggest a gynecological cause. A history of missing a period or an unusually scanty period suggest ectopic. Fainting following acute lower abdomen is highly suggestive of disturbed ectopic. Chills of fever are suggestive of inflammatory conditions like salpingo-oophoritis. A high temperature is not expected with ectopic pregnancy or appendicitis.
- Sequence of events, spreading pain and development of ileus suggest peritonitis.
- Relation to posture or a certainmovement suggests orthopedic pain.

Menstrual problems: should be compared with previous menstrual normal. Menstrual irregularity is commonly complained of without basis in infertility cases for the normal variability has been indicated above. The more irregular the bleeding is, the higher the probability of organic lesion. Intervening episodes of amenorrhea and response to hormonal treatment suggest a dysfunctional bleeding. During the childbearing age, complications of pregnancy should be always considered. The relation to use of contraceptives should be also considered. The abnormalities of menstrual function may persist for some months after discontinuation of progestogen - only injectables. The relation of postmenopausal bleeding to hormone therapy should not be forgotten. On the other extreme of life bleeding in a teenager can be a manifestation of a hemorrhagic diathesis.

Vaginal discharge:

- Onset: sudden onset can be related to sexual relation to a stay in the hospital or intake of antibiotics.
- The color and the amount of discharge.
- Associated pruritus, suggest monilial or trichmonal infection.
- Associated dyspareunia.
- Associated lower urinary tract infection.

Infertility:

- Do not neglect:
- Age of the couple.

- Extent of consummation of marriage.
- Sexual history.
- Possible past PID and other STDs.
- Menstrual problems.
- Previous investigation and treatment.

Sexual history:

The patient may be presenting for a sexual problem or it is felt during her interrogation that there can be a sexual background for the problem. In these cases data about the sexual life are obtained. The patient can be shy or unwilling to discuss sexual matters with her doctor. However, full sexual history can be obtained when the patient has unsatisfactory aspect in her sexual life and once she feels the physician is trustworthy. Details about sexual life can be obtained by direct simple questions in the same way as the inquiry about the urinary tract or gastrointestinal function. In no way should the patient feel the doctor is embarrassed or particularly inquisitive during posing such questions. Decent words and expressions should be chosen.

The sexual history includes data about:

- The usual frequency of sexual relations with her husband.
- Has the frequency markedly changed?
- Is he having loss of interest?
- Is he having difficulty in completing the act?
- Is she experiencing difficulty in obtaining satisfaction from the act?
- Is she having difficulty or pain during the act? In the latter case is the pain at the entrance of the vagina or deeply seated? Is it related to a special coital position, or a certain time in the cycle? Most importantly is the painful intercourse a new development?

Not all the questions are administered as a routine.

Urinary incontinence: The anamnestic data (data from the history) are occasionally very critical in differentiation between stress incontinence, detrusor instability and the incontinence resulting from a fistula.

The present history include at certain additional items besides establishment of the diagnosis. These are:

- *Previous investigation done:* Documents are preferred and should be asked for. But failing, these verbal reports are considered.

- *Previous treatment received for the present condition:* This can help in the diagnosis through what can be a therapeutic test. Besides this, one should build upon what has been achieved before whether it is positive or negative. The physician should not repeat mistakes.
- *Initiation of the process of counseling about management:* This will be completed after establishment of the diagnosis. Counseling about the therapeutic options is another medical skill (or art) which is gained through practice and observing seniors. During the initial history taking, the presence of contraindication of important line of management should be considered. Example; poor surgical fitness, having special sensitivity to a group of drugs, previous bad experience with an important line of management, e.g. postmenopausal hormone therapy or certain contraceptives.
- *Health education:* The interview with the patient should initiate a dialogue about ways of achieving better health including better hygiene, weight observance, diet, exercise, contraception and even care about her children.

The role of the health care provider has evolved from treating disease to ensuring health of the body to ensuring health of body and mind and to ensuring better quality of life. This attitude should be emphasized during medical teaching and learning.

7. *Past History*

Only relevant disease or procedures are reported. These include diseases like hypertension, diabetes, heart disease, or operations like appendectomy or laparotomy for exploration or specific management.

8. *Family history*

- Hypomenorrhea or amenorrhea in her sisters.
- History of breast, ovarian and endometrial cancer.
- History of general disease like hypertension, diabetes or coronary heart disease

B. Examination

▪ General considerations

1. The examination continues, after history taking, in the process of *elucidation of the possibilities.* Emphasis on eliciting certain physical signs or doing special tests is dictated by the history.
2. New problem(s) can be discovered during examination. This is the value of *systematic examination* covering all the systems of the body, and especially all genital parts. The

body is an integrated systems, disease in one system influences the others. It is never excusable to miss a heart problem in a gynecological case. It is mandatory to consider certain general systemic disease as a cause or complication of genital disease. Examples include hypothyroidism as a cause of menstrual abnormality and renal failure as a sequel of long-standing prolapse. Both these conditions result in a group of nonspecific symptoms and signs that will not be detected unless searched for. The need to go systematic becomes a must when local examination is reached. Some tumors of the genital systems are frequently asymptomatic e.g. ovarian tumors and myomas.

3. *Ethical aspects* in gynecological examination: Ethics is discussed in a special section. Hereafter are a number of summarizing points:

    a. *Chaperoning:* A third party should be attending. This is better to be a trained female nurse. Failing this, an elderly relative acceptable to the patient e.g. mother or sister should be present. The husband may not be the best person; the examination may be uneasy if done in his presence.

    b. The patient should not be unduly uncovered. Only the part of the body being examined is uncovered. When the physician moves to another area of the body, the first should be covered. This is, in our culture, better than having the patient nude wearing a gown.

    c. A decent examination room ensuring privacy.

    d. Adequate light and instrumentations. Sterile or disposable equipment should be used to prevent spread of infection.

    e. Step-by-step the patient is told what will be done to her and encouraged to relax.

    f. Never pose new questions during examination unless necessary for the examination e.g. do you feel pain? This is especially during vaginal examination.

    g. All the findings good or bad about the private parts or even the whole body are sole property of the patient and confidentiality is ensured and assured. This unless she allows discussion in the presence of third party. Information about STD is sensitive issue; sometimes the husband should be told, but better after taking clearance from the patient.

▪ General Examination

General examination should be systematic in order not to miss an important problem. By practice the physician will learn to put special stress on examining one system or organ and to complete the general examination in a short time. The following items should be covered:

1. ***The general appearance of the patient.*** She can look toxic or ill, flushed, pale, underweight, cachectic (Cachexia = loss of weight + toxemia), overweight. She may be

uncomfortable and dyspneic on lying down. The physician can feel during history taking that the patient is anxious, irritable or psychologically unstable.

- He can notice that she is having an abnormal gait, weight or height.
- Evident endoerinopathy e.g. Froleich's, Turner's.
- Goitre.
- Hirsutism.

2. ***Vital signs including.***
   - The temperature.
   - The pulse: counted for one minute, plus assessment of increased or decreased pulse volume.
   - The blood pressure is measured with the patient semisitting, and the upper arm not constricted by clothes. The systolic pressure is recorded at the point of first hearing of the pulse sounds, and the diastolic at the point of their disappearance. The exceptions to the latter rule are states of hyperdynamic circulation including pregnancy when the pulse sound gets muffled a long time before disappearance; in these states the diastolic pressure is recorded at the time of sudden muffling of the pulse sound.
3. ***Heart auscultation*** for abnormal sound. Detailed examination of the heart should be reported when heart disease is suspected.
4. ***Lung auscultation;*** and detailed examination is done in cases of suspected lung disease.

▪ Breast examination:

This is usually necessary when there is any complaint related to the breast including galactorrhea and nipple discharge. It is also done when pregnancy is suspected or mentioned to note the changes as a result. It should be routinely done at gynecological examination of women aged more than 35 years for the sake of early detection of breast cancer. Palpation of the breast should utilize the flat of the fingers besides their tips in order to detect masses felt between the examining hand and the chest wall. Six areas of the breast need be palpated that way: the four quadrants, the area behind the nipple and axillary tail. The opportunity can be used to teach the patient how she should practice self-examination for early detection of breast tumors.

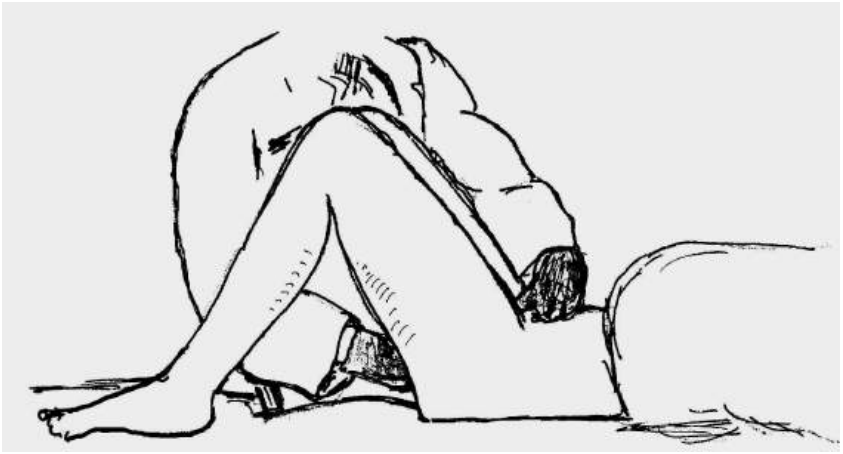
▪ Local Examination

These are the constituents, which should receive detailed examination in a gynecological case. These include five steps:

1. Abdominal examination; many gynecological diseased conditions can be missed if abdominal examination is missed or done casually.
2. Examination of the external genitalia.
3. Vaginal and bimanual examination.
4. Speculum examination.
5. Special office procedures.

Positions:

- ***Dorsal position:*** This is the usually used position. It just needs a hard table of width that accommodates the usual patient and a suitable height (a stair step should be present to help the patient to decently climb atop of the bed). The thighs and knees are flexed and the patient is brought to near the distal edge of the table. The patient will be more comfortable if a sheet covers her abdomen and thighs. The nurse should help to put the patient to this position before the doctor steps in. She or he stands on the right of the patient where he completes the abdominal examination. For the subsequent steps the examining doctor moves partially to the caudal end of the table. From this angle he can do the examination of the external genitalia, the vaginal bimanual and speculum examination. The bimanual examination is done with fingers of the right hand in the vagina and the left hand on the lower abdomen from over her right thigh. Occasionally the abdominal hand need approach the abdomen from the inside of the right thigh (Figure 1). For this the gynecologist is directly distal to the patient's buttocks. The gynecologist may be in need to sit on a stool to be able to inspect a vaginal or cervical lesion.



Clinical assessment (Figure 1): Bimanual examination in dorsal position. *The draping over the thigh is not shown.*

- ***Left lateral position:*** The patient is put on her left side and the gynecologist stands behind her (Figure 2). This position allows easy inspection of the external organs, the perineum and anal region, and may be appreciated by a shy patient.

Clinical assessment (Figure 2): left lateral position.

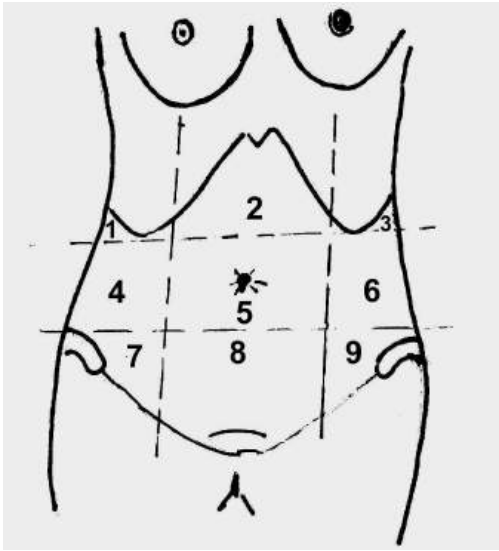
- ***Sims position:*** This is an exaggerated left lateral position. The left arm is put behind the back, and the right tilted forward. The right thigh and leg are flexed to the patient's abdomen, while the left thigh is extended (Figure 3). In this position the pelvis is tilted downside up, the abdominal contents fall away from the pelvis, and then when a Sim's speculum is put in the vagina from behind air will get in, and balloon the vagina. The gynecologist from his angle to the right of the buttocks can easily inspect the anterior vaginal wall and the cervix.

Clinical assessment (Figure 3): Sim's position; *sim's speculum inserted patient. Coverings are not shown.*

- ***Lithotomy position:*** This is used for vaginal surgery and for examination under anesthesia. The patient is on her back and the buttocks are brought to slightly beyond the edge of the table and the legs are put on supports.
- ***Knee-chest position:*** This is an awkward position that is rarely needed for inspection of the anterior vaginal wall.

I. Abdominal Examination

This comprises the four cardinal steps of clinical examination: inspection, palpation, percussion and auscultation. These should cover the nine quadrants of the abdomen. These are roughly divided by two imaginary longitudinal lines, the midclavicular lines; and two transverse lines, the subcostal line and interiliac (between the two iliac crests) line (Figure 4). The quadrants are known as the right and left hypochondrics, the epigsatric, the right and left lumbar regions, the umbilical, the right and left iliacs and the hypogastric (suprapubic) regions.



Clinical assessment (Figure 4); nine quadrants of the abdomen: *1,3= Right and Left Hypochondrial regions; 2= epigastric; 4,6= Right and Left Lumber regions; 5= Umblical; 7,9= Right and Left liac regions; 8= Hypogastric.*

A. Inspection:

The examiner should record free or restricted respiratory movement of the abdominal wall, the presence of any *swelling, enlargement or distention* of the abdomen. The enlargement is described as longitudinal or transverse according to whether the enlargement

is more in the longitudinal or transverse diameter. *Striae gravidarum, striae albicans and linea nigra* are recorded.

The female distribution of pubic hair, *female escutcheon* with the abrupt transverse upper edge is different from the masculine escutcheon with the hairs tapering towards the umbilicus. The latter distribution may be present in some (10%) of otherwise normal females.

Any *scar* on the abdomen is reported upon as healed by primary or secondary intention. Incisional or other ventral *hernias* should be demonstrated by asking the patient to cough. Inguinal hernia may not be demonstrable except on standing. Divercation of the recti becomes apparent when the patient lifts her head unsupported. Weakness, redundancy of the abdominal wall, long torso or a large panniculus is reported.

The back need examination for bone deformation or a mass.

B. Palpation

This comprises *light and deep palpation* and covers the whole abdomen. Light palpation detects tenderness and rigidity. Deep palpation feels organs and masses in the abdomen. The right hand is used to feel structure in the upper abdomen since it looks upwards. In contrast; the left hand is used to feel structures in the lower abdomen. However, both hands complement each other.

The palpation approaches the organ from an empty site in the pathway of its possible enlargement in order to detect the edge of the enlarging organ. If palpation starts from the front of an enlarged structure one can detect a phantom edge created by irregularity in the surface. The enlarged uterus is approached from above it, may be at the zephisternum and moving the ulner border of left hand downwards until it catches the fundus. The enlarging liver is palpated by the right hand laid on the right iliac region and moving upwards. The enlarging spleen is palpated from either the right or left iliac regions i.e. the two possible directions of splenic enlargement. The kidney is palpated starting from a point in the corresponding iliac region. Feeling the kidney is helped by pushing it forward by the left hand placed in the renal angle i.e. the angle between the lowest rib and the muscles on the side of the spine, besides asking the patient to take deep inspiration.

Normally the edge of the right lobe of the normal liver is felt in a thin subject reaching to about one or two-finger breadth below the costal margin. The edge of the soft liver may need percussion to detect it. The lower pole of the right kidney (the lower of the two) can be palpable. No other organ can be felt in the abdomen, except when tosed or enlarged.

A mass in the abdomen should be methodologically described including the following ten features:

1. Whether it is intraperitoneal or present in the abdominal wall. Abdominal wall tumors are diagnosed by becoming more prominent when the abdominal wall is made to contract. This can be achieved by either asking the patient to inflate her abdomen or to lift her head from the bed unsupported. In contrast intraperitoneal masses disappear or become less defined when the abdominal muscles contract.
2. Whether the mass is *abdominal or pelviabdominal*. The lower edge of the abdominal mass can be reached and the hand can be insinuated between the mass and the symphysis pubis. The pelviabdominal mass dips into the pelvis.
3. The *site* of the mass and degree of its encroachment on the different quadrants of the abdomen.
4. The *size* of the mass as estimated in centimeters or the corresponding week of pregnancy size e.g. a sixteen-weeks pregnancy size corresponds to a pelviabdominal mass reaching to nearly midway between the symphysis pubis and the umbilicus.
5. The shape of a mass is described as: globular when its breadth equals its width, oblong when its length is more than its width, pyriform when it has a broader upper part like the pregnant uterus, or irregular in shape. The tumor or the mass can be described as ill defined when the edges merge in the periphery without definition.
6. The *surface* is described as smooth, bossy when it has multiple elevations, irregular.
   The preceding 5 features are the five Ss.
7. The consistency of the mass is described as hard when it feels like bone, firm when it feels like the tip of the nose, soft when it feels like the lobule of the ear. It is described as cystic only when it shows fluctuation (pressure on one side raises the other side) in *two perpendicular plains*. The consistency can be heterogeneous e.g. when having solid and cystic parts.
8. *Mobility* is assessed from side-to-side and from below to upward. Fixity suggests inflammatory nature, malignant extension or impaction.
9. *Tenderness* over the mass indicates inflammation or degeneration.
10. *Relation to other structures: e.g.* fixation to the abdominal wall or to the scar of a previous lapartomy is noted, umbilicus or bones.

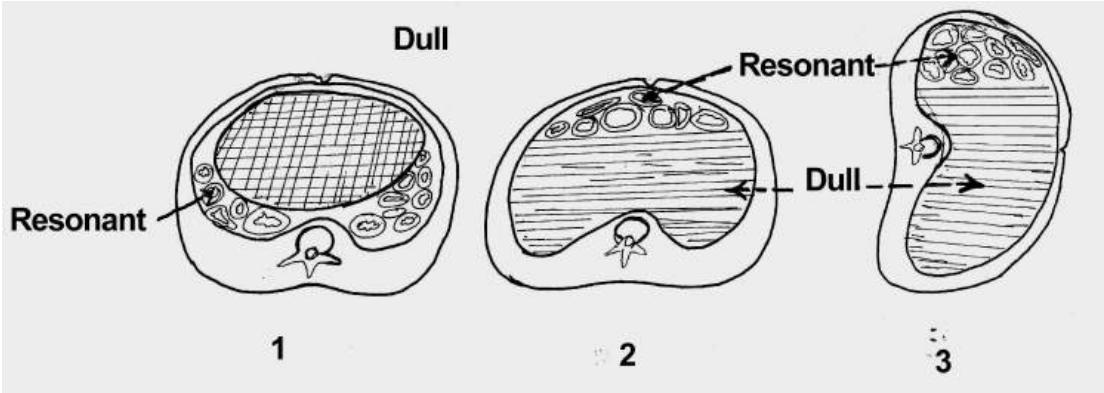
C. Percussion

The time spent in careful percussion of the abdomen is never wasted. Percussion of the abdomen is a light one. Gynecological tumors reaching the abdomen are directly behind the anterior abdominal wall. Therefore, they are homogenously dull. Presence of areas of resonance on the front of the abdominal swelling indicates presence of intestinal segments on

its surface and usually suggests a retroperitoneal origin, e.g., mesenteric cyst, retroperitoneal sarcoma, encysted tuberculosis in the peritoneum.

With the patient on her back, the intestines usually fall to the sides, and consequently the flanks percuss resonant except in obese patients or in the presence of laden colon or free fluid in the peritoneal cavity like ascites. In the latter condition, both flanks are dull. A patch of resonance in one of the flanks with the patient on her back excludes free ascites. To diagnose the latter condition, it is not enough to have both flanks dull, but there should be shifting resonance. The abdomen is lightly percussed first with the patient on her back. Both flanks will be dull because of gravitation of the free fluid, and there will be middle-like resonance caused by the lighter intestines moving to the top of the fluid. The patient is then put to one and then the other side. Percussion in the lateral position shows that the resonance has shifted to the flank and dullness to the paraumbilical part (Figure 5).

Percussion will serve to exclude phantom masses suspected in cases of pseudocysis, obesity (large panniculus) or abdominal distension. Percussion can serve to delineate the edges of the organs and masses. Percussion usually starts from a resonant area and proceeds until it meets a dull edge.



Clinical assessment (Figure 5): *1= gynecological mass without ascites (resonant flanks); 2 and 3 Ascites showing shifting dullness.*

D. Ausculation

Using Doppler stethoscope the fetal pulse can be detected by the 10th to 12th week of pregnancy. It sometimes needs to be differentiated from the maternal pulse by simultaneous feeling of the radial pulse. The old Pinard stethoscope usually could not detect the fetal heart sound except at the 24th week of pregnancy.

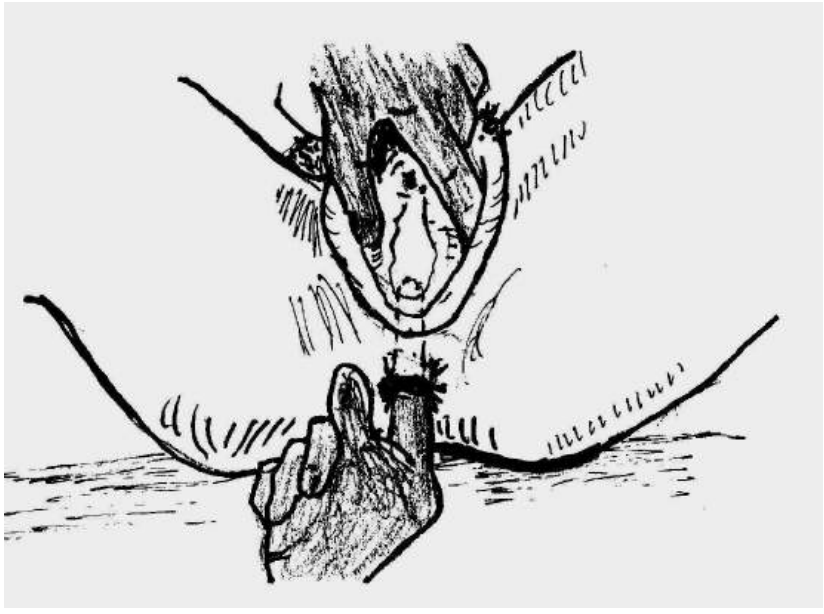
Hearing the intestinal gurgling sounds is a sign of resumption of intestinal mobility after major abdominal surgery. One may need to wait for a minute or two to hear the sounds. Their absence indicates ileus, while exaggerated sound suggests intestinal obstruction.

A peritoneal rub is heard over an acutely inflamed tumor surface with inspiration. It is similar to pleural rub heard on pleurisy.

II. Examination of external genitalia

This means examination of the parts for inflammation, recent or old injury. Short defective perineum external piles or anal fissure are noted. The patient is asked to strain down to detect tendency for genital prolapse. Usually the anal orifice should be supported by the physician thumb to give the patient security that flatus will not escape as a result of straining down. A patient may not be able to demonstrate her prolapse while lying on her back; she can be allowed to assume the lateral or squatting position. Sometimes a slight traction by an atraumatic volsellum is needed to demonstrate the extent of the prolapse. The pathological anatomy of the prolapse need be carefully described.

It is sometimes difficult to judge on the integrity of the hymen in a case of disputed premarital virginity. Cooperation of the unfortunate girl is required. The index finger may need to be passed into the rectum and bent forward to put the vaginal introitus to stretch in order to detect the usually small tear (Figure 6).



Clinical assessment (figure 6): Rectal examination putting the hymen to stretch.

In vulvovaginitis the external genitalia has on it a discharge, the character of which is described. The lower anterior vaginal wall is stroked down to milk out any urethral discharge.

Palpation between the index and thumb is used to detect a pathological bartholin gland under the posterior part of the labia majora; the normal gland is not palpable and the orifice of its duct is not normally visible

III. Vaginal and bimanual examination

▪ *General considerations*

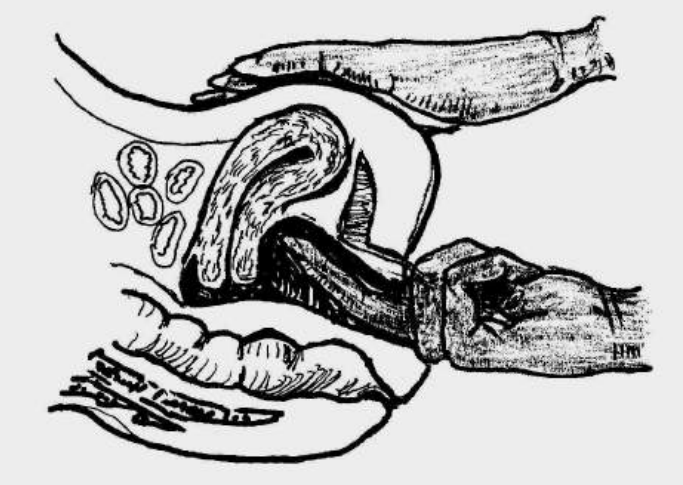
- It is sometimes more advantageous to do a speculum examination before finger examination e.g. when bacteriological or cytological specimens need be obtained.
- To gain the cooperation of a nulliparous woman, one finger vaginal examination is tried first. Once the confidence is obtained, a two-finger examination is done. If one finger cannot be willingly allowed, it is usually useless to insist, and an examination under anesthesia may be needed.
- The vulva is opened by the left hand and the index and middle fingers of the right hand are passed into the vagina in an upward and backward direction. In order not to hurt the patient, the lower urethral meatus and the anterior vaginal wall should not be shuffled.
- One should be methodological and having in his mind all what he wants to gain from pelvic examination. It is a poor practice to need to repeat the inconvenience of vaginal examination.
- All that can be needed should be handy; like specula sound, swabs, and spatulas. ...etc. before the examination is started.
- Bland water-miscible lubricant is utilized. Disinfectants can cause burning or sometimes allergy. Sterile gloves and specula are used.
- The bladder needs be emptied before vaginal examination.
- In the bimanual examination one utilizes the two hands to feel the pelvic structures. Short fingers are not a reason not to achieve a good examination.
- The patient is persuaded to relax her pelvic floor by abducting the thighs, and her abdominal muscles be taking repeated deepin breathings. Sometimes the patient is asked to raise her buttocks off the table by supporting herself on her feet and upper back. The contraction of the extensors of the trunk, inevitably relaxes the flexors on the front.

▪ *Steps*

- The vagina and cervix are easily felt by the vaginal fingers. The body of the uterus, the adnexa the fornices and other pelvic structures are felt bimanually. The abdominal hand starts from the level of the umbilicus and moves down towards the vaginal fingers. The body of the uterus is recognized, usually in middle line, by continuity with the cervix. It is usually felt above the anterior fornix due to the anteversion-flexion (Figure 7). In case of retroversion-flexion (an anatomical variant present in about 15% of normal women) it will be more difficult to feel the body of the uterus. The vaginal fingers are moved to the

posterior fornix and the abdominal hand needs to markedly insinuate the anterior abdominal wall to feel the body of the uterus. This is not always attainable.

- Thereafter the vaginal fingers are moved to the right and left lateral fornices and the abdominal hand to the corresponding iliac regions. Normally the tubes, broad ligament and patrmetrium are not palpable. The right ovary may be palpable because it is towards the front of the vaginal fingers. Pressing on the ovary caused a sickening pain. Also squeezing the uterus between the two hands is painful.



Clinical assessment (Figure 7): Bimanual Examination of the uterine corpus.

- For each organ or structure palpated in the pelvis reporting is needed on its site shape, size, surface, consistency, mobility, tenderness and relation to surrounding structures. The information obtained is complementary to the findings of the abdominal examination. The paravavinal structures are subtle and not palpable unless pathological.
- The cervix is barrel-shaped, and firm. In a nullipara it feels like the tip of the nose with a rounded external os. In a parous woman the cervix feels like the pursed lips with a transverse-slit external os. With the usual anteverted-anteflexed uterus the external os is directed downward and backward with the anterior lip at a lower level than the posterior. This makes one expect to feel the corpus uteri above the anterior fornix. With retroversion-flexion the external os is directed downward and forward and the anterior lip may be flush with the anterior fornix. Deep cervical lacerations are usually overlied by indurations resulting from parametritis.
- The corpus uterus is normally pear-shaped anteroposteriorly flattened, about 5 - 6 cm in length, firm in consistency and mobile. The early pregnancy uterus is globular and soft; and if the examination is prolonged it can be felt to harden up by rhythmic contractions. A tumor in the uterus should be fully described.

- The other pelvic structures are usually not palpable. A laden colon may be felt in the Douglas pouch. It is recognized by indentible fecal matter.
- Pelvic masses should be assessed as regards their relationship to the corpus uteri. Extrauterine swelling may show the following suggestive features:
    a. The corpus uterus is felt separate from the mass.
    b. The presence of deep indentation between the lower pole of the mass and the cervix.
    c. Movement of the mass is not conducted to the cervix.
    d. Sounding the uterus will show a normal length in contrast to the enlarged cavity in case of uterine tumor.

IV. **Speculum examination**

This is usually done by a bivalve speculum: *a Cusco's or Graves speculum*. In the latter, the blades are hinged at one side only allowing its removal after fixation of instruments to the cervix (as in hysterosalpingography in order not to have the metal speculum masking the cervical canal). They are available in different sizes and is advantageous to select small sized specula for mulliparas. Plastic disposable specula are now widely used. The blades are hinged together at their distal ends and each is connected to a handle. When the two handles are pressed together the tips of the blades are separated allowing seeing the vagina and cervix in between. The speculum can be kept open by drawing in a screw-on a pivot.

For insertion the blades of the bivalve speculum, the blades are held pressed together between the index and middle fingers of the right hand (in order to keep the blades opposed and not shuffling the labia) and it is passed into the vulva with the blades in the vertical plane (the vulva is an anteroposterior slit). The speculum should enter in an upward and backward direction (the normal direction of the vagina). In order not to be shuffle the vulval parts are separated by the index and thumb of the left hand. Once the speculum is in, its blades are tuned 90 degrees, to bring the blade to the transverse plane of the vagina (which is anteroposteriorly flattened). The handles are then pressed together and screwed together. Gentle manipulation should be strived for. Sims' speculum is formed of two grooved vaginal retractors of different size joined together. It is used to retract the posterior vaginal wall in order to see the anterior vaginal wall.

Rectal examination

This is done by the index finger. It is done to detect any pathology in the anal canal or rectum. It can be used instead of vaginal examination in a virgin, or when there is any risk of doing repeated vaginal examination. Bimanual examination is possible. It is even more

advantageous that vaginal examination for feeling the parametrium. It can be combined withvaginal examination to detect an enterocete.

V. Office tests and procedures

- **Sounding of the uterus:** The uterine sound is bent at an obtuse angle at about 3 cm from the tip. This is in order to negotiate through the angle of flexion of the uterus. The tip is slightly more bulbous and is about 3 mm in diameter. The sound is marked at one-centimeter distances. It can detect the direction of uterine flexion but is used mainly to measure the length of the uterine cavity. When it is passed into the uterus the bulb will first hold at the internal os and this permits measuring the cervical length. With gentle pressure the bulb passes into the uterine cavity until it holds at the uterine fundus. This gives the total length of the uterus and allows estimation of the cervico-corpareal ratio that is normally 1:2 in the adult uterus.
- **Vaginal and cervical smear:** See under carcinoma of the cervix.
- **Cervical biopsy:** See under carcinoma of the cervix.
- **Bacteriological swabs for the cervix or uterine cavity:** See under reproductive tract infection.
- **Endometrial biopsy, Endometrial suction biopsy:** See under uterine bleeding.
- **Ultrasonography examination:** There has been increasing use of ultrasonography particularly vaginal probe sonography. This should not be in any way a replacement of good clinical appraisal. On the contrary, office sonar should heighten the expertise in eliciting physical signs. Ultrasonography will be handled in more details in the "obstetrics" book.

Diagnosis

The complete diagnosis should include, in order, the following:

1. The probable disease condition(s).
2. Stage of the disease.
3. Etiology of the disease.
4. Complications of th**e disease.**

Chapter 30

ETHICAL ASPECTS IN GYNECOLOGY

Contents

Course objectives

Ethical considerations are integral to the practice of gynecology. Through her or his training and practice, the gynecologist should amass information and skills pertaining to medical ethics, and gradually develop values and attitudes. Learning or teaching medical ethics should aim at gaining the following three objectives:

1. The *cognitive skills* which comprise knowledge about:
   - Theories and principles of medical ethics.
   - Bioethics in specific subjects like abortion, contraception, assisted reproductive technologies, woman abuse, ablative surgery, STDs. ....etc.
2. The *behavioral skills* are mostly gained by model teaching or apprenticeship. The latter has been a time-honored approach for learning medicine, and is principally gained through bedside teaching. The novice will learn by observing how the master is treating the patients, taking history, eliciting physical signs, making the diagnosis, and eliciting the treatment procedures. Through observation, the apprentice will develop the rules of conducting himself with patients, colleagues and situations.
3. *3. Development of characters:* Through the course of learning medical ethics, the characters of the practitioner will be developed. She or he will develop a set of ethical values and a methodology of judgment.

The following discussion of medical ethics in Gynecology covers:

- ***General ethics***
- ***Applied ethics: Ethical dilemmas in Gynecology***
- ***Hypothetical cases relevant to the practice of Gynecology in Egypt***

General Ethics

Evolution of ethical rules

Ethical rules evolve from the good judgment of good people. The good people are professional and societal leaders who agree on a set of rules. The ethical rule is established through standing the test of time and being followed by a good majority of practitioners. There are two ways of evolution of ethics: The first pertains to what is called *descriptive ethics.* These are rules formed by taking opinion of a representative sample of practitioners about an issue e.g. hysterectomy for dysfuntional uterine bleeding. The questionnaire should be free and methodological, in order to yield an acceptable rule. The second methodology is the evolution of *normative ethics.* This is the formulation by a process of logical thinking, which is better to be group judgment. The deliberation should go in a defined course: the issue at hand, e.g. surrogacy or organ transplant should be clearly defined and dissected to clarify all its components and consequences i,e *Clarity. Comprehensiveness* is mandatory; concealing or neglecting any aspect can result in seriously defective judgment. The issue is then considered against ethical theories and principles. This consideration should be complete (*completeness*) not neglecting any aspect. The consideration should be characterized by *consistency* and *coherence.* It is better to consider only the *clinically applicable* issues. Issues

still in the pipeline of research are better deferred until they are completed in order to wait until all implications are defined (exception is the consideration of the ethics of the research when done on human beings). These terms form the famous six Cs = clarity, comprehensiveness, completeness, consistency, coherence and clinical applicability which define the methodology of evolution of normative ethics in medicine.

Ethical theories

These have comprised the following rules of morality:

1. Deontology: rule-based morality.
2. Utilitarianism: outcome-based morality.
3. Virtue: right and wrong.
4. Casuistry: choice between alternatives.

No single theory can be always applied.

Religions give their own judgment, which is binding to devout followers regardless of all of the above theories.

Ethical principles

This is a second layer of thinking and this stratum comprises the following principles:

1. ***Beneficence*** and *nonmalfeasance* (*primum no nocere* = first no harm). The medical practitioner should cause no harm and strive to give benefit.
2. Respect for the patient ***autonomy***. Individuals exercise their personal preference in most aspects of life; they have the right to also exercise this in the management of their diseased conditions.
3. ***Justice:*** The medical profession should equally render its services to all people regardless of their age, ethnicity, sex, and ability to pay for. The profession should not give less care to the fetus, infants, old people, women, the poors or the enemies.
4. ***Fidelity:*** Truth-telling and promise keeping.
5. ***Competency:*** This comprises not only knowledge but also skills. Relevant to the first in the now recently, emphasized evidence-based medicine.
6. ***Confidentiality:*** all information about the disease and its management is the sole property of the patient. Confidentiality is rarely violated when there is a definite risk on another person or the community.
7. ***Prevention of disease*** is part of the work of medical profession. The practitioner should strive to prevent any future disease in his patient (e.g. screening for cancer) or in his contacts (spread of STDs) or to the community (in epidemic and endemic conditions). Even the physician should have responsibility to the ecology.

8. ***Advocacy:*** This emanates from the fact that the physician is a responsible member of the community, e.g. she or he can have an active attitude towards issues like gender discrimination and violence against females e.g. female genital cutting.

   Principles can conflict one with another; the profession and individual doctor should exercise sound judgment in the choice. Such judgment may differ between different societies.

9. ***The "Doctor's Oath"*** delivered at the time of graduation tries to cover the above principles.

   We cite hereafter a translation of the "Doctor's oath" suggested eight centuries ago by Mousa Ibn Meimoun (1135 - 1204) the physician of Saladin (Salah-El-dein).

   Quote: "I swear to strive to use all the skills of my profession only in the purposes I believe, after revising my conscience, will contribute to ensuring peaceful life to all living creatures. And also in the purposes which preserve the well-being and dignity of human being". "I also believe that achieving this goal comprises ensuring all the essential needs of life including good nutrition, healthy air, pure water, good clothes and shelter. It also includes ensuring for human beings the right to enjoy natural and artificial beauty, education, the opportunity to fulfill the goals of his existence, and the opportunity to improve his skills, and creativeness, and the ability to get the required experience by his own hand and brain.

   I also swear to struggle, through my work, to lessen the harm, noise and all attempts to vitiate the purity of earth and avoid pollution of water and air. I swear to resist all attempt to destroy the natural beauty and loss of elements and natural life". (End of the quote).

10. Religion and medical ethics

In this part of the world and indeed in many other parts, religions have a great role in deciding medical ethics and other aspects of social behavior. Religion has a say in most aspects of life. Religious authorities should be consulted on any established practices or new developments in the medical profession. The religious authority "Fakeih" should be given a clear, complete and comprehensive description of the issue. He then will apply the principles of religious rule concerning what is permitted (halal), not permitted (haram), required (wageb), recommended (mandoub) or better avoided (makrouh). In applying these rules and others, he should exercise consistency and coherence. The principles of theological judgment have become a clearly defined science in Islam (Osoul Al-Fekh).

Only qualified Fakeihs can do the required ruling, after getting the opinion of

qualified medical scientists. On most issues, the Islamic ruling has agreed with the logics accepted by other populations. However, where there is a difference, the religious ruling should be always respected. Couples should abstain from sex not because it is harmful but because it is "haram".

The orthodox church of the Egyptian Copts has its ruling on many ethical issues. Overall, these rules are not different from Islamic rulings.

Applied Ethics

• *Ethical aspects in gynecological examination*

These include ensuring the following aspects:

1. Adequate facility

- The set up should ensure adequate space, privacy and light. There are usually two examination tables, one for the general and abdominal examination and the other for pelvic examination. There should be space for the patient to do the necessary undressing and to keep in her clothes. The examination is better to be carried out in a room or cubicle attached to the consultation room and not in the consultation room.
- Good set of instruments
- Good light
- Better, fresh bed lining and covering for each patient
- All the provisions should be taken to prevent cross infection including use of disposable gloves, sterile (may be disposable) specula, sound, swabs,. ...etc. This is to avoid transfer of infection from one patient to another.

2. Gender difference

This is a growing problem in gynecological practice in many Muslim countries. A male gynecologist examining and treating women should however, be possible and allowable. Gynecological consultation is a "necessity" state that allows the required exposure and contacting the private parts of the woman. The private parts of the woman from the point of view of Islamic rules (Awra) are the whole of her body except her face and hands. These should not be exposed or contacted by any foreigner (other than her husband), be it a man or a woman except for "necessity". The necessity includes purposes of medical consultation and treatment. It is the woman's right to choose for this important purpose the best one that can render the required service, again regardless of the gender difference. Some women may find it easier to be served by female doctors; this is their full right.

3. Chaperoning

This is the presence of a third party during gynecological examination or treatment. The best third party is a female nurse. The nurse can also serve to help the patient to prepare and take the proper position, but even if she does not help, she should be present. This function may be fulfilled by a relative or a friend. The husband may not be the best third party, some woman may be shy to undress or be examined in the presence of her husband.

Chaperoning is an established rule in the European practice.

4. Undressing

Only the part of the body being examined is uncovered. After moving to another part of the body, the first should be covered, and so on. This is more comfortable to patients in our culture. It is also more acceptable to have the thighs covered with linen sheet during pelvic examination. Having a patient nude with an open gown is not acceptable practice in our society.

5. Medical interrogation and examination

- All the required time should be availed to the patient (see under clinical approach).
- All effort should be made to gain confidence of the patient. Regular and respectable appearance, clothes and conduct are required from the physician. A white gown is necessary.
- The proper decent language should be used. No problem should occur in discussing the sexual problem(s) of the patient if this is done in the same manner of discussing other bodily functions and complaints. The patient should not sense in her doctor any curiosity or shyness.
- All the required exposure should be ensured, e.g. the breasts should be fully exposed whenever this is required. The physician should never accept incomplete or inadequate examination.
- All unnecessary manipulation of the body of the patient should be avoided.

6. Sexual harassment

This includes what is said or done to the patient in attempt to persuade her to have any sort of sexual relation. The responsible physician should avoid any word or conduct that creates this suspicion in the mind of the patient. Sexual harassment is a serious violation of medical ethics. In other communities, it is a common professional liability.

• *Clinical counseling*

The medical counseling is a two-way process that helps the patient to make an

informed choice regarding the management of her disease. It should respect the patient's autonomy and involve her in the decision making process. The decision takes in consideration the ethical principles of beneficence, nonmaleficence, autonomy and fidelity.

Clinical counseling should proceed in the following pattern:

1. *Gaining the confidence* of the patient: This is mainly achieved through showing her sincere care. Confidence is gradually built up during interrogation and examination. Persuading the patient to accept the doctor's advice has been an "art" of medicine, which is only excelled by involving the patient in the decision, making process.
2. *Disclosure of information:*
   - All the information about the diseased condition and its implications should be told to the patient. Sometimes, this is made stepwise. This disclosure of information should be all truthful. Simple language should be used and all effort should be made to explain technical words. The clinician should be sure that the patient has understood.
   - The possible management is then described. Usually there are alternative approaches. The advantages and disadvantages of each alternative are made clear. More emphasis can be made on the better choice from the viewpoint of the physician. Sometimes the patient is coming with a predetermined choice. This should be given all the due consideration and the alternatives are discussed.
   - All questions of the patient regarding the disease or the treatment options should be *answered*.
   - Involving a third party is sometimes advisable, like the husband or a friend, if this is acceptable to the patient.
   - Time can be given for the patient to reconsider the information and to discuss it with friends and relatives.
   - The consequence of the disease and its treatment must be made clear to the patient and her close relatives (if they have been involved in the counseling). Sometimes a gloomy outcome is better concealed from the patient but the close relatives should know.
   - *Printed material:* pamphlets and written information about the diseased condition and the management procedures can be made available. They are very helpful.
   - *Information about the institution*, its facilities, staff members, statistics and results should be also available.
3. *Decision:* This should be gradually developed. It should respect the patient's preference. The best outcome is when the medically sound decision represents the patient's preference. When this agreement is not achieved, the doctor's advice should be documented on the records along with the patient's refusal to abide with. Her refusal of medical advice should not deprive her from receiving medical care along the next optional but acceptable medical care.

Sometimes the patient may be requesting a medical intervention which is not medically, morally or personally acceptable to the physician e.g. termination of pregnancy or sterilization while young. The unfavorable implications of the patient's choice should be clearly explained to her. If she insists, the doctor usually has the right not to do what he does not believe correct. However, certain institutional or judicial rules may impose on a doctor to perform or not perform procedure against his personal preference. For example, in countries where abortion service is given in health institutions upon patient's request, a refusing doctor finds himself in an awkward position. On the other hand, a staff in a governmental hospital in Egypt cannot perform female genital cutting even if they believe that the practice is right.

- ***Informed consent***

- The process of counseling culminates in the patient accepting certain medical management. This acceptance should be documented on a special certificate of consent. This should be included in the patient's file. A consent is required for all surgical procedure, for invasive, or potentially risky diagnostic procedures, e.g. diagnostic laparoscopy and hysteroscopy, and for potentially hazardous medical treatment e.g. chemotherapy of malignant disease.
- The consent form contains the name of the institution, name of the patient, the date, the name of the counselor, the diagnosis, a short description of the medical intervention, its important consequence including benefits and risks, indication of knowledge of the alternatives to this management, indication that all questions about the diseased condition and the management have been answered. Then the consent contains a clear statement of acceptance of the management. If there are possible additional procedures that may become necessary during the planned operation, these possible developments should be written and the patient indicated her acceptance of undergoing their required management. It is not ethically satisfactory to make the patient sign a statement like "I agree to undergo all what the doctor sees necessary". The patient may not be aware of a serious consequence like removing the uterus. If the latter happening is possible, consent of hysterectomy in case of need should be included. The consent ends with the patient's clear signature.
- The *wording* of the consent form should be clear, simple and not containing technical words.
- A second party may be required to sign the certificate of consent e.g. the husband consenting to removal of the uterus of his wife. However, if he declines to sign, this should not prevent the wife from having the necessary treatment she consents to

undertake.

- If the aptitude of the patient is impaired or absent e.g. because of being a minor (less than 16), unconscious, mad, or comatosed her closest kin (e.g. father, son, brother, husband) should sign the consent form.
- If *unforeseen development* has occurred during an operation or as an emergency that necessitates the removal of an important organ or special hazardous procedure, permission from available close relatives can help. If these are not available, a second opinion of a colleague better being a senior should be obtained if he or she can be summoned in a reasonable time. If this is not available, the physician should exercise the best judgment and perform what is medically sound. He needs to document in detail what has happened and what he did. He should never try to conceal what he has done; it will become known in a short time.

• *Documentation*

This is an official obligation, which has important ethical aspects. The documents required from the doctor comprise the following:

1. Admission record.
2. Case record.
3. Reports on investigation procedures.
4. Operation report.
5. Discharge report.
6. Medical report (final report).
7. Court reports.

All these forms of reports are parts of the obligation of the doctor to the patient. They should be characterized by clarity, comprehensiveness, completeness and truthfulness. It is the right of the patient to have a copy of all medical reports concerning his case.

Confidentiality should be ensured to all information about the patient. Patient's permission is generally required before this confidentiality is broken. Court order is a reason for breaking this confidentiality. However, under certain circumstances information about the patient is passed to a third party, e.g. the spouse in case of sexually transmitted disease and health authorities in case of communicable disease.

Ensuring confidentiality of the hospital database is the responsibility of the administration. Numbers instead of names may ensure it through coding information in the database.

With computerization of the hospital, data violation of confidentiality should be avoided. A certain password should be given to a limited group of hospital staff that gives

them the necessary admittance to the records of the patient. He or she should be held responsible for keeping the confidentiality of the records.

From the Islamic point of view, the medical report is a form of witness, which should not be willfully withheld. The Moslem is obliged to give the witness in the right way and for a cause, which fulfills the aims of the religion.

Applied Ethics in Gynecology

Ethical aspects of different gynecological subjects:

1. Female circumcision: Female genital cutting

(See under Anatomy of Female Genital System and Traumatic lesions)

- This is still a common practice in Egypt.
- It has many immediate and remote complications.
- Circumcision is usually done under unfavorable circumstances that increase the risk of complications.

The religious basis of female circumcision is not certain. It is not practiced in may other Moslem countries. There is division of opinion between scholars about female circumcision. Some of them are of the opinion that the Hadeeth about circumcision is not certainly authentic, and therefore the practice is considered to have no religious endorsement. Others permit a limited circumcision that removes only the prepuce or the hood on top of the clitoris. In a situation of difference of opinion of Fakeihs, one should depend on his conscience. No one other than the gynecologist can see better the bad effects and lack of any real benefit of female circumcision. Islam does not allow harm or what may lead to harm.

The legal aspect of female circumcision: If a qualified doctor performs this act, he is considered to have inflicted a simple wound that is subject to punishment under Article 242, Paragraph one of the Penal Code, and in addition to the Civil Liability that commits him to payment of compensation.

The responsible gynecologist can have an advocacy role against female circumcision.

2. Intersexuality

Disclosure of the genital information is not always in the interest of the patient. A famous example is the androgen insensitivity syndrome. This individual is better off as a female. “She” has been reared as a female and usually has the normal phenotype of a female other than having no internal genitalia. A vagina can be artificially fashioned.

Congenital adrenal hyperplasia (CAH) should be diagnosed as early as possible (because of possible metabolic component). The female patient should receive the proper

medical and surgical treatment as early as possible. The sex assignment and the name should be changed and the baby should be reared as a female. The share in inheritance should consequently change. Future siblings have a 25% chance of being similarly affected.

Sex reversal is not allowed in Islam except for certain cases of physical intersex like CAH. Transvistism is not an acceptable reason for medical intervention to change the sexual organs. It is taken as an attempt to change God's creation.

3. Menstruation

Religious implications of menstruation and nonmenstrual bleeding:

The gynecologist should be familiar with the religious implications of menstruation and abnormal uterine bleeding.

During menstruation, the Muslim woman is not allowed to observe the following religious functions:

1. The prayers: She is not required to pray the missed prayers. She is required to return to performing the five daily prayers once the menstruation has ended, and she has had the end-of-menstruation body wash (Tohoor).
2. Fasting whether the required fasting of Ramadan or any volunteered fasting. She is subsequently required to fast the days she missed of Ramadan.
3. All the parts of pilgrimage are allowed during menstruation except El Tawaf of Kaaba (going around the Kaaba which is equal to praying).
4. Reciting the Koran or touching the Book (the Koran).
5. Staying in the mosque.

The same rules apply to the puerperium (the forty postpartum days). Sexual intercourse is not allowable during menstruation. Divorce, in the opinion of most scholars cannot occur during menstruation. These rules do not apply to any discharge other than blood. This does not even result in loss of Al Wodoa. Abnormal bleeding other than menstruation has its own rules of Al-Esthada.

It is not widely appreciated that the above rules apply only to menstruation and do not extend to any other abnormal vaginal bleeding, whether cyclic (i.e. prolonged for more than the usual days of bleeding) or acyclic (i.e. occurring at other times). Therefore, and due to inadequate information, abnormal vaginal bleeding is an unwelcome occurrence particularly if it happens in special times e.g. during Ramadan or Pilgrimage.

According to Islamic doctrines, the abnormal bleeding is called "Estehada" (menstruation-like bleeding), and does not prevent from observing the above functions. The Prophet Mohamad (God's prayer and peace upon him) was careful to clarify this point when he was asked about a woman whose bleeding exceeded the usual duration of her

menstruation. He advised that she should act according to her own previous "habit" (one of the names for the menses in Arabic), and treat the extra days as an Estehada. The Prophet said "these are not menstruation, but a discharge; she should abstain during the days of her habit and then wash and can pray". The washing required after such episode of untimely bleeding, and before starting prayer, is a vulval wash. Afterward, she wears a protective pad to contain any blood, and then carry out the usual Wodoa. This latter is different from the total body wash she is required to carry out after the end of the days of menstruation and after having sexual intercourse (Tohoor). It is even less widely appreciated that the woman is sinning if she knows these rules but does not observe her religious duties during the days of Estehada.

Sexual intercourse can occur during Estehada.

The puerperium, though can last for less than forty days (from the religious point of view), However,if the bleeding persists for more than this, the extra days are days of Estehada.

4. Sexually transmitted diseases (STDs)

There are a number of ethical issues in the medical management of STD:

1. The possibility of having acquired the infection from the spouse, an embarrassment.
2. Disclosure of extramarital relations of the patient or the spouse, a greater embarrassment.
3. The risk of transferring infection to the spouse.
4. The risk of transferring infection to the offspring.
5. Some of the STDs have serious health consequences and can be fatal, e.g., HIV infection.
6. Some of the infections have reached a public health dimension e.g. AIDS.
7. Sexual relations have certain religious and social implications in different settings and countries. There is great variation in the attitude of the society towards extramarital sexual relation and towards homosexuality and anal intercourse. Islam severely prohibits extramarital relations and permits only penovaginal sex between wife and husband.

The management of an STD includes the possibility of the following courses of action:

1. Encouraging the patient to inform the spouse. This can be most embarrassing and can be resisted by the patient.
2. Insisting on having the spouse simultaneously treated.
3. In certain serious infections e.g. HIV, the spouse should be informed regardless of refusal of the patient. This is a violation of confidentiality but should be religiously and legally allowed, i.e. this conduct is defendable in court.

4. In certain infections of public health importance, e.g. HIV, notification of health authorities may be required.
5. Informing young infected patients about the expected risk of transferring the infection to the fetus and newborn can determine use of contraception or her request of induction of abortion. However, termination of pregnancy cannot be imposed on an infected expecting mother.
6. All efforts of prevention should be taken. These include:
   - Proper education of sex-related issues. Emphasis should be made on proper sexual relations, safe sex, and seriousness of STDs. Emphasis should be made on adolescents. All channels of conveying information should be utilized including schools and public media like radio, television, and Internet.
   - Facilitation of early marriage through removal of societal barriers.
   - Increasing availability of condom that can markedly diminish the chance of contracting infection.
   - Early and effective treatment.
   - Vaccination: In spite of all efforts no effective vaccines have been developed, for HIV.

7. ***Screening*** the population or special sectors of population for STDs. There are certain provisions that need to be fulfilled before submitting noncomplaining individuals to screening programs:
   a. The disease should be common.
   b. It should be serious.
   c. Availability of diagnostic tests which have good diagnostic reliability = sensitivity, specificity, high positive detection rate and low false positive detection rate. The tests should be practical and affordable.
   d. Presence of confirmatory test.
   e. The presence of possible management. The knowledge of having the disease should allow treatment and/or diminishing the chance of transmission e.g. administering zidovudine to pregnant mother with AIDS.
   f. Cost-efficacy of the program should be acceptable.
   g. Screening should remain voluntary.
   h. Confidentiality of information should be guaranteed.

5. Organ oblation in nonmalignant diseases

This includes removal of the uterus and/or the healthy ovaries. The ethical aspects in removing these organs have been dealt with under the chapter on Hysterectomy.

6. Gynecological Oncology

Pretreatment counseling

(This has been dealt with under general ethics)

- Disclosure of information.
- Need for clear comprehensive description of risk and benefits of the various possible interventions.
- Involvement of the patient in making choices about treatment plan
- Written consent.

Euthanasia

Euthanasia is mercy killing of a hopelessly diseased terminal patient. Terminal cancer is attended by severe suffering that may raise the issue of euthanasia to shorten this suffering. The killing of the patient can be actively achieved by giving certain medication or by cutting vital support or positively determined by denying him certain treatment. In spite of the fact of presence of an element of mercy, euthanasia is not acceptable with Islamic ruling (nor with Christian ruling). Endurance of pain and suffering is required and imposed on individual by God wish, and may be for his good. Euthanasia is punishable and Penal Code. There is no distinction of Euthanasia from intentional murder in the Egyptian law.

In place of assisted suicide, the medical profession is encouraged to develop means of pain relief (without any fear of development of addiction) and methods of lessening the suffering for patients with advanced cancer.

7. Infertility

The problem of infertility is an important pressing problem in the Egyptian culture. Childlessness is a disgrace in certain communities and social status is sometimes determined by the number of children particularly males. The couple may seek treatment at any price. Adoption is not permitted in Islam. The religion has the final word in human reproduction. Pregnancy is only allowable within wedlock and during the life span of the couple.

The techniques utilized in assisted reproduction should have verified safety for the couple and offspring. *The attitude of the religion towards different techniques of assisted reproduction has become defined:*

- **Intrauterine insemination** (IUI) is only allowable by utilizing the husband sperm. No donor insemination is allowable. Storage of collected gametes for future use is allowable. This allowed the collection of gametes before exposure to radio-or chemotherapy. These should be used within the life of the couple. Posthumous pregnancy is not permitted. Equally not acceptable is the use of the gamete after divorce. The usually necessary

washing (and other treatments) of the seminal sample are acceptable.

- **In Vitro Fertilization and Embargo Transfer (IVF/ET):** The grand Moftee of Egypt issued a statement allowing IVF and ET in 1980. This ruling has also been similarly accepted by similar Islamic bodies in other Islamic countries.

  Posthumous reproduction through preservation of gametes is not accepted.

  To ensure a better success rate a big number of ova are retrieved after overstimulation of the ovaries and fertilization of most of them. This resulted in two problems: the first is discarding unused fertilized ova, which stirred some ethical objections. It is better to cryopreserve the unused zygote for use in a future cycle should the present attempt fail, or even if it succeede, in order to get another future pregnancy for the couple. Some countries have put an upper limit on retrieved or fertilized ova. The second problem resulted from the transfer of a number of fertilized ova to the uterus, is the increased probability of twin pregnancy and higher order multifetal pregnancy. The latter carried definite maternal and fetal risks particularly the compromised chance to achieve maturity of the fetuses. The use of embryocidal procedures to reduce the number of embryos in high order pregnancy has been used to improve the chances for one or two left behind. This procedure can be seen as preventing a big harm by a smaller one. Embryocide raises a number of emotional and ethical concerns and may lead to loss of the whole pregnancy. The couple should be carefully counseled and the risks of the alternative of keeping the whole set should be made clear., their choice should be respected. Some centers limit the number of embryo transferred to three.
- **Intracytoplasmic sperm infection (ICSI):** The ethical issues are not different from those of conventional IVF. However, additional elements include the risk in obtaining sperm from the testis, and, the so far theoretical concern of increasing the chance of genetic abnormalities resulting from fertilization by suboptimal sperm. The technique of needle aspiration or better open micromanipulative biopsy has been mastered. The data resulting from worldwide registry of offspring of ICSI has indicated a slightly increased genetic risks.
- **Preimplantation genetic diagnosis:** This is achieved by sampling one blastomere for genetic studies and transferring only normal embryos. Usually the technique of fluorescent In Situ Hybridization (FISH) is used and it gives the result in the same day. More elaborate genetic study takes two days and delays the transfer. This approach has evidently allowed choice of the sex of transferred embryo. This can legitimately be used to prevent sex-linked disease, but can be utilized to determine the sex of begot children for social reasons (i.e. inheritance issues).
- **Surrogacy:** Through in vitro fertilization, a surrogate mother can carry the pregnancy if the biological mother is having no or grossly defective uterus or general disease

contraindicating the pregnancy. There has been an attempt to simulate surrogacy to breastfeeding and lactational mother who has a defined position in Islam. However, the present position does not allow surrogacy mainly depending on a dictum in Koran indicating that mother is the one who has given birth. There can be also doubt that the uterus has already been occupied by a conception from another man.

- **Cloning:** A historical biological achievement has been recently attained by cloning a female sheep. This cloning involved transferring the genetic material from the differentiated adult diploid somatic cell (of the udder) to a fertilized egg from which the nucleus had been removed. The egg was stimulated to divide into an embryo, which was transferred to a surrogate ewe for gestation and birth. The resultant "Dolley" sheep has one genetic parent of which it is a copy or a clone. The possibility of cloning man has stirred a great concern and interest. The possibility of cloning a certain (stem) cell line e.g. bone marrow stem cells may open a new line in therapeutics. Although the ethical consideration should await clinical availability, the ethics of research in human cloning should receive the due consideration. The USA government has banned federal expenditure on human cloning. Concerns are raised about the possibility of producing deformed embryos and genetically weak or aged offspring. Other social and psychological concerns have led to some asking for prevention of cloning research.

8. Contraception

- In spite of the fact that Muslims are religiously encouraged to reproduce, couples can use temporary contraception for family planning. The recognized motivations in Islamic doctrines include the wife's weakness or disease, the desire to space births to have better or stronger offspring. Some scholars have even allowed contraception for the sake of preserving the beauty of the wife. The couple should agree on family planning. Some couples may opt for family limitation. This is not an acceptable motivation in the view of most Islamic scholars unless it entails prevention of health risk on the mother.
- Coitus interruptus was the only contraceptive known at the time of the Prophet Mohamed (God's prayer and peace upon him) and he did not advise against it.
- Most Moslem scholars allow the use of the methods of safe period, oral combined pill, progestogen-only pills, progestogen-only injectables, implants and other similar hormonal contraception. There is no objection to using the IUCD since the mechanism of its action does not involve wasting an already formed pregnancy. All detailed studies have indicated that the IUCD principally interferes with fertilization. It may interfere with nidation but does not cause abortion.

- Concerns about emergency or postcoital contraception are mostly unfounded. They principally act by preventing fertilization and nidation. "Menstruation induction", on the other hand, is entailing a probability of early induction of abortion. For those who do not accept induction of abortion the menstruation induction should be unacceptable.

9. Abortion

- From the religious point of view induction of abortion is only allowable in case of necessity, if the continuation of pregnancy entails a definite risk to the life or health of the mother. This can occur at any stage of pregnancy.
- Apart from this, induction of abortion is not allowable. Some religious scholars (Fakeehs) have allowed induction of abortion before the end of the fourth month of pregnancy, the time of ensoulment. However, most scholars considered the embryo alive from the time of conception and consequently do not allow abortion at any stage of pregnancy.
- The state of necessity referred to above should be agreed upon by a number (rather than one) of reliable doctors.
- Induction of abortion of grossly deformed fetus is only allowable before 120 days calculated from the day of fertilization (i.e. 16 weeks) if a panel of a specialized doctor testifies that the fetus is severely deformed (The theological consortium of the league of Islamic World 1990).
- The termination of pregnancy should entail no risk to the mother greater than that of continuation of pregnancy.
- A written consent signed by the couple is mandatory before embarking on induction of abortion.
- Conflicting an abortion by mistake by a physician or any other person is punishable by paying compensation to the patient. This is called Ghorra (it is 5% of the compensation (Deyya) paid in case of killing an individual). This is in addition to the need to fast two successive months, or feeding 60 poor people.
- Abortion has its implication on inheritance for which religious scholars should be consulted.
- From the legal point of view, induction of abortion is not permitted. The Egyptian Penal Code makes induction of abortion a punishable crime. The practitioner who does or helps it can be punished by imprisonment penalty that can reach temporary hard labor. The Code is silent about the state of necessity. Court precedence considers "necessities" as an ameliorating excuse.

Hypothetical cases

1. You, a male gynecologist, is requested by a female colleague, to perform a hysterectomy

operation she cannot competently do for a patient who does not accept to be exposed to a male doctor. The arrangement is that you will step in after the patient has been anesthetized and draped, and the patient will not know of this arrangement. Comment.
Commentary: Not acceptable -- discuss why.

2. You are offered a comprehensive report about a patient's case. The patient is in another city or refused to be examined by a male doctor. You are requested to prescribe the treatment.
Commentary: You can only give an opinion and guideline. The prescription is made by the managing physician. Elaborate.

3. A mother is bringing her eight-year-old daughter to a doctor to perform circumcision. Comment.

4. A forty-years old lady presenting for uterine bleeding is found to have multiple big myomas. Her hemoglobin is 8.5 g/dl. She has four living children including two males. She refused the idea of hysterectomy. Discuss how are you going to manage her.

5. Thirty-years old lady with a son and a daughter is coming requesting tubal sterilization. Comment on what you can do for her.

6. Twenty years old unmarried girl presented for primary amenorrhea. She has a normal feminine phenotype but she is found to be having no vagina or uterus. Discuss how you are going to manage her. Give the due consideration to the ethical aspects of the problem.

7. A 4 years child with ambiguous external genitalia has been reared as a male and is suspected to be a female with congenital adrenal hyperplasia. Due to inheritance implications, the parents are reluctant to proceed with the clinical effort to fully diagnose and treat the condition and that may end in changing "his" gender assignment. Comment on how you are going to establish a diagnose and convince the parents of the proper management.

8. A woman has taken two packets of oral contraceptives to postpone her menstruation during pilgrimage. However, during the intake of the second packet she started to have spotting before she has completed all parts of pilgrimage. What sort of advice do you give her?

9. A young lady who has delivered 30 days ago and the bleeding has stopped. Thereafter, on the two occasions she had sexual intercourse when she had postcoital bleeding. What sort

of advice do you give her?

10. A 25 years old lady tested positive for HIV at the 8th week of her pregnancy. Describe how you are going to counsel and manage her.

11. A para 7+1 aged 35 years with 4 male and 2 female children is having amenorrhea. She is definitely anemic. The uterus is found to be symmetrically enlarged but with no focal lesion. Discuss the management plan including how you counsel the patient about the plan.

12. Discuss the genetic concern in carrying ICSI when the husband is having congenitally absent vas deferens. How are you going to manage such a case?

13. A patient is asking to use injectable contraceptves but is asking to conceal that from her husband.

14. An enthusiast claims that contraception is a sort of Waad (killing of children). Comment.

15. A primigravida pregnant 27 weeks is requesting termination of her pregnancy because of a diagnosis of moderate fetal hydrocephaly. She has already had failure to induce labor by misopristol vaginal suppository. Comment - Discuss the ethical aspects.

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THE AUTHOR

Mamdouh Mohammed Shaaban **graduated from the school of medicine Cairo University in the year 1959. In 1964, he joined the faculty of medicine of the then newly initiated, Assiut university in Upper Egypt. He was appointed professor of Obstetrics and Gynecology in this university in the year 1973, a position he still keeps till the present time. Professor Shaaban has been active as a clinician, educator, researcher and scientific administrator. He traveled to many parts of the world both for obtaining training and scientific contribution. He served as temporary consultant to a number of international organizations.**

The BOOK

The book covers the needs of Diploma and Master candidates in Gynecology and Family Planning. It gives basic information required in Doctorate examination. It can serve as a reference to an active undergraduate. The book contains many practical points that guide the gynecology specialists in their clinical work. It puts together a 40-year experience added to an updated literature.