CONTENTS

CHAPTER 1 GENITAL EMBRYOLOGY & ANATOMY

(I) Embryology

i) Development of the urogenital system

The development of the external and internal genital organs is closely linked with urinary system in embryonic period.

Three pairs of embryonic kidneys form consecutively from the mesoderm;

- Pronephros: rudimentary and degenrates;
- Mesonephros: develops excretory tubules that filter and remove body wastes through mesonephric (or wolffian) ducts. This primitive kidney regresses when definitive kidney develops;
- Metanephros: later becomes the definitive kidney.

The mesonephric ducts develop into male internal structures (except prostate)—Seminal vesicles, Epididymis, Ejaculatory duct, Ductus deferens (*Aide memoire:* SEED). In females, it degenerates into Gartner's duct.

The *paramesonephric ducts* develop on each side from longitudinal invaginations of the *mesothelium* on the lateral aspects of the two mesonephros and gonads (see Figure). Depending on gonadal secretion of hormones (*including anti-mullerian hormone*);

- It develops into müllerian tubercle and later female upper genital structures— fallopian tubes, uterus, cervix, upper portion of vagina (lower portion of vagina develops from urogenital sinus, see Figure);
- It degenerates in male embryos into appendix testis.

These paramesonephric ducts extend caudally to project into the posterior wall of the urogenital sinus as the ***Mullerian tubercle***;

- These fuse in the midline distally to form the uterus, cervix and proximal two thirds of the vagina;
- The unfused caudal segments form the fallopian tubes;
- The distal vagina is formed from sinovaginal bulbs in upper portion of the urogenital sinus (see Figure).

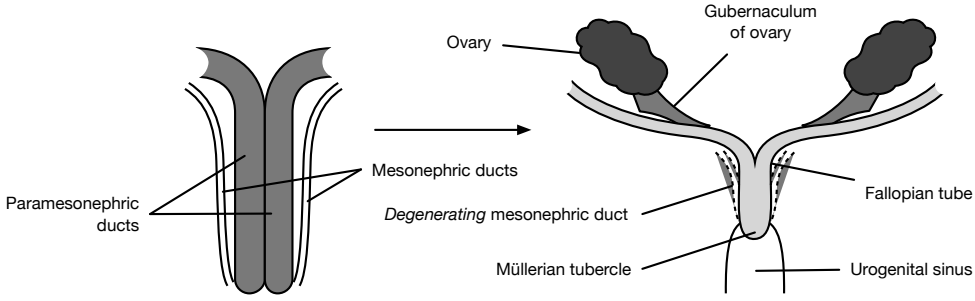


Figure. Development of the mesonephric and paramesonephric ducts.

Between the fifth and seventh weeks of life, the cloacal folds— which are a pair of swellings adjacent to the cloacal membrane fuse anteriorly to become the genital tubercle.

- The ***urorectal septum*** starts forming during the 5th week and later divides the cloaca into the ***urogenital sinus*** anteriorly and ***anorectal canal*** posteriorly. The upper part of the urogenital sinus will form the bladder and the lower part will form the urethra.
- The external genitalia are recognizable female by the end of 12 weeks of gestation.

ii) Development of the gonads

The primitive gonad is first evident in embryos at 5 weeks of gestation. The early genital systems in the two sexes are similar and is referred to as *the 'indifferent stage of sexual development'*.

The gonads (testes or ovaries) are derived from 3 sources;

- Mesothelium (mesodermal epithelium) lining the posterior abdominal wall;
- Underlying mesenchyme (embryonic connective tissue);
- Primordial germ cells.

During the 5th and 6th weeks, germ cells **migrate through mesoderm from the yolk sac** (near the allantois) to the urogenital ridge. The mesenchyme of the urogenital ridge and migrated germ cells fuse with each other and differentiate into male or female types based on chromosomal genotype.

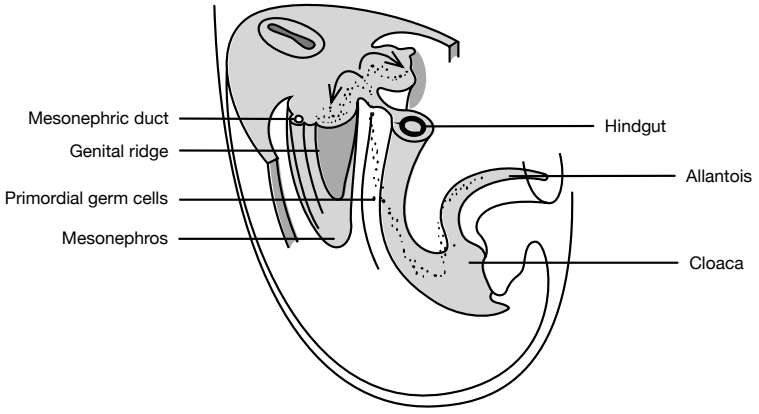


Figure. Cross section of posterior abdominal wall showing genital ridge and migration of primordial germ cells.

Morphological development of the ovary occurs about 2 weeks *later than* and is *slower than* that of testes.

- As the primordial germ cells get surrounded by a ring of pre-granulosa cells as they are called, 'oocytes';
- The oocytes enter prophase I stage of meiosis and undergo arrest in this stage till menarche.
- The ovarian stroma develops from the mesenchyme.

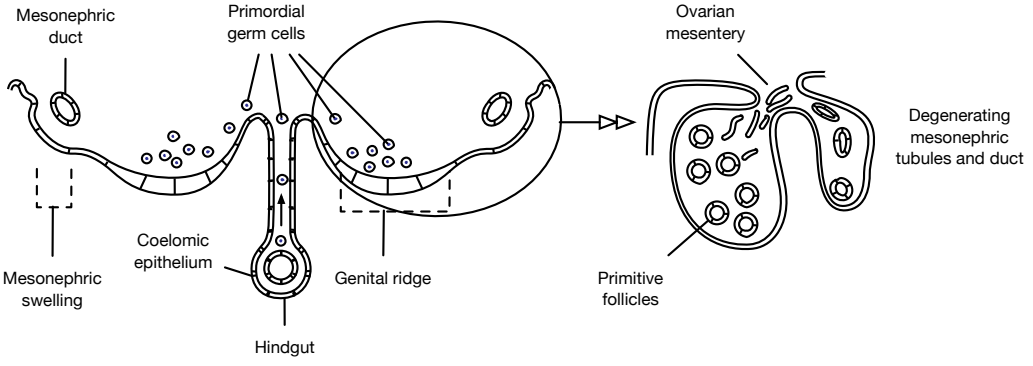


Figure. Development of the ovary.

During the embryonic development, there is also descent of the ovaries into the abdominal cavity (extraperitoneal). The bilateral caudal genital ligaments guide the ovary to reach its final adult location. These caudal genital ligaments later divide into *the ovarian ligament and the round ligament of uterus*.

(II) Anatomy of genital organs

i) External genitalia

The female external genitalia refer to the mons pubis, vulva, labia majora, labia minora, vestibule, clitoris and greater vestibular glands.

- The mons pubis is the fibrofatty tissue cover of the pubic bones.

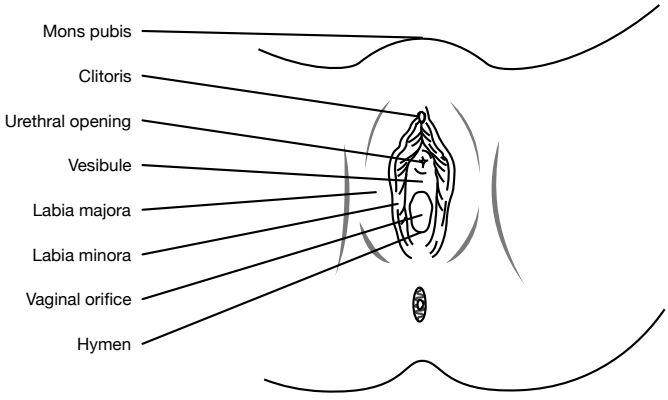


Figure. The female external genitalia.

- The labia minora are two thin folds of skin that lie between the labia majora;
    - Anteriorly they divide into two to form the **prepuce** and **frenulum** *of the clitoris*;
    - Posteriorly they fuse to form a fold of skin— the fourchette;
    - They contain sebaceous glands but have no adipose tissue. They are not well developed before puberty, and atrophy after menopause;
    - Their vascularity allows them to become turgid during sexual activity.
- The clitoris is a small 1 cm erectile structure but has a highly developed nerve supply and is very sensitive during sexual arousal.
- The vestibule is the *cleft* between the two labia minora;
    - The urethra, the ducts of the Bartholin's glands and the vagina open in the vestibule;
    - The vestibular bulbs are two oblong masses of erectile tissue that lie on either side of the vaginal entrance.
- Bartholin's glands, each about the size of a small pea, lie at the base of each bulb and open via a 2cm duct into the vestibule between the hymen and the labia minora. These secrete mucus-like fluid (*more details are discussed in later chapters*);
- The hymen is a thin fold of mucous membrane across the entrance to the vagina;
    - There are usually openings in it to allow menses to escape;
    - The hymen is partially ruptured during first coitus and is further disrupted during childbirth;
    - Hymenal tags that remain after its rupture are known as **carunculae myrtiformes**.

ii) The vagina

The vagina is a fibromuscular canal lined that leads from uterus to the vulva;

- It is longer in the posterior wall (~ 9 cm) than anterior (~ 7cm);
- The vaginal walls are rugose with transverse folds;
- It is lined by stratified squamous epithelium;
- The epithelium is thick and rich in glycogen. But, before puberty and after the menopause vaginal epithelium is devoid of glycogen because of *relative oestrogen deficiency*.

The vaginal walls are normally in apposition, except at the vault, where they are separated by the cervix. This enables arbitrary division of vagina into four fornices— posterior, anterior and two lateral. The cardinal ligaments and the uterosacral ligaments support the upper part of the vagina (see Figure);

- Anteriorly, the vagina is in direct contact with the base of the bladder;
- The upper posterior vaginal wall forms the *anterior peritoneal reflection* of the pouch of Douglas.

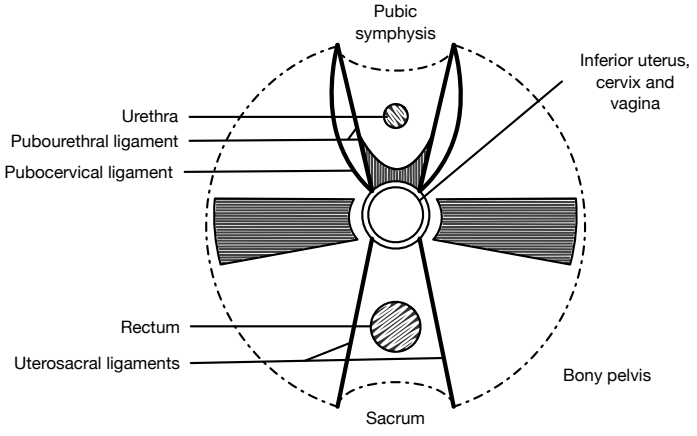


Figure. Figurative illustration of ligamental support of lower part of uterus, cervix and upper vagina.

The middle third of vagina is separated from the rectum by pelvic fascia;

- The midvagina is a transverse slit and the lower portion is H-shape in transverse section;
- Anteriorly, the urethra runs down the lower half in the midline to open into the vestibule;
- Laterally at the fornices (see below), the vagina is related to the *cardinal ligaments*.

Inferiorly, the vaginall walls are surrounded by levator ani, ischiorectal fossae and perineal body (see Figure).

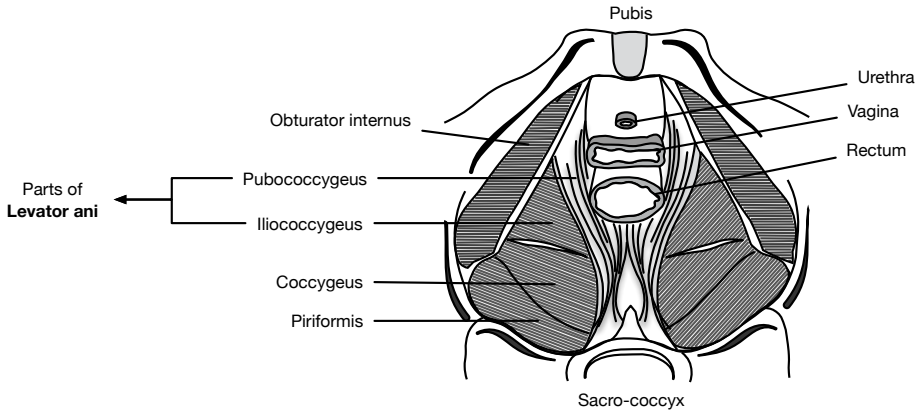


Figure. Pelvic floor musculature— *superior view*.

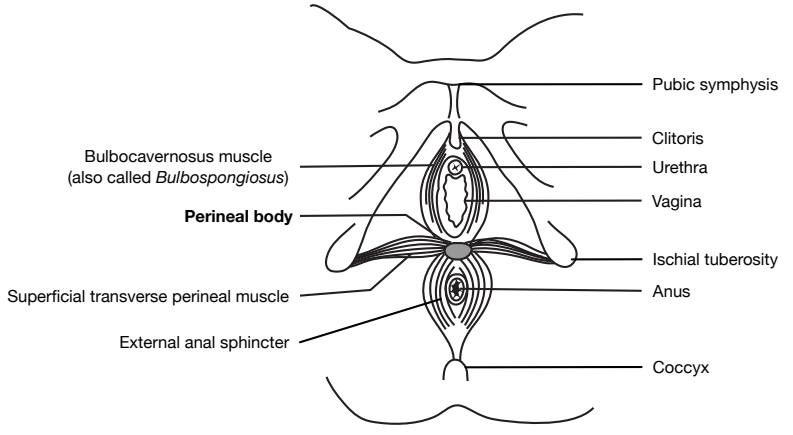


Figure. Perineal body and the perineum— *inferior view*.

The vagina is kept moist by secretions from the uterine and cervical glands and by some transudation from its epithelial lining but has has no glands.

Döderlein's bacillus is a normal commensal of the vagina. It metabolizes glycogen to form lactic acid, producing a pH of around 4.5— giving protective role for vagina in decreasing the growth of pathogenic organisms.

iii) The cervix

The cervix is approximately 2.5cm in length. Unlike the vagina, cervix has numerous deep glandular follicles that secrete a clear alkaline mucus.

The epithelium of the endocervix is ciliated columnar epithelium but changes to stratified squamous epithelium around the region of the external os— referred to as the squamocolumnar junction or transformation zone. This is the site of rapid cell division and approx. *90% cervical carcinomas arise in this area*.

Anatomically, due to antiflexion or retroflexion, the long axis of the cervix is not the same as the long axis of the body of the uterus (see Figure);

- Most commonly, the uterus is flexed forward on itself at the isthmus and tilts anteriorly at a right angle to the vagina— 'antiflexion' and 'antiversion' respectively;
- Less commonly, however, the uterus may be tilted backwards— retroversion or retroflexion. This has no pathological significance in most individuals, but retroversion that is fixed and immobile may be associated with endometriosis.

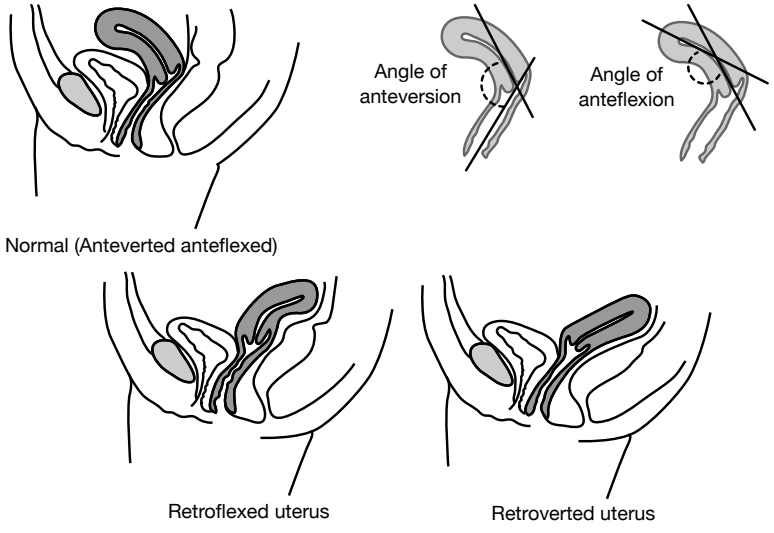


Figure. Illustration of long axis uterus, cervix and vagina with variations.

Thus, the cervix projects obliquely into vagina and can be divided into vaginal and supravaginal portions;

- The supravaginal portion consists mostly of involuntary muscle— *the endocervix*;
- The endocervix also has characteristic radiating folds visible over the mucosa. These are termed '**arbor vitae**' resembling tree branches. These folds and crypts are belived to provide a reservoir for sperm;
- In contrast, the vaginal portion is mainly fibrous connective tissue— ectocervix. It projects into the vagina to form *the four fornices* (see below).

iv) Uterus

The uterus is shaped like an inverted pear;

- In the non-pregnant state is situated entirely within the pelvis lined by thick muscular walls;
- It is hollow and tapers inferiorly towards the cervix.

It consists of;

- The upper part— body/corpus of uterus;
- The cornu— the area of insertion of each fallopian tube;

- The fundus— the part of the body above *the cornu*;
- The cavity of the uterus is the shape of an inverted triangle;
- The uterus tapers *inferiorly* to a small central constricted area, the isthmus, and below this is the cervix;
- The constriction at the isthmus where the corpus joins the cervix is the **anatomical** *internal os*. In contrast, ***histological internal os*** *(or* ***transformation zone****)* refers to the site where the mucous membrane of the uterus becomes that of the cervix.

The uterus consists of three layers: the outer serous layer (peritoneum), the middle muscular layer (myometrium) and the inner mucous layer (endometrium);

- The peritoneum covers the body of the uterus and, posteriorly, the supravaginal portion of the cervix;
- The serous layer spreads laterally as part of broad ligament of uterus— anatomical supportive structure.

The muscular myometrium forms the main bulk of the uterus and comprises interlacing smooth muscle fibres with blood vessels, nerves and lymphatics.

The endometrial layer is covered by a single layer of columnar epithelium. It has tubular secretory glands. The endometrium undergoes cyclical changes during menstruation with varying thickness of 1-5 mm.

v) Fallopian tubes

Each Fallopian tube extends outwards from the uterine cornu to end near the ovary. They convey the ovum from the ovary towards the uterus and provides oxygenation and nutrition for sperm and ovum or zygote if fertilization occurs.

The fallopian tube runs in the upper margin of the broad ligament known as *mesosalpinx*. The fallopian tubes are enclosed by mesosalpinx over all but a narrow inferior strip.

Each tube is about 10 cm long and is described in four parts— interstitial portion, isthmus, ampulla and infundibulum (or fimbrial portion, see Figure);

- The interstitial portion lies within the wall of the uterus;
- The isthmus is the **narrow portion** adjoining the uterus;
- The ampulla is the **widest and longest portion**;
- The infundibulum (or fimbrial portion) is a funnel-shaped opening of the tube into the peritoneal cavity. It has finger-like outgrowths termed 'fimbriae'.

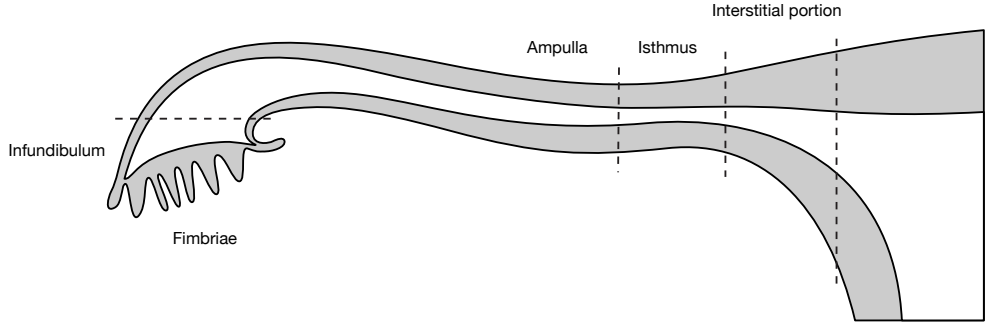


Figure. Illustration of parts of a fallopian tube.

The epithelium of the Fallopian tubes contains two functioning cell types— the **ciliated columnar cells** aiding flow towards the uterus and **secretory cells**, which contribute to the volume of tubal fluid;

- Together, these are so-arranged to make the epithelium in branched folds, or plicae;
- There, however, is no submucosa or glands;
- Menstrual cycle influences changes in the epithelium but there is no cell shedding during menstruation.

vi) The ovaries

In the young adult, they are almond-shaped and measure approx. 3 cm long and 1.5 cm wide;

- Each ovary is attached to the cornu of the uterus by the ovarian ligament (also called *utero-ovarian ligament,* see Figure) and at the hilum to the broad ligament by the mesovarium. The mesovarium carries blood vessels and nerves to the ovaries.
- Laterally on each side, the ovaries are attached to the suspensory ligament of the ovary with folds of peritoneum that overlie psoas major muscle;
- Anterior to ovaries lie fallopian tubes, the superior portion of the bladder and uterovesical pouch;
- Posterior to the ovaries lie the ureters which run in front of the internal iliac arteries (*aide mémoire— water under the brige*).

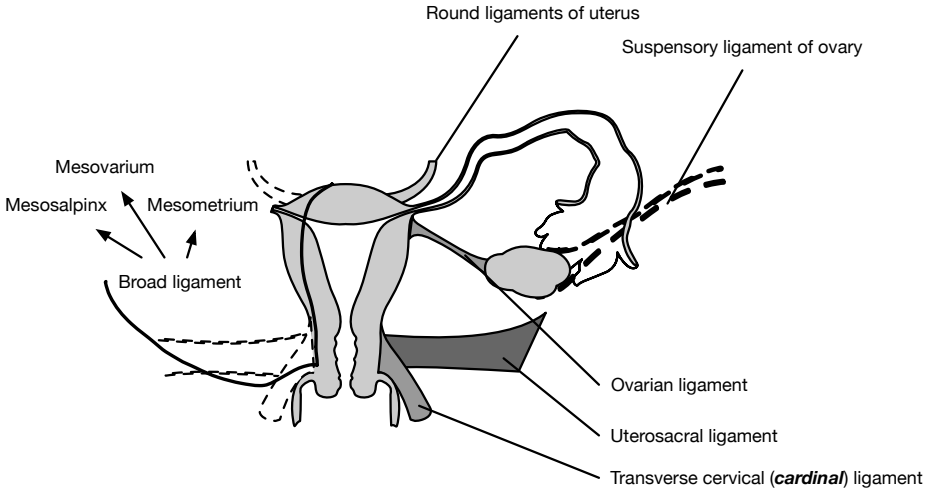


Figure. Illustration of ligamental support of internal genital organs.

The ovary has a central medulla and overlying cortex;

- The surface of the ovaries is covered by a single layer of cuboidal cells, the germinal epithelium;
- Beneath germinal epithelium lies an ill-defined layer of connective tissue— 'tunica albuginea';
- The cortex consists of networks of reticular fibres and fusiform cells;
- The medulla consists of loose connective tissue containing elastin fibres and non-striated muscle cells.

The size and appearance of the ovaries varies with age;

- At birth, numerous primordial follicles are in the cortex, but some may be found in the medulla;
- With puberty, some primordial follicles develop each month into the graafian follicles;
    - Under gonadotrophic hormonal control ova are formed and ovulate out;
    - This leads to formation of corpus lutea and eventually atretic follicles— 'corpora albicans'.
- After menopause, no active follicles are present, and the ovary becomes smaller with a wrinkled surface.

The ovary is the only intra-abdominal structure not to be covered by peritoneum.

CHAPTER 2 PUBERTY AND ABNORMAL SEXUAL DEVELOPMENT

All normal fetuses have an undifferentiated gonad which has the potential to become either a testis or an ovary.

The presence of a Y-chromosome and the expression of testes-determining genes (i.e. **S**ex determining **R**egion on **Y**-chromosome (SRY) gene) is involved in the induction of differentiation of gonads into testes.

The female phenotype was previously considered the default pathway for development of a fetus in the absence of expression of genes that induce testicular development. However, ovary-inducing genes have also been discovered.

Loss of a sex chromosome is usually incompatible with life, except in the case of Turner syndrome which may occur from a complete or partial absence on one X chromosome (genotype: 45XO).

(I) Puberty

Adolescence is the time between the beginning of sexual maturation (puberty) and adulthood. It is the time period between age 13 and 19 (teenage).

i) Pubertal development

Puberty is the time in which child's sexual and physical caracteristics mature. It occurs due to hormone changes that lead to body changes and development of 2° sexual characterisitics;

- Pulsatile GnRH release begins around the age 9 years. This pulsatile secretion of GnRH induces pituitary gland to make FSH and LH;
- FSH and LH stimulate the gonads to produce predominantly testosterone (from testis), or estrogen (from ovaries);
- Testosterone and estrogen influence is the basis of secondary sexual characterisitics and menarche during pubertal growth (*mean age of occurrence ~ 12.8 years*).

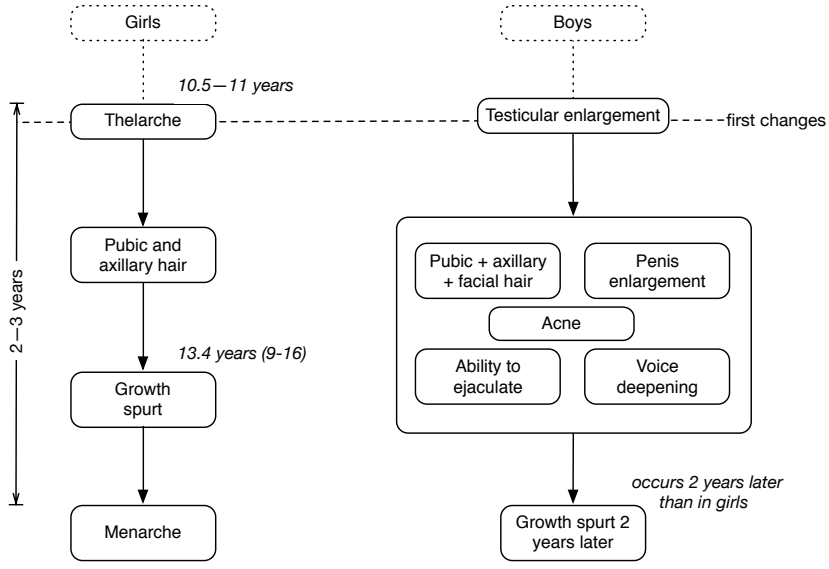


Figure. Puberty in males and females.

ii) Assessment of pubertal development

Assessment of pubertal development was described by Tanner— where the stages of breast and pubic hair development are often referred to as Tanner stages 1 to 5.

Table. Illustration of Tanner stages of development in females.

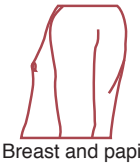
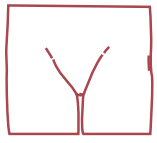
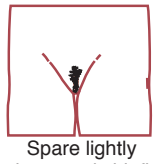
	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Breast					
		Breast and papilla are elevated as small mound. Areolar diameter increases	Further enlargement of the breast bud with loss of the contour seperation between breast and areola	Aerolar and papilla form a secondary mound	Mature areolar is part of the general breast contour
	'Prepubertal'	***'Breast Bud'***	***'Breast Elevation'***	***'Areolar Mound'***	***'Adult Contour'***
Pubic hair					
		Spare lightly pigmented chiefly along the medial border of the labia majora	Darker beginning to curl, increased amount spreading over the mons	Increased amount of course, curly but limited to the mons	Adult feminine triangle with spread to the medial surface of the thighs
	'Prepubertal'	***"Presexual Hair'***	***'Sexual Hair'***	***'Mid-Escutcheon'***	***'Adult Escutcheon'***

Figure. Illustration of Tanner stages of secondary sexual characterisitics in females.

iii) Delayed puberty

Delayed puberty is said to occur when there are no secondary sexual characteristics by the age 14 years in females and 14.5 years in boys.

Any deviation of pubertal development, whether early or delayed is classified into two types, based on site of pathology, as central (hypothalamic-pituitary axis) or peripheral (gonadal disorders);

- Central: ***Hypo***gonadotrophic hypogonadism (↓ FSH and LH);
    - Constitutional delay;
    - Anorexia nervosa;
    - Excessive exercise;
    - Diabetes;
    - Renal Insufficiency;
    - Pituitary tumors;
    - Kalman's syndrome/Immotile cilia syndrome.
- Peripheral: ***Hyper***gonadotrophic hypogonadism (↑ FSH and LH);
    - Turner's syndrome;
    - XX gonadal dysgenesis;
    - Or, essentially any disease process where a suboptimal ***hormonal*** response of ovaries to gonadotrophs (FSH and LH).

a) Precocious puberty

It is defined as onset of secondary sexual characterisitics before 9 years of age in boys and 8 years of age in girls. It is more common in girls.

It is also classified into central and peripheral types based on aetiology.

It is associated with intracranial tumors in male children as central type. On the other hand, it is usually idiopathic in females, or it could be due to increased hormonal states e.g. congenital adrenal hyperplasia (CAH).

(II) Abnormal sexual development

i) Terminology

Following is the summary of new terminology for Disorders of Sex Development (DSD);

Table. Comparison of new terminologies for DSDs with older terminologies.

Previous	**Newly Proposed**
Intersex	Disorders of Sex Development
Male pseudohermaphrodite Undervirilization of XY male Undermasculinization of XY male	46, XY DSD
Female pseudohermaphrodite Overvirilization of an XX female Masculinization of an XX female	46 XX DSD
True hermaphrodite	Ovotesticular DSD

ii) XY gonadal dysgenesis

In this disorder of sexual development, the genotype is 46, XY but there may be deletion of testis-determining genes (e.g. *SRY gene in deletion* is seen in upto 10% cases);

- This leads to failure of induction of indifferent gonad into testis;
- As a result, the individual possesses a streak gonad that produces little or no hormones.

iii) Swyer syndrome

*It is a more severe form of **XY gonadal dysgenesis***. The gonads remain as streak gonads and **do not** produce any hormones leading to;

- Absence of Anti-Mullerian hormone ⟶ female internal genital organs (i.e. uterus and fallopian tubes do not regress, despite individual having XY chromosomal constitution);
- Absence of testosterone production ⟶ no virilization of fetus is seen, despite having XY chromosomes.

a) Clinical Presentation

A phenotypic female usually presents during adolescent age, with failure to go into spontaneous puberty.

b) Treatment

- The dysgenetic gonad must be removed soon after diagnosis to reduce the risk of gonadal malignancy;
- Puberty must be induced with estrogen to attain pubertal growth and 2° sexual characterisitcs;
- Pregnancy, in future, is possible with donor oocytes.

iv) 46XY DSD (aka Androgen Insensitivity Syndrome)

In this syndrome, there is no response to androgens (i.e. testosterone) due to defective androgen receptors;

- Presence of SRY gene (Y-chromosome) in these individuals induces testes development;
- Testes produce Anti-Mullerian hormone (AMH) ⟶ Paramesonephric ducts regress;
- Testes produce testosterone, but its androgenic effects are not seen. As a result, virilization of the external genitalia does not occur;
- At birth, female external genitalia (less developed) are seen with partially descended testes.

a) Clinical Presentation

It is a diagnosis to consider in a primarily amenorrheic female that shows normal breast development but no

axillary or pubic hair at puberty. Vaginal shortening may also be noted.

b) Management

- Vaginal dilation with moulds ⟶ most effective for improving shortened vaginal length.
- Vaginal reconstruction surgery.
- Gonadectomy— to reduce the risk of testicular malignancy (↑ risk with undescended testes). However, this can be delayed till puberty *by choice*, so that individual may attain maximum prepubertal growth under influence of endogenous testicular hormones.
- Life-long hormone replacement therapy (HRT) post-gonadectomy is usually the norm.

v) 5-Alpha Reductase deficiency (5α Reductase)

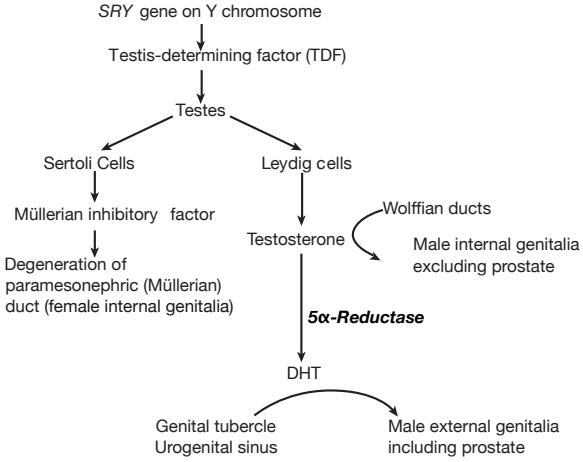


Figure. Schematic of enzymes involved in embryologic development of genotypic males (46, XY).

As shown in the schematic, there is an inability to convert testosterone into Dihydrotestosterone (DHT);

- The individual possesses male internal genitalia;
- There are low levels of DHT (due to 5α Reductase deficiency) ⟶ external genitalia do not differentiate into male external organs. As a result, ambiguous external genitalia may be seen at birth;
- Masculinization and male pattern secondary sexual characteristics are seen at puberty as testosterone levels surge.

vi) Congenital Adrenal Hyperplasia

It is due to a group of enzyme defects which prevent the synthesis of cortisone from progesterone.

The most common enzyme defect is C21-hydroxylase deficiency (~ 90% of cases, *see Figure*);

- ↓ cortisone positively feedbacks hypothalamus–pituitary axis to ↑ ACTH secretion.
- ↑ ACTH stimulates the adrenal gland to secrete androgens in a progressive fashion, leading to *hyperplasia of adrenal glands*.

a) Clinical Features

All congenital adrenal enzyme deficiencies are characterized by an enlargement of both adrenal glands due to ↑ ACTH stimulation (*which, in turn, is due to* ↓ cortisol). However, the onset of their clinical manifestations may vary;

This group of enzyme defects can manifest clinically in a variety of presentations. It can be subtyped into;

- Simple virilizing non-salt wasting CAH;
- Nonclassical ***late-onset*** CAH;
- Classic salt-wasting CAH.

Virilization of the external genitalia at birth or shortly thereafter is seen in **classic** *and* **simple virilizing subtypes** of CAH.

Nonclassical late-onset CAH features a gradual occurrence of hirsutism. There may be menstrual abnormalities and anovulation. *Elevated 17-hydroxyprogesterone levels and a relatively non-obese BMI (Body Mass Index; kg/m^2)* ***distinguish*** *this subtype of CAH from polycystic ovarian syndrome (PCOS).*

Less frequently, a *more severe form* of C21-hydroxylase deficiency is seen and is referred to as a ***classic salt-losing syndrome (****also called* ***salt-losing subtype of CAH)***. Such individuals have;

- ↓ ↓ Cortisone and ambiguous genitalia;
- ↓ ability to produce aldosterone ⟶ life threatening hemodynamic and electrolyte imbalance.

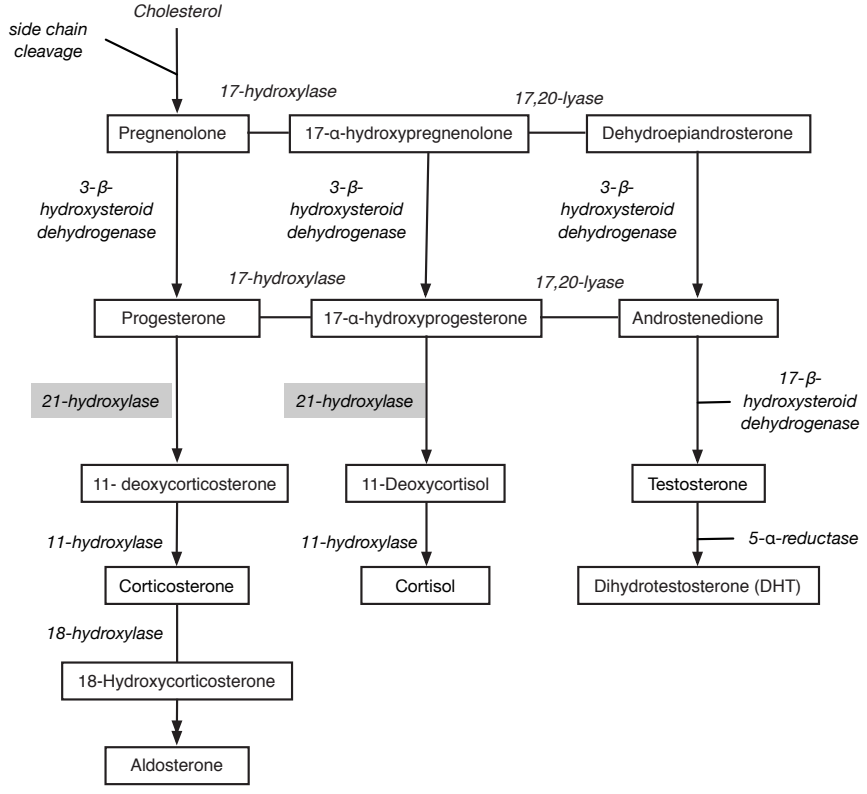


Figure. Illustration of 21-hydoxylase pathway.

b) Treatment

- Lifelong corticosteroid replacement is indicated— to ↓ ACTH (negative feedback) and thus ↓ *endogenous androgen overproduction* from progresterone and 17-hydroxyprogesterone (17-OHP);
- In cases of salt-losing subtype, death can occur due to mineralocorticoid deficiency. These individuals require fludrocortisone (mineralocorticoid effect) in addition to hydrocortisone;
- Surgical treatment of ambiguous genitalia is generally deferred till the infant is well and stabilized on a *corticosteroid replacement regime*.

vii) Mullerian tract abnormalities

a) Imperforate hymen

Incomplete canalization of mullerian duct-derived structures gives rise to this condition. This manifests as *apparent* failure to menstruate at menarche in a genotypic and phenotypic female with normal well developed secondary sexual characteristics.

However, a history of cyclic pelvic/abdominal pains every month since menarchal age (*similar to features of menstrual cycles*) can be noted.

The most common site of defective canalization/obstruction is the junction of the lower 1/3rd with upper 2/3rd of the vagina— i.e. *the level of the hymen*.

The retained menstrual blood stretches the vagina causing a haematocolpus (blood in the vagina). This can cause a large pelvic mass and in addition can usually be seen as a bulging membrane at the vaginal entrance. The *aide mémoire* for imperforate hymen is a *bluish-hue of a bulging membrane* on vaginal speculum exam.

Treatment is simple with a surgical incision of the hymen and drainage of the retained blood.

b) Mullerian Agenesis

This condition is also known as **Mayer-Rokitansky-Kuster-Hauser (MRKH)** syndrome;

- Agensis of mullerian derivative structures leaves a short blind ending vagina (noted on speculum/ bi-manual examination) with absence or presence of *rudimentary upper genital organs*:
- Ovarian function is preserved, and the ova can be extracted for *in-vitro* fertilization.

These individuals have female external genitalia and present during pubertal period when there is a failure to menstruate in these individuals due to absent/rudimentary uterus.

The major differential diagnosis of this condition is *androgen insensitivity syndrome (46XY DSD)*, however, the differentiating point here is that these patients with MRKH have public and axillary hair **well developed** as part of secondary sexual characteristics (*due to intact ovaries*).

(III) Investigating a child with ambiguous genitals

Virilization of the cloaca can also occur if the fetus is exposed to androgenic drugs during embryonic period. Hence, history taking can be helpul in ruling out possible exposures *in utero*.

Any child with ambiguous genitals should be investigated for;

- Chromosomal abnormalities;
- Classical C21 Hydroxylase deficiency;
- Salt-wasting subtype of C21 Hydroxylase deficiency (severe).

The best initial screening tests for these conditions are;

- Blood levels of 17-hydroxyprogesterone (>7 mmol/L confirms the diagnosis);
- Serum electrolytes;
- Ultrasound of pelvis— *to assess internal genital organs*;
- Determining the chromosomal sex.

At birth, investigation of the chromosomes, the endocrine status of the infant and ***ultrasound of the internal organs*** will lead to a rapid diagnosis, revealing whether the child is;

- A female with a virilization state, which is most likely to be congenital adrenal hyperplasia, or;
- A male who has been under-masculinized.

CHAPTER 3 THE MENSTRUAL CYCLE, ITS DISORDERS AND DISEASES

The menstrual cycle is a set of endocrinological changes that transform a female child into an adolescent who is capable of conceiving a child.

- The most marked changes of puberty occur in the 2 years before the girl's first menstrual period (menarche) due to hypothalamic induction of gonadotrophic releasing hormones and their effects;
    - ↑ height, and weight;
    - ↑ secondary sexual characterisitics;
    - ↑ growth of sexual organs.
- The hypothalamus begins to release gonadotrophin-releasing hormone (GnRH) in an episodic pulsed manner. These episodic pulses bring about pituitary release of gonadotropins (FSH and LH).

It is hypothesized that the greater amount of body fat permits the greater aromatization of androgens to oestrogens. Thus, obese females may undergo menarche earlier.

The menarche may be delayed in women who are of low body weight, have anorexia nervosa, or those who are athletic exercisers.

(I) Estrogen

Estrogens affect genital tract and development of breast tissues.

Estrogens cause endometrial proliferation in uterus and stimulates growth of vulva and vagina after menarche;

- 17-β oestradiol is the most active and the predominant oestrogen in the reproductive years;
- In blood, 60% of estogen is bound to albumin, 37% to sex hormone-binding globulin, and 3% is free;
- Once attached to the specific binding sites oestradiol is transferred to the cell's nucleus, where it activates genes, leading to RNA synthesis;
- Following nuclear gene activation, oestradiol is rapidly converted to the relatively inactive oestriol, transported to the liver for conjugation with glucuronic acid. This conjugate is excreted in the urine.

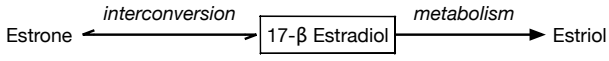


Figure. Interconversion and metabolism of estrogens.

The great increase in circulating oestrogen in pregnancy causes the rapid growth of the uterus, *and later* lack of this hormone after menopause leads to uterine atrophy.

(II) Progesterone

Progesterone also acts on tissues with estrogen receptors but here a sensitizing effect by estrogens is also noted;

- Progesterone renders cervical mucus viscous;
- Progesterone also increases the thickness of an estrogen-primed endometrium, preparing it to accept a fertilized egg.

Progesterone is also thermogenic, raising body temperature by 0.2–0.5 °C— commonly seen post-ovulation.

(III) The menstrual cycle

With reference to periodic changes in female reproductive organs, it has four distinct cycles;

- Ovarian cycle;
- Uterine cycle;
- Cervical cycle;
- Vaginal cycle.

i) Ovarian cycle

Germ cells are maximum (~ 7 million) at 16–20 weeks of intra-uterine gestation. They undergo atresia by apoptosis and are 2 million at birth but approx. 300,000 remain at puberty;

- At puberty, majority of the oogonia are surrounded by layers of cells, many of which have developed fluid-filled cavities (antra) to become primary follicles;
- Each month, under the influence of pulsatile hypothalamic releasing hormone GnRH, and consequent pituitary gonadotropins FSH and LH, these primary follicles are stimulated;
    - Within the primary follicles, there are two cell types which are involved in the processing of steroids— estrogen and progesterone;
    - These are the theca and granulosa cells, which respond to LH and FSH stimulation, respectively. LH **first** stimulates production of androgens from cholesterol within theca cells;
    - These androgens are **then** converted into estrogens by the process of aromatization in granulosa cells, under the influence of FSH.

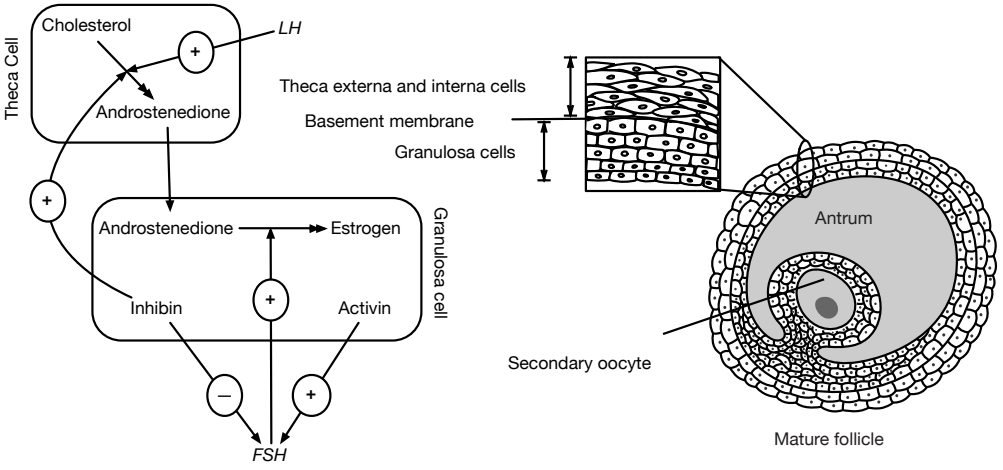


Figure. Illustration of hormonal control by gonadotropins from epithelial cells of ovaries.

- Out of the few follicles that are stimulated, a follicle (occasionally more than one) becomes relatively dominant, reaches the ovarian surface and is released as ovum into the fallopian tubes;
    - Both FSH and LH are required to generate a normal cycle with adequate levels of estrogen.
    - Initially in the cycle, rising levels of oestrogen exert a negative feedback, reducing FSH release. However, towards midcycle higher oestrogen levels exert a positive feedback, causing a sudden peak release of LH (***the LH surge***)— *thus inducing ovulation*.
    - The LH surge occurs over 24–36 hours and induces luteinization of granulosa cells in the dominant follicle (corpus luteum or 'yellow body'). This results in increasing amouts of progesterone to be produced.
    - Failure of this sequence will lead to anovulation and irregular cycles.
- If an ovum is released and conception does not occur, the corpus luteum starts involuting ('*luteolysis*') after 7 days, as there is a consequent fall in levels of progesterone and estrogen with eventual menstruation. The luteal phase lasts approx. 14 days.
- If conception and implantation occur, hCG secretion from trophoblastic cells of the zygote maintains corpus luteum to continue progesterone secretion.

ii) Endometrial Cycle

Menstruation as part of endometrial cycle is the periodic discharge from the uterus of blood, tissue fluid and endometrial cellular debris.

Menstruation normally occurs at intervals of 22–35 days (counted from day 1 of the menstrual flow to day 1 of the next) and the menstrual discharge lasts from 1 to 8 days. The mean blood loss is 30 mL (range ~ 10–80 mL).

The day 1 of menstrual cycle marks the start of shedding the proliferated endometrial epithelium from the previous cycle.

a) Proliferative phase

During the ovarian follicular phase, the endometrium undergoes proliferation (the 'proliferative phase');

- This proliferation repairs the endometrial surface by metaplasia of stromal cells and outgrowth of epithelial cells of endometrial glands;
- In early proliferative phase, endometrium is mostly thin and scarce cuboidal glandular epithelium;
- With estrogenic stimulation, epithelial glands increase, and their cell linings become columnar with basal nuclei in late proliferative phase;
- The endometrium is supplied by basal arteries in the myometrium that traverse at right angles to supply the superficial endometrium— **to become** spiral shaped (*spiral arteries*);
- This spiral organization of arterial vessels aids in an efficient blood supply of the growing endometrial layers with uncoiling;
- This decidualization, or the formation of a specialized glandular endometrium, **is an irreversible process** by itself but *endometrial apoptosis occurs if there is no embryo implantation*.

b) Secretory phase

The ovarian luteal phase corresponds to the 'secretory' phase of the endometrium. Drastic changes are seen in endometrium after ovulation. This is an important event as characteristic endometrial changes of secretory phase may not be observed in ***anovulatory cycles***;

- Secretory basal vacuoles develop rapidly in the endometrial glands, thereby pushing nuclei of glandular epithelium apically. These vacuoles contain mucoid material for secretion onto the endometrial surface. The endometrial glands appear remarkably tortuous as a result;
- The endometrial secretory phase is at its peak of development by sixth day post-ovulation. This coincides with ovum reaching the endometrial cavity for implantation *if conception has occurred*;
- The intracellular vacuoles have streamed past the nucleus. Some have discharged mucus into the cavity of the gland while others are full of mucus, showing a saw-toothed appearance;
- The spiral arteries also increase in length by uncoiling during secretory phase.

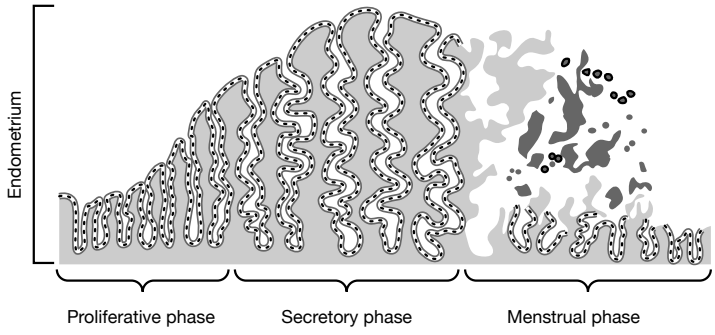


Figure. Endometrial cycle—changes in endometrial glands and vessels.

c) Menstrual phase

A decreasing pattern of progesterone is seen as corpus luteum begins to involute. This brings about changes in stromal cells of endometrium in association with certain prostaglandins— $PGF_{2\alpha}$, PGE_2, and PGI_2;

- $PGF_{2\alpha}$ → *powerful vasoconstrictor and causes uterine contractions*;
- PGE_2 → *stimulates uterine contractions and vasodilatation*;
- PGI_2 (also called **prostacyclin**) → *vasodilator, causes muscle relaxation and inhibits platelet aggregation*;
- An increased ratio of $PGF_{2\alpha}$ to PGE_2 and PGI_2 is seen— *due to free arachidonic acid and endoperoxidases accumulating in stromal cells*;

As a result, blood flow is reduced due to predominant vasoconstriction. Endometrial thickness decreases and recoiling of spiral arteries occurs;

Hypoxia and ischemic necrosis of of superficial and middle endometrial layer ensues and sheds off into menstrual blood. *The deeper basal layer, however, is spared*.

The central role of COX-2 enzyme in regulation of prostaglandins' synthesis makes it an effective target by **non-steroidal anti- inflammatory drugs (NSAIDs)** to treat heavy and painful periods.

iii) Cervical Cycle

Certain characteristic effects of hormones are observed on cervical secretions;

During the early follicular phase of ovarian cycle, glands lining the clefts of the cervical canal proliferate and secrete thick mucus, which forms a mesh in the cervical canal.

The increasing levels of estrogen before ovulation affect the character of the cervical mucus;

- It becomes *thin and forms long elastic strands*— if stretched between glass slides;
- Dried cervical mucus under microscope also shows a **characteristic pattern of ferning** (see Figure).

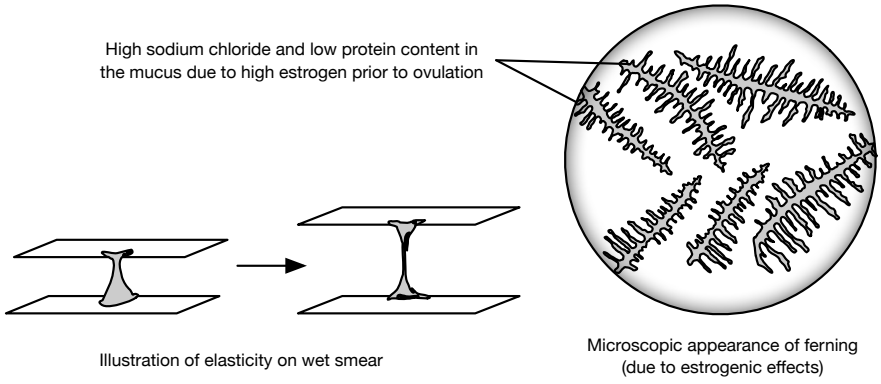


Figure. Illustration of observable effects of estrogen to cervical secretions.

After ovulation, however, progesterone from corpus luteum alters the nature of the cervical mucus— it again becomes thick and looses elasticity and ferning disappears completely after 21st day of cycle (see Figure).

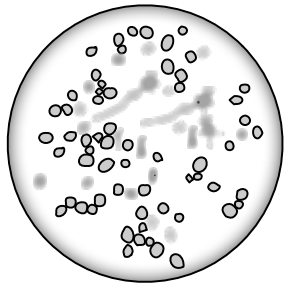


Figure. Illustration of thick and cellular mucus due to effects of progesterone.

The presence of **ferning** on smears even after 21st day of cycle suggests **anovulation**. On the other hand, its disappearance is considered a ***presumptive evidence of successful ovulation***.

(IV) Vaginal Cycle

Cyclic changes occur in the vaginal epithelium which are dependent on the ratio between oestrogen and progesterone;

- In the follicular phase, superficial and large intermediate cells predominate;
- As ovulation approaches, the proportion of superficial cells increases, and few leucocytes can be seen;

- Following ovulation, a marked change occurs as progesterone ***increases***— the superficial cells are replaced by intermediate cells and leucocytes increase in number.

(V) Disorders of menstruation

Menstruation is considered normal if it has following characterisitics;

- Occurs at intervals of 22–35 days (measured from day 1 of menstruation to day 1 of the next period);
- Average duration of the bleeding < 7 days (*although longer may be normal for some*); and
- If the menstrual blood loss is less than 80 mL.

Menstrual discharge consists of:

- Blood (50–80%);
- Tissue fluid (20–40% of the total discharge);
- Fragments of the ischemic endometrium.

i) Definitions

The menstrual cycle is expressed as XX/YY, whereby XX stands for the number of days of spotting/bleeding, and YY is the expression of interval (number of days) in between two menses.

For example, 5/29 means: menses last for 5 days, and occur approximately every 29 days.

a) Changes in the length of the menstrual cycle

As a deviation from normal;

- Menstruation may occur at intervals longer than 35 days; this is termed ***oligomenorrhoea;***
- Menstruation may also occur at intervals of less than 21 days, this is termed ***epimenorrhoea*** or ***polymenorrhoea.***

b) Changes in the amount of menstrual loss

The quantity of menstrual discharge may vary, with or without changes in regularity of menstruation;

- Scanty or light menstrual discharge in menstrual cycles is termed hypomenorrhoea;
- Heavy menstrual bleeding (HMB)— blood loss of >80 mL ***per period***. This is now the preferred terminology over the previous term "menorrhagia".

HMB may be characterized as an excessive amount of ***blood loss***, or due to an ***increased loss of tissue fluid*** in menses.

HMB may occur in association with an organic condition in the uterus, or in the absence of any detectable uterine abnormality. In the latter case, it is termed Bleeding of Endometrial Origin (BEO, previously called ***dysfunctional uterine bleeding, DUB***).

c) Disorders of regularity

- Primary amenorrhea— if menstruation has not started by the age 16 years;
- Secondary amenorrhea— if menstruation does not occur for >3 months after previous menarche in the absence of pregnancy.
- Metrorrhagia— bleeding occurring at irregular intervals with inconsistent amounts of bleeding. It can be further sub-classified as;
    - Intermenstrual bleeding (IMB)— bleeding between periods;
    - Postcoital bleeding (PCB)— bleeding after sexual intercourse;
    - Postmenopausal bleeding (PMB)— bleeding more than 1 year after cessation of periods.

Bleeding of endometrial origin (BEO)— this is a diagnosis of exclusion, which has replaced previously cited term '*dysfunctional uterine bleeding*' (DUB).

ii) Heavy Menstrual Bleeding (HMB)

- It is a clinical and subjective diagnosis, because of poor correlation with diagnostic testing.
- Low haemoglobin and MCV does not coincide well with HMB, however can acertain need for iron therapy or transfusions *for iron-deficiency blood loss anemias.*

a) Evaluation of HMB

Further evaluation on history-taking can be suggestive for diagnostic testing as (see Table);

Table. Aetiology of HMB, associated symptoms and relevant diagnostic testing.

Associated symptoms	**Suggestive of**	**Diagnostic testing**
Irregular bleeding Intermenstrual bleeding Postcoital bleeding Post menopausal bleeding	Endometrial/cervical polyp or other cervical abnormality	Colposcopy/hysteroscopy
Abdominopelvic swelling/lump	Pressure from fibroids	Ultrasound/***hysteroscopy***
Headaches Vision changes	Pituitary tumors	Brain imaging
Unusual vaginal discharge	Pelvic inflammatory disease	Vaginal/ endocervical swabs
Weight change, skin changes, fatigue	Thyroid disease	Thyroid function evaluation
Excessive bruising Bleeding from other sites *Previous* postpartum haemorrhage Excessive postoperative bleeding Excessive bleeding in dental procedures Family history of bleeding problems Anticoagulant drugs therapy	Coagulation disorder should be considered in cases of '*unexplained*' heavy menstrual bleeding.	Coagulation profile testing

Physical examination pertaining to evaluation of HMB includes abdominal and pelvic examination in all affected individuals;

- Pelvic masses can be palpation in most cases;
- Visuation of cervix can give clues to cervical polyps or carcinoma and thus cervical smears can be taken;
- Cervical swabs can also be taken with suspected infection.

Ultrasound scanning, preferably transvaginal (TVUSS) is less invasive and can detect uterine pathology;

- The presence of submucous myomata can be detected;
- The width of the endometrium can also be measured to *rule out need for endometrial sampling* (biopsy) *or curettage to exclude* ***endometrial hyperplasia***;
    - If > 15 mm in a pre-menopausal woman (depending on the stage of menstrual cycle), or;
    - If > 5 mm in a postmenopausal woman are considered suspicious for pathology.

An endometrial biopsy (EB) has special considerations in evaluation of HMB. Its indications include;

- PMB and endometrial thickness on TVUSS >4 mm;
- HMB after 45 years of age;
- HMB associated with IMB;
- Treatment failure;
- Prior to endometrial ablation procedures.

If no organic cause for menorrhagia is found, a diagnosis of BEO (*previously termed 'DUB'*) is made.

b) Management of HMB

The management can be grossly divided into medical and surgical approaches;

- If diagnostic testing identifies an organic cause, treatment should target causative factor. e.g;
    - Thyroid dysfunction;
    - Hyperprolactinemia caused by drugs or tumors;
    - Pelvic Inflammatory Disease (PID);
    - Uterine fibroids;
    - Coagulation disorders.
- For BEO cases (previously called *dysfunctional uterine bleeding*), idividuals can be offered medical or surgical treatments based on fertility preferences to reduce bleeding and improve quality of life;
    - Oral NSAIDs e.g. Mafenamic acid;
        - First line treatment, concurrent analgesia for those with painful periods;
        - Oral 500mg can be used upto 3 times/day;
        - Blood loss reduction by upto 20-25% amount;
        - Contraindicated, however, in individuals with duodenal ulcer.
    - Oral Tranxenamic acid;
        - Orally 1grams upto four times/day and is highly effective in cases of **acute HMB**;
        - **Menstrual Blood Loss (MBL)** reduction by ~ 50% amount.
    - Oral Combined Oral Contraceptive Pills (COCPs);
        - Offers contraceptive cover as well as reduces BEO symptoms;
        - *Contraindicated in* active smokers, overweight individuals, those at risk for thromboembolism, and in individuals with break cancer.
    - Oral Progestin-only Pills (POPs);
        - These provide contraceptive cover but is comparably not as effectively;
        - Norethisterone is taken cyclically from day 6 to day 26 at a dose 5-10mg PO TDS;
    - Levenorgestrel Intrauterine System (LNG—IUS, *aka Mirena*);
        - MBL reduction *upto 95% by one year*;
        - **Higly effective**, and should be considered before surgical options;
        - Initially, irregular and breakthrough bleeding can occur for several months.
    - GnRH agonists (e.g. gosrelin, triptorelin, buserelin);
        - These agents inhibit pituitary gonadotropin (FSH/LH) production and can lead to a hypoestrogenic state;
        - Their use is often limited due to side-effects e.g. irregular bleeding, osteoporosis, flushing and sweating episodes secondary to the induced '**hypoestrogenic state**';
        - Due to their side-effects, they are recommended for <6 months use only. Addition of Hormone Replacement Therapy (HRT) can *also* be considered to counter their side effects.
    - Endometrial ablation;
        - This surgical procedure destroys superficial endometrial lining of uterus to prevent regeneration;
        - MBL reduction upto 90%— very effective and is recommended *before choosing an elective hysterectomy*;
        - Transcervical resection of endometrium with *electrical diathermy loop or roller-ball ablation* are older 1st generation techniques;
        - Second generation newer techniques include *impedence controlled endometrial*

ablation, thermal uterine balloon therapy, and microwave ablation;

- Complications include risk of uterine perforation, haemorrhage, fluid overload, infection etc.

- Uterine artery embolization, myomectomy or transcervical resection of fibroid can be considered before hysterectomy in cases of fibroid uterus.
- Hysterectomy (*more details in Chapter 15: Common Gynecological Procedures*);
  - It is the removal of the uterus. A bilateral salpingo-oopherectomy (BSO) is a procedure where *both ovaries and fallopian tubes* are removed.
  - Subtotal abdominal hysterectomy (STAH) is removal of the uterus while the cervix remains. This is carried out when the patient states this as her preference or when adhesions prevent safe removal of the cervix.
  - Total abdominal hysterectomy (TAH) is removal of uterus along with cervix. This procedure carries a slightly higher risk of bladder injury.
  - It can be performed by abdominal approach, vaginal approach, or laparoscopically. *STAH, however, can not be performed via the vaginal approach*.

- Reassurance and counselling in most cases has a positive impact on quality of life, when a causative factor is not found.

iii) Dysmenorrhea

Dysmenorrhea is defined as pain during menstruation. It may occur without any identifiable organic pathology ('primary dysmenorrhea', *very common*), or may occur as secondary to;

- Uterine fibroids;
- Endometriosis (presence of endometrial tissue outside uterus) and Adenomyosis (presence of endometrial tissue within the myometrium of uterus);
- Pelvic inflammatory disease (PID);
- Cervical stenosis and hematometra (= *uterus distended due to blood inside, rarely*).

Early detection and management of these conditions is important for preventing complications.

a) Clincal Evaluation

Although dysmenorrhea can be common symptom, its severity should be assessed on historic evaluation;

- Presence of vaginal discharge;
- Need for analgesic medication during periods;
- Time taken off work or school;
- Presence of dyschezia— pain during defecation;
- Presence of dyspareunia— pain during sexual intercourse.

Physical examination findings may identify *certain characteristic signs*;

- Identification of an adnexal mass as manifestation of fibroid uterus or endometriosis— e.g. endometriomas, or chocolate ovarian cysts;
- A retroflexed fixed uterus (due to adhesions of endometriosis);
- Digital rectal examination may show tenderness/nodules in pouch of douglas (endometriotic nodules).

b) Investigations

- High vaginal swabs (HVS) and endocervical swabs (for PID);
- U/S scan may show an enlarged uterus with heterogenous texture (suggestive of adenomyosis);
- Diagnostic laparoscopy is gold-standard test for detection of endometriosis, but is relatively invasive;
- Cervical stenosis can be investigated by hysteroscopy but is a rare cause of dysmenorrhea, hence hysteroscopy is not a routine investigation in the workup.

c) Management

- Warm compresses;
- Lifestyle changes: low fat and vegetarian diet, exercise;
- NSAIDs e.g. mafenamic acid;
- LNG-IUS (effective for cases with endometriosis and adenomyosis);
- COCPs;
- GnRH analogues.

Ovulation suppression by COCPs or GnRH analogues and hysterectomy are considered for resistant cases.

iv) Oligomenorrhea and Amenorrhea

When menstruation occurs at intervals longer than 35 days, it is termed **oligomenorrhea**.

Amenorrhea is the absence of menstruation. It can be of two types;

- Primary Amenorrhea (failure to menstruate by 16 years of age in a ***phenotypic female***);
- Secondary Amenorrhea (absence of menstruation for ≥ 6 months during reproductive age, not due to pregnancy[1], lactation[2] or menopause[3]).

a) Aetiology

Anatomical abnormalities;

- Genital tract abnormalities;
    - Mullerian agenesis;
    - Vaginal agenesis;
    - Transverse vaginal septum;
    - Imperforate hymen.
- Asherman's syndrome (post-uterine curretage intrauterine adhesions, preventing menstruation).

*In conditions such as vaginal agenesis, transverse vaginal septum and imperforate hymen, menstrual discharge can not escape from the genital tract. This is termed **cryptomenorrhea** (vs. amenorrhea).*

Gonadal disorders;

- Anovulation;
- Premature ovarian failure (**POF**, cessation of menstruation before 40 years of age). This can be result of;
    - Autoimmune disease;
    - History of chemotherapy or radiation;
    - Chromosomal disorders e.g. Turner's mosaicism state (i.e. 46XO/46XX configuration).
- Gonadal dysgenesis.

Disorders of hypothalamic-pituitary axis (HPA);

- Disruption of HPA by stress, eating disorders, or excessive exercise;
- Hypothalamic compression by craniopharyngiomas or gliomas— that block dopamine *thus releving dopamine's inhibitory action of prolactin*;
- Head injury;
- Kallman's syndrome— 'anosmia with hypogonadotrophic hypogonadism' is a classic description;
- Infiltrative disease of HPA, e.g. sarcoidosis, tuberculosis etc;
- Drugs that disrupt HPA e.g. progestogens, HRT, dopamine antagonists etc. *Contraceptive medications work by inhibiting pituitary gonadotropin secretion. Therefore, it can take some time for menses to get regular after their discontinuation. This phenomenon is called **post-pill pituitary insensitivity;***
- Severe depression or acute or chronic illness may also be contributory factors;

- Pituitary tumors (prolactinoma most common);
- Post-partum Sheehan's syndrome— refers to ischemic pituitary necrosis as a result of prolonged hypotension after obstetric hemorrhage.

b) Clinical Evaluation

Table. Clinical evaluation of aetiology of oligo- and amenorrhea.

Historical information required	**Relevant factors**	**Possible diagnoses**
Developmental history including menarche	Delayed/incomplete	Congenital malformation, or chromosomal abnormality
Menstrual history	Oligomenorrhoea Secondary amenorrhoea	PCOS POF
Cyclical symptoms	Cyclical pain without menstruation	Congenital malformation Imperforate hymen
Weight	Dramatic weight loss Difficulty losing weight	Hypothalamic malfunction PCOS
Reproductive history	Infertility	PCOS Congenital malformation
Hair growth	Hirsutism	PCOS
Lifestyle	Exercise, stress	Hypothalamic malfunction
Past medical history	Systemic diseases, e.g. sarcoidosis	Hypothalamic malfunction
Past surgical history	Evacuation of uterus	Asherman's
Drug history	Dopamine agonists, HRT	Hypothalamic malfunction
Headache		Pituitary adenoma
Galactorrhoea		Prolactinoma
Visual disturbance		Pituitary adenoma

Physical examination should be done to assess;

- Body Mass Index (BMI);
- Development of secondary sexual characteristics;
- Signs of other endocrine dysfunction;
- Pelvis/abdominal mass;
- Genital tract anomalies via vaginal speculum examination;
- Visual fields (if suggested by history).

c) Investigations and workup

The best initial test is a β-hCG level to rule out **gestational amenorrhea**;

Suggested by history, relevant investigations can be ordered;

- U/S of the genital tract to detect anomalies;
- Levels of FSH and LH on day 2-3 of cycle, and U/S of the ovaries for **PCOS**— *LH:FSH ratio ≥ 2:1 is higly suggestive*;
- Thyroid profile;
- Prolactin levels for prolactin-producing tumors or drug-induced hyperprolactinemia;
- MRI of the pituitary gland for adenomas;

- A raised FSH level indicates of primary ovarian failure or POF (if age ≤ 40 years);
- Karyotyping for turner syndrome (46XO or 46XO/46XX mosaicism);
- Hysteroscopy for asherman's syndrome adhesions and cervical stenosis.

d) Progestogen challenge test (PCT)

PCT or progesterone stimulation test (**PST**) is often employed to determine whether uterus responds to progestogen withdrawal in affected individuals.

Medroxyprogesterone acetate 5 mg is given daily for 5 days;

- On stopping after 5 days, bleeding will occur if there is sufficient circulating estradiol (>150 pmol/L);
- If menstrual bleeding occurs within 7 days— the test is positive, and clomifene is likely to benefit and induce ovulation;
- If no bleeding— i.e. a negative PCT is an indication for FSH/LH levels (see Algorithm below).

This test is somewhat an indirect determination whether circulating estradiol levels in blood are above a critically low level. This aids in workup of individuals affected with secondary amenorrhea (see Figure).

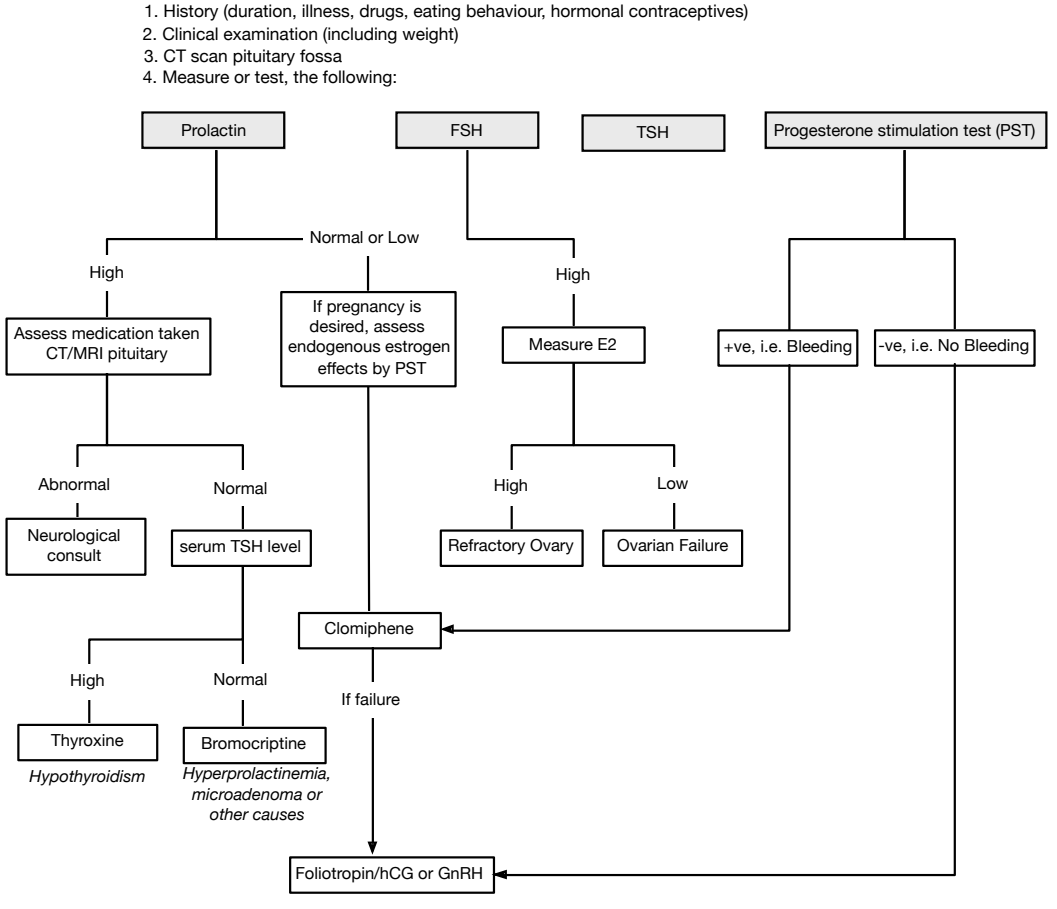


Figure. Algorithmic approach to workup of secondary amenorrhea. *E2: Estradiol.*

e) Treatment

Treatment is mainly centered around the cause (*see Table)*.

Table. Summary of oligo- and amenorrhea and management options.

Causes of oligo-/amenorrhea	**Management**
Low BMI	Dietary advice and support
Hypothalamic lesions, e.g. glioma	Surgery
Hyperprolactinaemia/prolactinoma	Dopamine agonist (e.g. cabergoline or bromocriptine) or surgery if medication fails
PCOS	See below
POF	HRT or COCPs
Asherman's Syndrome	Adhesiolysis and IUD insertion at time of hysteroscopy (to prevent recurrence of adhesions)
Cervical stenosis	Hysteroscopy and cervical dilatation

v) Polycystic ovarian syndrome (PCOS)

PCOS is a syndrome of ovarian dysfunction. It is classically described as a triad of menstrual abnormalities (oligomenorrhea or anovulatory cycles), cystic ovaries and hyperandrogenism.

PCOS is the most common cause of **anovulatory infertility**, affecting around 6–10% of premenopausal women.

a) Aetiology

Its etiological basis is unclear; however, research suggests multiple factors may be involved. These include;

- Positive family history— a theory about *in utero* 'programming' of fetal ovary has also been described;
- Insulin resistance is also present in most women with PCOS— a complex interplay of high-insulin levels has been described that leads to ↑ androgen levels.

b) Clinical features

It can be asymptomatic, or it may present with subfertility;

- Oligomenorrhoea or amenorrhoea— most common feature (associated with chronic anovulation);
- Signs of androgen excess— hirsutism, acne;
- Obesity;
- Acanthosis nigricans— increased velvety skin pigmentation in axillae and other flexural surfaces.

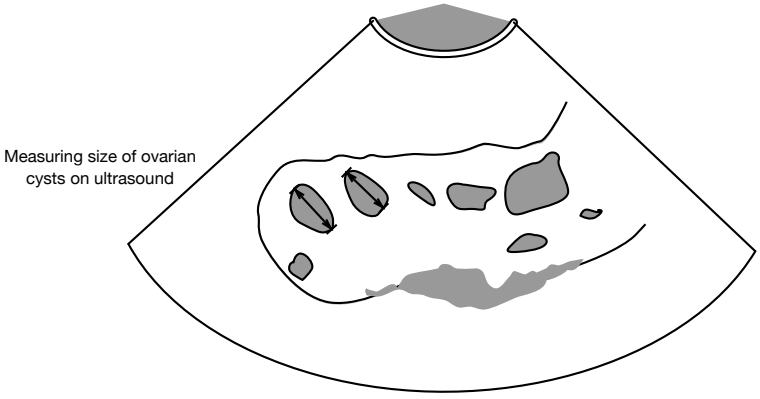


Figure. Illustration of polycystic ovaries on a transvaginal ultrasound scan (TVUSS).

c) Investigstions and diagnosis

Elevated serum LH levels, biochemical evidence of hyperandrogenism and raised insulin resistance are also common features.

As polycystic ovaries can be present in upto 20% of normal females with normal androgen levels and regular menses, diagnosis here is aided by the '***Rotterdam criteria***'. A positive diagnosis is likely if there are ≥ 2 of the following features;

- Oligomenorrhoea or anovulation;
- Clinical and/or biochemical hyperandrogenism;
- Polycystic ovaries on ultrasound— ***a mean of ≥ 12 follicles*** measuring 2-9 mm in diameter in both ovaries.

However, other causes must **also** be excluded, e.g. congenital adrenal hyperplasia, androgen-secreting tumors and Cushing's syndrome— making PCOS a diagnosis of relative exclusion.

d) Management

Depends on the symptoms, past history, underlying cause and the wishes of the woman.

In asymptomatic individuals, a conservative approach without targeted management can be considered;

- Improving lifestyle and health, with particular attention to current eating behaviour and exercise;
- Counselling about increased time needed for spontaneous pregnancy and ↑ rate of miscarriage and possible need for assisted conception.

If the woman wishes to conceive, she should be screened for glucose intolerance before pregnancy;

- Metformin can be considered— acts by ↓ hepatic glucose production and ↑ peripheral tissues' sensitivity to insulin ***pre-pregnancy***.
- On the other hand, clomifene is **most effective for** inducing ovulation.

For targeted management of PCOS, options are;

- Monophasic oral contraceptives (*see Chapter 5: Fertility control*)— reduce further 'cyst' formation, acne, and lower androgens;
- Metformin— improves insulin resistance, fertility, aids weight reduction and reduces miscarriage;
- Spironolactone— blocks androgen effects on the body, slightly improves insulin resistance.

e) Complications

Other common complications seen with PCOS include;

- Acne and hirsutism;
- Obesity and ↑ risk of type 2 diabetes and cardiovascular events;
- Relatively ↑ risk of developing endometrial carcinoma if the anovulation persists for a number of years.

vi) Management of other disturbances of menstruation

Epimenorrhoea or polymenorrhoea— refers to menstruation occurring at intervals <21 days. Here the bothersome symptoms can be regulated by prescribing an oral contraceptive.

Hypomenorrhoea— refers to relatively scanty menstruation in menstrual cycles is most commonly observed in women taking oral contraceptives. Affected women can be reassured that it has no abnormal consequences.

Premenstrual or postmenstrual staining— refers to slight menstrual staining occurring 2–3 days before or following the end of a normal menstrual period.

- It is thought to be associated with a complex interplay between relatively early decrease of estrogen production from corpus luteum despite continued production of progesterone.
- The condition has no sinister consequences and affected individuals should be reassured.
- Management, if needed, is with a COC or norethisterone 2.5mg from days 20 to 25 of menstrual cycle for a few months.
- In other cases, evaluation for endometriosis can be considered for its rare association with the disorder.

CHAPTER 4 INFECTIONS OF GENITOURINARY TRACT

(I) Anatomy and physiology

i) Epithelia

The genital tract in females is lined by epithelial lining which varies as;

- The external genitalia, i.e. the labia— lined by stratified squamous epithelium that is keratinized.
- The vaginal canal;
    - Is lined by non-keratinized stratified squamous epithelium abundant in glycogen;
    - Bartholin's glands have mucinous secretions and are located bilaterally at the posterolateral vestibule. Their ducts empty secretions into vestibule at approx. 4 and 8 o'clock positions;
    - However, contrary to previous belief, most of the lubrication of the vagina during sexual arousal comes from transudation of fluid from the lamina propria underneath vaginal epithelium, mixed with cervical gland secretions *and not from Bartholin's glands*.
- The cervix;
    - The ectocervix is lined by the same stratified squamous epithelium as the vaginal canal;
    - The endocervix is, however, lined by tall-columnar epithelium with mucinous glands;
    - The transformation zone of this change in epithelium lies at the cervical os (subject to change in pre-menarche, after puberty, and post-menopause, *details discussed later*).
- The uterus;
    - Is lined by columnar epithelium (partially ciliated). Endometrium also has characteristic tubular mucinous glands;
    - It consists of two layers— stratum functionalis and stratum basalis. The latter has the ability to regenerate under hormonal control.
- The fallopian tubes;
    - Are lined by columnar epithelium (ciliated);
    - The cilia help the sperms ascend and facilitate the passage of ova down to the uterus.
- The ovaries are lined by mesothelium covering.

ii) Normal flora and discharge

The lactobacilli are the predominant normal flora in the vagina;

- They feed on the transudates of glycogen and help maintain a acidic environment of pH 3.5 to 4.5;
- After menopause, the epithelium becomes atrophic, the lactobacilli population decreases making a relatively alkaline pH of 7.0.

Physiological vaginal discharge can occur under hormonal influence during menstrual cycles. Its characteristics include;

- White → yellowish colour due to oxidation on contact with air;
- It consists of mucous, desquamated epithelial cells, bacteria (lactobacillius) and fluid;
- Thick mucinous or thin elastic cervical discharge under influence of estrogen or progesterone is also observed in periovulatory and luteal phases of menstrual cycle (*see Chapter 3: The menstrual cycle, its disorders and diseases → cervical cycle*).

(II) Lower Genital Tract Infections

Ascending vaginal infection is controlled to some extent by the following mechanisms;

- The vaginal walls lie in apposition and the vaginal secretions are acidic, which inhibits bacterial growth;

- Cervical mucus forms a meshwork which limits upward spread of infections except at time of ovulation;
- As is known, the endometrium is also shed each month during menstruation.

However, if the cervix is infected directly, the above mechanisms are less effective.

i) Bartholinitis

Bartholinitis— refers to infection of Bartholin's gland;

- The infection is usually due to *Escherichia coli* or staphylococci but may follow *Neisseria gonorrhoeae* or *Chlamydia trachomatis* infection;
- In the acute stage both the duct and the gland are involved. Untreated infections have a tendency to suppurate but can also subside spontaneously.

In acute bartholinitis, there is acute discomfort in the area of the gland. A reddened, tender swelling can be observed beneath the posterior part of labium majus *on the affected side* (see Figure).

Treatment consists of excluding sexually transmitted infections (STIs), analgesics and broad-spectrum antibiotic.

If an abscess has formed, it should be marsupialized. This involves;

- An elliptical piece of the vagina and the abscess wall, just inside the hymen, is removed;
- The vaginal and abscess walls are sutured to maintain patency ± insertion of a small drain.

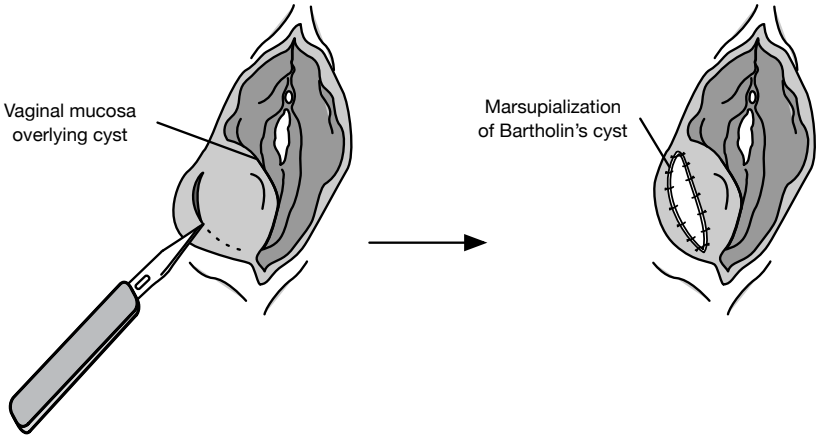


Figure. Illustration of a right-sided Bartholin's **abscess** and its marsupialization procedure.

Occasionally the gland becomes chronically enlarged following an inflammatory conglutination of the duct epithelium, to form a Bartholin's cyst. These cysts have a tendency to bleed and thus are often preferrably treated with a specialized "Word catheter" *instead of marsupialization* (see Figure).

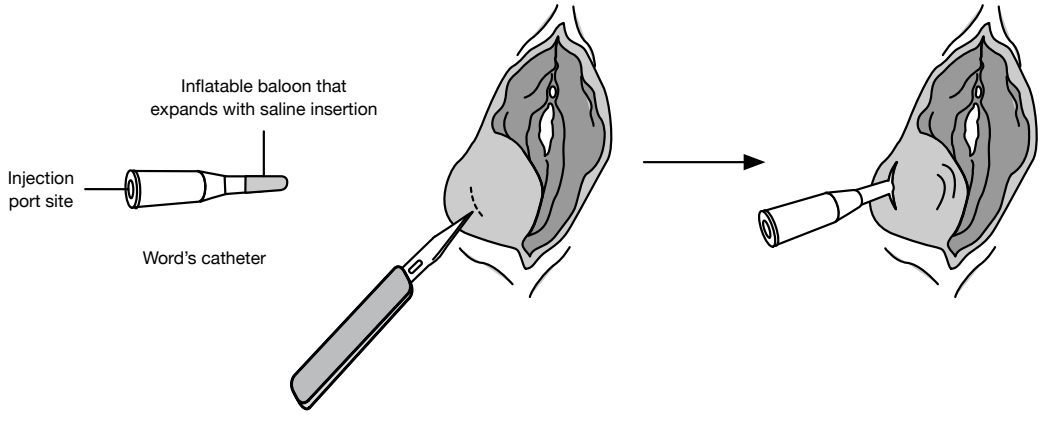


Figure. Illustration of a Word's catheter and method of insertion to a right-sided Batholin's **cyst**.

Insertion of Word's catheter in a Bartholin's cyst allows proper drainage and ***reduces recurrence***.

ii) Vulvovaginal Candidiasis

It is one of the most common lower genital tract infections.

Most common aetiological organism in upto 90% cases— *Candidia albicans.* Infections caused by *C. tropicalis, C. glabrata, C. krusei and C. parapsilosis* can be relatively more severe or recurrent.

a) Predisposing conditions

Candidal infections tend to occur more often in individuals who have altered normal flora, or a relatively immunosuppressed state, e.g;

- Pregnancy;
- Diabetes Mellitus;
- Use of broad-spectrum antibiotics;
- High-dose Combined Oral Contraceptives;
- Hormone Replacement Therapy (HRT);
- Other immunosuppressed states, e.g. HIV-Infection.

b) Clinical features

Vulval itching and soreness is commonly seen with vulvovaginal infections. In addition, there may be;

- Thick curdy vaginal discharge;
- Dyspareunia and dysuria;

On examination, vulval oedema, vulval excoriation, redness and erythema may be observed (ΔΔ include *other eczematous skin diseases*).

c) Investigations

- Vaginal pH is normal (an important diagnostic clue with high specificity relative to other causes of vulvovaginitis, e.g. trichomoniasis or bacterial vaginosis);
- KOH wet film examination of vaginal discharge under microscope visualizes spores and hyphae;
- Fungal culture by direct plating;
- In severe/**recurrent cases (≥ 4 episodes of infection/year or moderate-heavy growth of *C. albicans*)**;
    - Pregnancy-testing (this is a predisposing condition, and is also a contraindication for use of certain systemic antifungals, i.e. oral fluconazole but not their topical applications);
    - Workup for diabetes mellitus;
    - Species-typing may be needed, as *C. krusei* can be resistant to fluconazole antifungal.

d) Treatment

Inviduals that are asymptomatic do not need treatment (includes asymptomatic pregnant females).

Those having symptoms should be;

- Counselled against use of soaps, perfumes, synthetic underwear, and **douching**;
- Antifungal therapy options in uncomplicated infections;
    - Local application of imidazoles (e.g. clotrimazole, miconazole etc.) via creams/pessaries. Pessary clotrimazole 500mg use for 1 day or 100mg use for 6 consecutive days, **or**;
    - Nystatin antifungal cream/pessary, **or**;
    - Oral fluconazole 150mg single dose, or oral Itraconazole 200mg twice a day for 1 day.
    - There is no evidence to support any benefit in treating an asymptomatic male partner.
- Antifungal therapy in severe/recurrent cases;
    - Such cases need maintainence in addition to treatment of acute infection;
    - Fluconazole 150 mg is given in three doses orally every 72 hours followed by a mainte-

nance dose of 150 mg weekly for six months. (90% cure rate at 6 months);

- If pregnant, then ***a topical imidazole should be used instead*** for 2 weeks for induction, followed by a weekly dose of clotrimazole 500mg for 6-8 weeks. Oral imidazoles are contraindicated in pregnancy.

- Probiotic therapy (i.e. oral/vaginal lactobacillus) have no proven use in evidence-based medicine.

iii) Trichomoniasis

This infection can occur in lower genital tract and urinary tract causing vulvovaginitis or UTI. The causative organism *Trichomonas vaginalis,* a flagellated protozoan, is usually sexually transmitted.

a) Signs and symptoms

The infection may be asymptomatic— carriers, or it may present with;

- Vulval soreness and itching;
- Foul smelling vaginal discharge, sometimes *frothy yellowish green* in nature;
- In cases of urinary tract involvemend, dysuria may be encountered;
- On speculum examination, a characteristic appearance of strawberry cervix is often observed. This is due to presence of punctate haemorrhages.

b) Investigations

Both partners should be tested and also screened for other sexually transmitted infections;

- Microscopy of vaginal discharge;
- Wet mount (vaginal discharge mixed with saline under a microscope) shows motile protozoal organism with the typical flagellae (60-70% sensitive);
- Culture of discharge requires specialized Finnberg–Whittington or Diamond's media.

c) Treatment

Both partners should be treated;

- Metronidazole single oral dose of 2 g, or 400 mg twice daily for 7 days are equally effective or tinidazole single oral dose of 2 g;
- Treatment failure occur if the partner has not been treated, with compliance issues, or with resistance.

iv) Bacterial Vaginosis (BV)

It occurs due **overgrowth** of anaerobic species with simultaneous reduction of lactobacillus flora in the lower genital tract. This brings about changes in the vaginal pH to become ***more alkaline*** (4.5 to 7.0).

Aetiological organisms— ***Gardnerella vaginalis*** (*most common cause*), *Mycoplasma hominis*, Bacteroides spp. and Mobilincus spp.

a) Clinical Features

The infection may be asymptomatic, or it may present with;

- Foul-smelling (fishy malodour) vaginal discharge with **no obvious inflammation (minimal vulvar itching/soreness);**
- More prominent symptoms during and following menstruation.

On examination, creamy or greyish-white vaginal discharge commonly adherent to the wall of the vagina is observed.

b) Investigations and diagnosis

Gardnerella vaginalis is commonly isolated in women with no clinical signs of infection, so the diagnosis should be symptomatically correlated.

For this purpose, several diagnostic criteria are described to aid in diagnosis;

c) Amsel criteria (≥ 3 out of 4 needed for diagnosis— most commonly used)

1. Presence of clue cells on microscopic examination. Clue cells are epithelial cells which are covered with bacteria giving a characteristic stippled appearance on examination.
2. Creamy greyish white discharge which is seen on naked eye examination.
3. Vaginal pH of more than 4.5.
4. Release of a characteristic fishy odour on addition of alkali: 10 per cent potassium hydroxide.

d) Hay/Ison criteria (requires microscopy)

- Grade 1. Normal: Lactobacillus predominate.
- Grade 2. Intermediate: Lactobacillus seen with the presence of Gardnerella and/or Mobiluncus spp.
- Grade 3. Bacterial vaginosis: Lactobacilli absent or markedly reduced with predominance of Gardnerella and/or Mobiluncus spp.

e) Nugent criteria

This criterion is based on the proportion of anaerobic species on microscopy. It gives a quantitative score between 0 and 10;

- Less than 4: Normal
- 4 to 6: Intermediate
- **More than 6**: Bacterial vaginosis

f) Management

Metronidazole orally 400 mg BD for 5 days. A single oral dose of 2g or topical intravaginal gel can also be used instead as alternatives.

Another alternative is clindamycin **for 7 days** as;

- 300 mg PO x twice daily, or;
- 5g of 2% clindamycin cream intravaginally x once daily, preferably at bedtime.
- There, however, is an ↑ risk of contraceptive failure and **psuedomembranous colitis** with clindamycin.

Bacterial vaginosis is associated with increased risk of preterm labor, and late second-trimester miscarriages. Metronidazole is safe to use in pregnancies if BV is suspected.

(III) Sexually Transmitted Diseases (STDs)

i) Gonorrhea

It is a sexually transmitted infection. The aetiological organism *Neisseria gonorrhoea* has a predilection for cuboidal-columnar mucous epithelium found in cervix, urethra, rectum, and oropharynx and spread via sexual contact.

a) Clinical features

The infection may be asymptomatic, or it may present as;

- Increased vaginal discharge with lower abdominal/pelvic pain;
- Dysuria with urethral discharge;
- Proctitis with rectal pain and discharge ± bleeding;
- Mucopurulent urethral discharge;
- Endocervical mucopurulent discharge and contact bleeding;
- On examination, pelvic tenderness with cervical excitation may be observed (in cases of ascent of infection to cervix). *This is in contrast to* ***Chandelier sign*** *seen in PID.*

b) Investigations

- Gram-staining (*Neisseria gonorrhoea* is a gram-negative diplococcus);
- Culture of endocervical/rectal/pharyngeal swabs on Thayer-Martin medium (inhibits growth of other organisms);
- Nucleic acid amplification testing (NAAT)— *highly sensitive compared to others*;
- Newer nucleic acid hybridization testing.

c) Treatment

Both partners should be tested and screened for other STDs. Effective treatment can be achieved by either of;

- Single oral dose of cefixime 400 mg, or;
- Single intramuscular dose of ceftriaxone 250 mg, or;
- Single intramuscular dose of spectinomycin 2 g, or;
- Single oral dose of ciprofloxacin 500 mg or ofloxacin 400 mg, or;
- Ampicillin 2 g or amoxycillin 1 g with probenecid 2 gm as a single oral dose.

In pregnant females, penicillins and cephalosporins are safe. *Tetracyclines and quinolones are* ***contraindicated***.

ii) Chlamydia

It is another sexually transmitted infection affecting the columnar epithelium of the genital tract.

Infection occurs elementary bodies of chlamydia enter cells through specific receptors. Once inside, they form inclusion bodies which divide by binary fission. These then reform into elementary bodies and get released from the cell. This destroys the cell with surrounding inflammatory response.

Aetiological organism: *Chlamydia trachomatis*, an obligate intracellular bacterium, has 15 serovars (A, B, Ba, C, D, E, F, G, H, I, J, K, L1, L2 and L3) capable of human infection;

- Serovars A–C infect the conjunctiva of eyes, potentially leading to ***trachoma of conjunctivum***;
- Serovars D–K infect the genitourinary system;
- Lymphogranuloma venereum is also a form of chlamydial infection by strains L1–L3 cause rectal infection and proctitis;

Chlamydia psittaci and *Chlamydia pneumonia*, infect the lungs causing pneumonia.

a) Clinical features

In the majority of cases, it is asymptomatic with slow and insidiously progressive infection. Symptoms include;

- Vaginal discharge and lower abdominal pain;
- Postcoital bleeding;
- Intermenstrual bleeding;
- Mucopurulent cervical discharge with contact bleeding;
- Dysuria with urethral discharge.

Untreated chlamydial infections tend to complicate. These complications include;

- Pelvic Inflammatory Disease (PID);
- Perihepatitis— Fitz-Hugh-Curtis Syndrome;
- Conjunctivitis and pneumonia in newborns (with vertical transmission);
- Conjunctivitis in adults;
- Reactive arthritis (Reiter's syndrome).

b) Investigations

Due to infective complications, individuals and their partners should be investigated with;

- Nucleic acid amplification technique (NAAT) tests are >90% sensitive. *Aptima Combo 2* and *BD Probetec* are the recommended tests for chlamydial infection;
- Real-time polymerase chain reaction (RT-PCR);
- Chlamydial culture (not recommended due to low sensitivity).

c) Treatment

Abstinence from any form of sexual contact till all partners are treated is recommended. Treatment is with:

- Doxycycline 100 mg orally twice a day – 7days, or;
- Erythromycin 500 mg orally four times a day – 7 days, or;
- Amoxicillin 500 mg three times a day – 7 days, or;
- Ofloxacin 200 mg orally twice a day or 400 mg once a day – 7 days.

In pregnant females, azithromycin 1 g orally in a single dose is the ***recommended treatment.***

Test of cure should be performed a minimum of 5 weeks after initiation of treatment, use of condoms should be encouraged to minimize STD transmissions.

iii) Genital Herpes

It is a common sexually-transmitted viral infection of the lower genital tract. Often infected individuals asymptomatically shed the virus.

Aetiological organism: Herpes simplex virus (HSV), has two forms. HSV-1 has **relative tropism** for oral cavity and causes oral cold cores while HSV-2 causes genital herpes. *However, this does not occur as a rule*.

a) Clinical Features

The first clinical attack of genital herpes is usually worse than the recurrences;

- The inner surfaces of the labia majora are mostly infected;
- There is a short period of itching/burning before painful, reddish papules appear which become vesicular/blisters within 24 hours. The blisters may ulcerate;
- Micturition may be very painful and secondary staphylococcal infection may occur in shallow ulcers;
- Over 5 days the ulcers crust over. Healing completes in about 7–12 days after the appearance of the blisters for **a primary infection** and lesser for recurrences. During this time, and intermittently, the virus is shed from the infected area and in vaginal secretions;
- The virus also enters the sensory nerves supplying the affected area, and tracks to lie dormant in the dorsal root ganglion. Reactivation attack may occur in times of stress or immunosuppression;
- Genital herpes recurrences wane as time passes and the attacks also become less severe;

Recurrences are more commonly observed in the luteal phase of the menstrual cycle, if the woman has other sexually transmitted infections.

b) Investigations

- Tzanck smear (=staining with Wright or Giemsa) of lesions— **multinucleated giant cells** on microscopy;
- For early vesicular lesions, vesicles should be pricked and vesicular fluid and the ulcers rubbed with a cotton tipped-bud for viral culture (*most accurate test*);
- For older lesions that have been scratched, testing by PCR is more sensitive;
- Serology by means of HSV type-specific IgG antibodies, (i.e. anti-HSV1 or anti-HSV2 IgG) are gaining widespread use in certain parts of the world;
    - When correlated with culture/PCR—these can be used to determine if the current infection is a *recurrence*;
    - When virologic culture/PCR testing *on genital secretions* detects a subtype of HSV which is the same as the type-specific IgG antibodies found *in serum*— it is suggestive of **recurrence**.

c) Management

- Counselling about long-term course of infection;
- Hand hygiene should be practiced to prevent transmission;
- Local applications of ice or anaesthetic gel for relief;
- Suprapubic catherterization may be considered for those individuals with severe dysuria or retention;
- Antiviral therapy;
    - Initial or recurrent HSV infection can be treated with oral acyclovir but is of benefit only if treatment is given within the first 72 hours. For immunosuppressed patients, it can also be given after 72 hours;
    - **Suppressive antiviral therapy** can be chosen for individuals having ≥ 5 lasting attacks/year . This involves use of oral acyclovir (or famciclovir or valacyclovir) daily for 6-12 months;
    - Use of foscanet is limited to treating HSV resistant to acyclovir.
- *A C-section is recommended if the mother has symptoms or signs of active genital herpes, or its prodrome, at the time of delivery to minimize neonatal transmission* (see Chapter 27: Infections in pregnancy).

iv) Condylomata acuminata

Also known as ***Genital warts,*** this sexually-transmitted viral infection causes characteristic warty-outgrowth of the skin of perineal region;

- Aetiological organism— Human papilloma virus (HPV) subtypes 6, 11, 16 and 18;
- HPV has no systemic illness and presents as characteristic cauliflower-like outgrowths in the perineal area, vagina and cervix;
- Additionally, subtypes 16 and 18 are linked with development of cervical adenocarcinoma. Because of this association, repeated dysplasia on pap smears in sexually active women prompts HPV testing;
- Genital warts on skin may be treated with podophyllotoxin application twice/week. Imiquimod cream 5% can be applied before bedtime so that it is left on the skin for 6–10 hours, three times/week;
- For resistant warts, diathermy laser or cryotherapy may be used.

v) Syphilis

It is a sexually transmitted disease syndrome caused by bacterium *Treponema pallidum*.

a) Clinical features

- The first sign of infection (primary infection) manifests as a ***painless hard chancre ± painless regional lymphadenopathy*** near the site of inoculation ~ 3 weeks after exposure. It is so called due to induration around the lesion. Sometimes, the cervix is involved as the site of primary infection and may go unnoticed. Untreated, this may disappear in approx. 3 weeks;
- Secondary syphilitic manifestations come about when treponemes disseminate into the body ~ 6 weeks after. This results in a *systemic syndrome* that may have malaise, fever, generalized lymphadenopathy, and cutaneous lesions such as condylomata lata, and **rash on palms and soles**. **Condylomata lata** are cauliflower-like wet lesions in genital areas or mouth that are teeming with treponemes;
- Untreated secondary syphilis may progress onto tertiary phase of infection or may become latent (= no active manifestations of infection);
- Tertiary syphilis is characterized by gummas, aortic obliterative endarteritis, and neurosyphilis. This phase of infection occurs after chronic untreated infection.

b) Investigations

- Most accurate test— dark-field microscopic visualization of treponemes (spiral movements) in chancres or secondary syphilis cutaneous lesions.
- Serologic testing is used in the absence of microscopy or later stages of infection. There are two forms of serologic testing— **specific tremonemal testing** (i.e. MHA-TP, FTA-ABS and EIAs), and **non-specific testing** (i.e. VDRL and RPR);

  - Microhemagglutination Assay-*Treponema pallidum* (MHA-TP), Flourescent Treponemal Antigen-Antibody (FTA-ABS) and Enzyme Immunoassays (EIAs), test antibodies that develop as a result of exposure to *T. pallidum*.
  - Venereal Disease Research Lab (VDRL), and Rapid Plasma Reagin (RPR) test antibodies directed against the cardiolipin-cholesterol-lecithin antigen (a.k.a. "reagin"). These are highly sensitive *but always need confirmatory testing* with specific treponemal testing for diagnosis.
- For screening individuals (e.g. pregnant women), EIAs that detect specific IgG and IgM antibodies is gaining popularity;
  - EIAs are replacing the **previously used** *non-specific antibodies + treponemal-specific antibody testing combination* for syphilis screening;
  - EIAs are >98% sensitive and >99% specific;
  - However, none of these serological tests will detect syphilis in its incubation stage, which may last for an average of 25 days.

c) Treatment

- Antibiotic therapy is the mainstay of treatment and can be with either of;
  - Procaine penicillin 1.2 million units daily I/M x 12 days or;
  - Benzathine penicillin 2.4 million units I/M repeated after 7 days, or;
  - Doxycycline 100 mg bd x 14 days, or;
  - Erythromycin 500 mg qds x 14 days.
- **Penicllin**, however, ***is the only form of treatment for pregnant women and newborns***. If the pregnant woman is penicillin-allergic, desensitization with penicillin should be carried out.

vi) Chancroid

This is a sexually transmitted disease, caused by bacterium *Hemophilus ducreyi*;

- It presents as multiple pus-filled papules that become painful shallow ulcers in form of a painful chancre together with suppurative (= pus-forming) regional lymphadenopathy;
- The diagnosis can be made by Isolation of Ducrey's bacillus on biopsy, or specialized culture for this hemophilus bacterium. *However, for practical purposes, this diagnosis is most likely in presence of a painful ulcer that has a negative RPR and no detectable HSV;*
- Can be treated with a single oral dose of Azithromycin 2g. Alternatives include ceftriaxone, and erythromycin.

vii) Granuloma inguinale "Donovanosis"

Donovanosis is very rare;

- The causative gram-negative organism *Klebsiella granulomatis* that produces a ***painless*** *nodule* that may or may not turn into beefy red painless genital ulcer;
- There is spread to the inguinal area producing bilateral soft tissue granulomas that look like lymphadenopathy ***(pseudo-buboes)****;*
- Biopsy of the lesion shows intracellular dark staining organisms (Donovan bodies) in phagocytes or histiocytes. Culture of this organism has low diagnostic yield;
- Treatment is with tetracycline or streptomycin.

(IV) Pelvic Inflammatory Disease (PID)

It is the inflammation and infection of upper reproductive tract, i.e. endocervicitis, endometritis, salpingitis, oophritis along with pelvic peritonitis and subsequently formation of tubo-ovarian and pelvic abscesses.

Multiple aetiological organisms have been implicated. Common are sexually transmitted *Neisseria gonorrhoea* and *Chlamydia trachomatis* infections. Secondary organisms include *Escherichia coli*, group B Streptococcus, Klebsiella, and anaerobes.

i) Clinical Features

As the infection ascends from lower genital tract, subjects develop;

- Pelvic pain, pain during intercourse (dyspareunia);
- Fever ± rigors;
- Vaginal discharge (may be muco-purulent);
- Menometrorrhagia (heavy and intermenstrual bleeding);
- On examination, cervical excitation is observed due to severe tenderness to bimanual examination—termed **Chandelier's sign**. Adnexal or pelvic masses can also be observed.

On the other hand, complicated cases may present with sepsis, or tender pelvic mass e.g. adnexal abcesses and hydrosalpinx (see Figure).

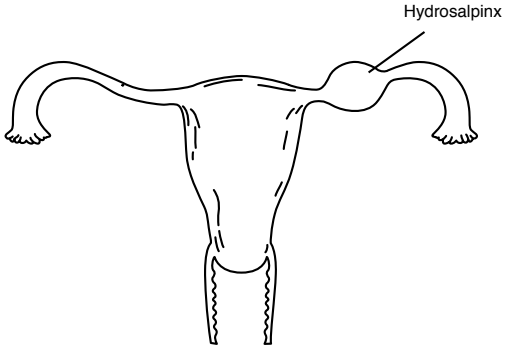


Figure. Illustration of a hydrosalpinx in left fallopian tube.

ii) Investigations

There is low sensitivity for diagnostic testing in PID, *and ectopic pregnancy should always be ruled out*;

- Neutrophilia or in more severe cases, neutropenia;
- Raised inflammatory markers, i.e. CRP and ESR;
- High vaginal/ endocervical swab for culture/sensitivity and chlamydia PCR;
- Pelvic ultrasound for adnexal masses, or free fluid in pelvis (transvaginal U/S has higher sensitivity);
- Culdocentesis fluid for analysis and culture/sensitivity;
- Laparoscopy is gold-standard for diagnosis in difficult cases.

iii) Treatment

Empiric treatment is recommended in clinical suspicion of PID (Green Top Guidelines by RCOG, 2008, updated with British Association for Sexual Health and HIV (BASHH) recommendations, 2011);

- Removal of IUD (intra-uterine contraceptive device), as this can serve as a nidus for infection;
- Contraception cover with barrier methods and COCs (have a protective effect);
- Outpatient treatment in mild disease;
    - Ofloxacin 400 mg PO x BD + Metronidazole 400 mg PO x BD for 14 days;
    - Ceftriaxone 500 mg I/M stat (single dose) + Doxycycline 100 mg PO x BD + Metronidazole 400 mg PO x BD for 14 days.
- Intravenous antibiotics are preferred in clinically severe illness and continued till 24 hours after clinical improvement:
    - Ceftriaxone 2g I/V x OD + Doxycycline 100mg I/V x BD followed by Doxycycline 100mg PO x BD + Metronidazole 400mg PO x BD for 14 days, **or;**
    - Clindamycin 900mg I/V x TDS + Gentamicin IV (2mg/kg loading dose) followed by

1.5mg/kg TDS *in divided doses* followed by ***either*** clindamycin 450mg PO x q6hr ***or*** Doxycycline 100mg PO x BD + Metronidazole 400mg PO x BD to complete 14 days, **or**;

- Ofloxacin 400 mg I/V x BD + Metronidazole 500mg I/V x TID for 14 days.

- In pregnancy;
  - Avoid Doxycycline, gentamycin and ofloxacin— due to *teratogenic potential*;
  - Here, a regimen of combination antibiotics— *cefotaxime* + *azithromycin* + *metronidazole* is better suited.
- CT scaning may be considered and surgical options, i.e. laparoscopy can be performed if there is—
  - Suspicion of pelvic abcess;
  - Need to rule out other abdominopelvic pathologies, e.g. ovarian pathology, appendicitis;
  - No clinical response to therapy.

iv) Complications

- Salpingitis resolves with scarring in the tubal lumen. This produces partial obstruction and pockets that can lead to subfertility and ectopic pregnancy.
- Pelvic peritoneal inflammation leading to tubo-ovarian abscess, distortion of anatomy, and with healing give rise to pelvic adhesions.
- Chlamydial and gonorrheal infections can concomitantly affect liver— **perihepatitis with violin-string appearance** on laparoscopy is diagnostic of ***Fitz-Hugh-Curtis Syndrome***.

-x-

CHAPTER 5 FERTILITY CONTROL

(I) Pearl index

Failure rates are traditionally expressed as the number of failures per **100 woman-years (HWY),** i.e. the number of pregnancies if 100 women were to use the method for one year.

Method of contraception	Failure rate (per 100 woman-years)
Combined oral contraceptive pill	0.1–1
Progestogen-only pill	1–3
Depo-Provera®	0.1–2
Implanon®	0.1
Copper IUD	1–2
Mirena®	0.5
Male condom	2–5
Diaphragm	1–15
Natural family planning	2–3
Vasectomy	0.02
Female sterilization	0.13

Implants, injectables and intrauterine contraception methods are also referred to as long-acting reversible contraception (LARC). This is a key strategy in reducing unplanned pregnancies.

(II) Periodic abstinence/ Natural family planning

- This is avoidance of sexual intercourse during fertile periods of a woman to avoid pregnancy. The fertile period can be calculated via various techniques, e.g;
    - **Observing change in basal body temperature;**

      After ovulation, progesterone raises basal metabolic rate and basal body temperature by 0.5–0.8°F or 0.2–0.4°C during the luteal phase.
    - **Observing change in cervical mucus (Billings' ovulation method);**

      This method is based on recognizing the changes in cervical mucus which becomes copious, thin, clear, slippery and can be stretched between two fingers slowly around the ovulation day and 3 days after. Around the same time, vagina and vulva feel moist. This persists for about 3 days. These are called **'wet days'** and *mark the peak of fertility*.
    - **Keeping track of cycle days**

      Ovulation occurs approximately 14 days before the start of menstruation. Periovulatory period and 5 days before are known as the **fertile period**. Intercourse during this time has a high probability of pregnancy.
    - **Combined approach**

      This involves keeping track of cycle days, body temperature, and cervical mucus to pinpoint fertile period and avoid intercourse during that phase.
- This natural method of family planning is not very effective as it is subjective and operator dependant.

(III) Lactational Amenorrhea Method (LAM)

With exclusive and regular on-demand breastfeeding of an infant, prolactin levels rise in the mother as part of milk-production-release reflex.

This serves to provide contraceptive cover upto 98% if used correctly but is not very reliable.

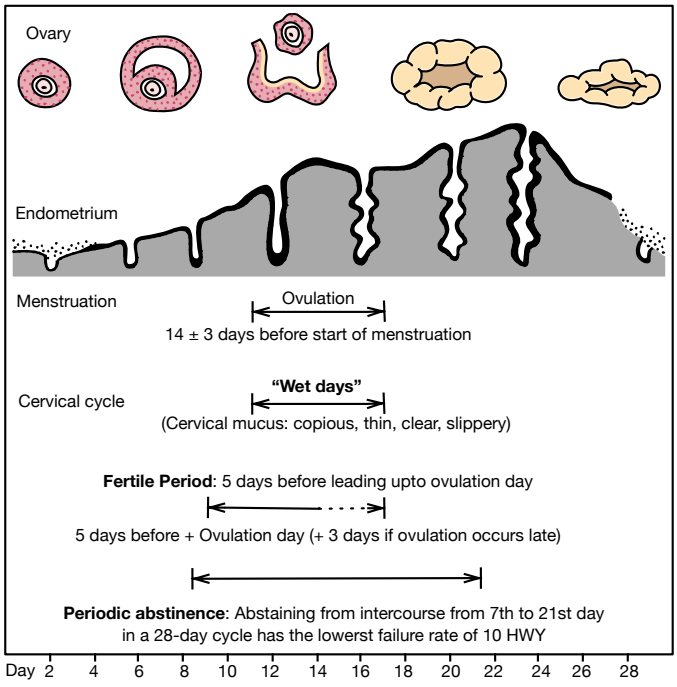


Figure. Fertile period with respect to ovulation and recommended abstinence period for family planning.

(IV) Coitus interruptus

Coitus interruptus or withdrawal method of contraception is a widespread practice of removing the penis from the vagina before ejaculatory emission for *contraception*.

It remains unreliable and combination with emergency contraception (EC, see below) should be considered.

(V) Barrier methods

These create a physical barrier to prevent fertilization. These have added benefit of preventing transmission of sexually transmitted infections (STIs).

i) Condoms

There are condoms for both genders;

- Male condoms are usually made of *latex rubber ± spermicide lubrication*. Hypoallergenic latex and plastic forms without spermicides are also available for those with allergic hypersensitivity;
- Female condoms are made of plastic. Though aesthetically displeasing, but cover whole of vagina and vulva, but they are offer good protection against infections and are less likely to burst;
- Use of a condom is operator-dependant. Additional contraceptive cover may be needed in cases of slippage or bursting during intercourse.

ii) Spermicides

- The famous spermicide **nonoxynol-9** is available in gel, foams, creams, and pessary preparations;
- They are designed to be used with additional barrier methods for higher efficacy;
- There has been a recent concern about increased HIV transmission risk in spermicide users. Individuals with HIV are recommended to avoid their use with anal or vaginal intercourse.

iii) Vaginal diaphragms and cervical caps

Diaphragms and cervical caps are also female-used barriers for contraception. A diaphragm creates a barrier over a larger surface area *relative to a cervical cap* that covers the ectocervix and surrounding area (see Figure);

- The vaginal diaphragm and the cervical cap consist of a thin plastic or latex dome attached to a circular flat, coiled or arching spring rim;
- It is recommended to use them with nonoxynol-9 spermicide preparations inserting the barrier immediately prior to intercourse and removal ≥ 6 hours after intercourse;
- These barrier methods protect against pelvic inflammatory disease (PID) to some extent. However, users are observed to have ↑ predisposion to urinary tract infections.

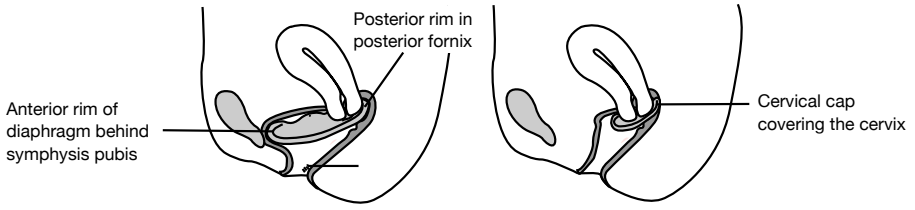


Figure. Illustration of the contraceptive diaphragm (left) and cervical cap (Right).

(VI) Combined hormonal contraceptives

These hormonal preparations consist of Ethinyl Estradiol (EE) and a progestogen (i.e. a synthetic derivative of progesterone);

- These are highly effective (depending on compliance) and can be very beneficial;
- These have both central-acting and peripherally-acting effects. They inhibit ovulation by feedback-inhibition of gonadotropins from the hypothalamus/pituitary glands. Peripherally, they alter the epithelial lining of cervix— ↓ sperm penetration, and induce uterine epithelium to be hostile to implantation.
- They are available in various forms;
    - Combined Oral Contraceptives (OCPs);
    - Injections;
    - Hormonal patch;
    - Combined Contraceptive Vaginal Ring (CCVR).

i) Limitations with combined hormonal contraceptives

- Broad spectrum antibiotics alter COCs-absorption from GI tract. Additional contraceptive measures should be taken during antibiotic therapy and for 1 week thereafter;
- Any woman who smokes must be advised to stop COCs by the age of 35 years;
- Ideally, discontinue COCs 2 months before an elective surgery that predisposes to prolonged immobilization (e.g. pelvic, leg surgery etc.) to ↓ risk of venous thromboembolism;
- Women with positive family history of VTE should always be tested for inherited thrombophilias before starting COCs.

ii) Side-effects

Table. Side effects of combined hormonal contraceptives.

	CNS	**GI**	**Reproductive**	**Breasts**	**Misc.**
Side-effects	Depressed mood Mood swings Headaches	Nausea Weight gain Bloatedness	Breakthrough bleeding Increased vaginal discharge	Breast pains Enlarged breasts	Chloasma (*facial pigmentation worsening on COCs*) Fluid retention

iii) Contraindications to Combined Hormonal Contraceptives

Combined contraceptives are the preferred choice in *young aged healthy* women because of their excellent efficacy and beneficial effects. However, it has contraindications (UK Medical Eligibility Criteria, 2006).

Table. Absolute and relative contraindications to combined hormonal contraceptives.

Absolute Contraindications (*Category 4*)	**Relative Contraindications (*Category 3*)**
Smoking ≥15 cigarettes/day and age ≥35	Smoking (<15 cigarettes/day) and age ≥ 35 years
Breastfeeding <6 weeks postpartum	Breastfeeding until six months postpartum
Multiple risk factors for cardiovascular disease	Postpartum and not breastfeeding until 21 days after childbirth
Hypertension: systolic ≥160 or diastolic ≥100 mmHg	Multiple risk factors for arterial disease
Hypertension with vascular disease	Hypertension: systolic blood pressure 140–159 or diastolic pressure 90–99 mmHg, or adequately treated to below 140/90 mmHg
Diabetes for ≥20 years or with severe vascular disease or with severe nephropathy, retinopathy or neuropathy	Diabetes mellitus with vascular disease
Current or history of deep-vein thrombosis/ pulmonary embolism	Obesity
	Some known hyperlipidaemias
Major surgery with prolonged immobilization	Migraine, even without aura, and age 35 years
Known thrombogenic mutations	Breast cancer with >5 years without recurrence
Current or history of ischaemic heart disease	History of cholestasis associated with combined oral contraceptives
Complicated valvular heart disease	
Current or history of stroke	Mild cirrhosis
Migraine with aura	Current or nonsurgically treated gallbladder disease
Migraine without aura *but age ≥35*	Taking rifampicin or certain anticonvulsants
Current breast cancer	
Active viral hepatitis	
Severe cirrhosis	
Benign or malignant liver tumours	

iv) Combined Oral Contraceptives (COCs)

The oral preparations of COCs can be of two types; monophasic and polyphasic;

- Monophasic types have fixed amount of EE and a 2nd or 3rd generation progestogen in all pills of a pack;
- Polyphasic type of *most COCs* contain fixed amount of EE but varying quantities of progestogen in every pill of a pack. The notion is to administer as low amount of hormones as possible while maintaining contraceptive effects during respective stages of a menstrual cycle.

v) Combined Contraceptive Vaginal Ring (CCVR)

A CCVR is a ring for *intravaginal use*. It is made of latex-free plastic and has a diameter of approx. 54mm. Once inside, it slowly releases a formulation of EE 15 µg/day and etonorgestrel about 120 µg/day.

A CCVR has the ***added benefit*** of very good cycle control by using it continuously for 21 days followed by 7 days ring-free period. The side-effects and risks are, however, the same as with patches and pills.

vi) Combined contraceptive patch

The hormonal transdermal patch releases norelgestromin (form of progestogen) and EE into the blood stream over 24 hours. They are used continuously for 3 weeks followed by one-week patch free period.

vii) Forgetting pills

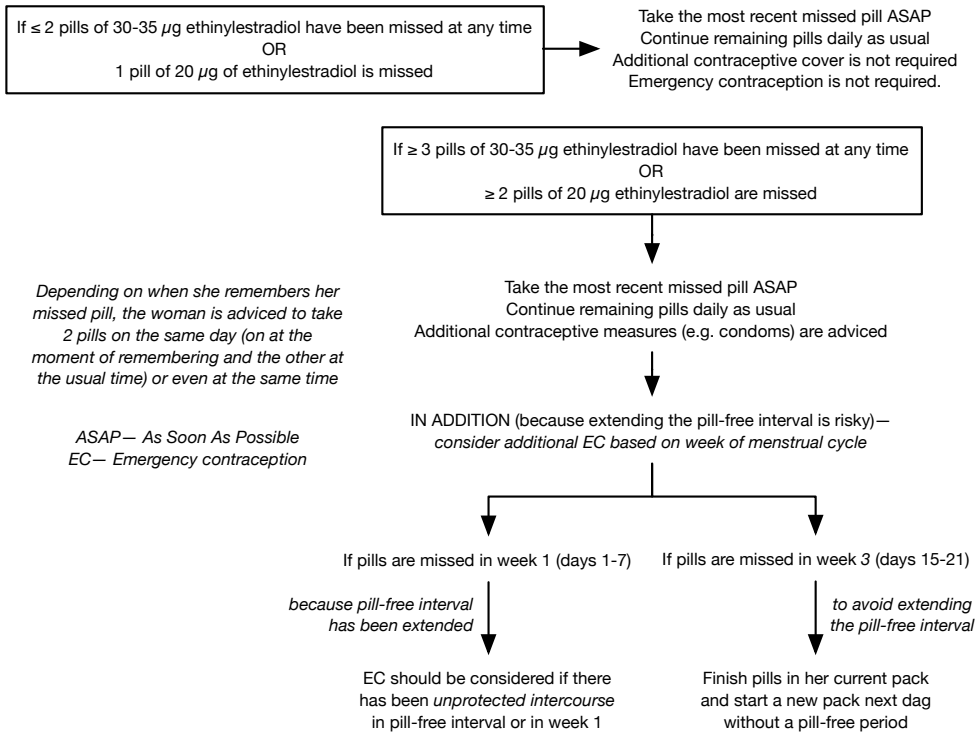


Figure. Flowchart outlining measures to take in case of forgetting pills— to maintain contraception.

(VII) Progestogen-only contraception

These hormonal preparations consist of a progestogen only; either 2nd gen (norethisterone, norgestrel) or 3rd gen (desogestrel).

- These are highly effective contraceptives (but less in comparison to COCs).
- These have predominantly peripherally-acting effects on cervix and endometrium. They inhibit sperm transport by altering cervical mucus and induce atrophy of endometrium (altering implantation). High doses of progestogens can *additionally* feedback inhibit gonadotropins and inhibit ovulation (especially ***desogestrel***).
- They are available in various forms:
    - Progestogen-only pill (also known as ***mini-pill***)
    - Subdermal implant
    - Injectables
    - Hormone-releasing intrauterine system
- These lack adverse-effects seen with estrogen and are considered safer. On one hand, these aid in cases of heavy menstrual bleeding (HMB) by ↓ blood loss. However, women may develop:
    - Erratic or absent menstrual bleeding.
    - Simple, functional ovarian cysts.
    - Breast tenderness.
    - Acne.

i) Progestogen-only Pills

- This oral form of contraceptive is taken everyday without a gap.
- They contain either a 2nd generation progestogen (i.e. norethisterone or norgestrel), or a 3rd generation progestogen (i.e. desogestrel).
- These are acceptable alternatives where COCs are contraindicated, e.g.;
    - Breast-feeding;
    - Old age;
    - Cardiovascular risk factors (women >35 years that are active smokers, HTN or DM).

ii) Injectable progestogens

- These injectables are slow-release forms of progestogens administered intramuscularly.
- Most famous ones are are Depo-Provera 150mg and Noristerat 200mg providing contraceptive cover for 12 weeks and 8 weeks, respectively.
- These are beneficial in cases of heavy menstrual bleeding (HMB), premenstrual syndrome (PMS) and in compliance issues with daily medication intake. Depo-Provera, however, is associated with ***low-estrogen*** and consequent *osteopenia/osteoporos*is in addition to;
    - Weight gain of around 2-3 Kg during the first year of usage;
    - Delay in return of fertility (upto 6 months longer) relative to other contraceptives e.g. COCs;
    - Irregular periods and users may become amenorrhoeic.
- Thus, long term use of Depo-Provera should be avoided in those with other risk factors for osteoporosis.

iii) Subdermal Implants

'**Implanon**' is a silastic rod implanted subdermally into the skin. It slowly releases etonorgestrel 25-70mg/day for upto 3 years. Etonorgestrel is metabolized to **desogestrel**, a 3rd generation progestogen highly effective for contraception.

Implanon has the added advantage of ***relatively quicker*** return of fertility when it is removed compared to othrt progestogen-based contraceptives. However, as with all progestogen-only methods, implanon can cause irregular periods— and this is the most commonly cited reason for early discontinuation.

Insertion is a special procedure (*see Figure*). Removal after 3 years can be complicated, hence ultrasound is often used to localize it before removal.

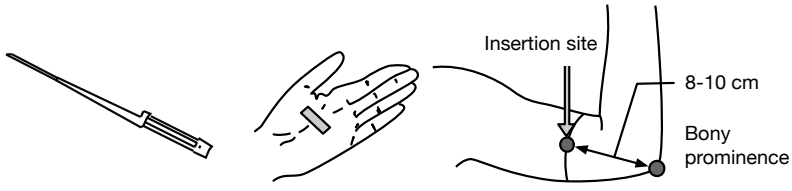


Figure: Implanon insertion instrument, its insertion site, and size of the Implanon silastic capsule.

(VIII) Intrauterine contraception

These contraceptives are hightly effective for long-term use and do not require regular compliance. These consist of a stem and 2 arms usually in the shape of a "T".

Insertion is a skilled procedure requiring trained professionals. Intrauterine contraceptives are protective against both intrauterine and ectopic pregnancy. *But in cases of failure, risk of an ectopic pregnancy is higher.*

There are two common types of intrauterine contraceptives;

- Copper Intrauterine Device (Copper IUD);
- Hormone releasing intrauterine system.

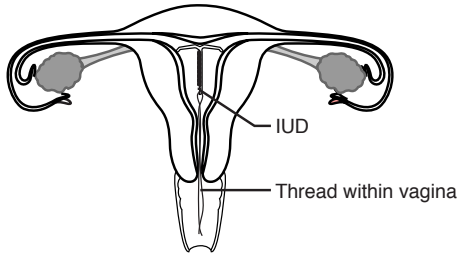


Figure. IUD in the uterine cavity

i) Copper IUD

The modern types of copper IUDs bear copper on its stem and arms. Evidence shows the more copper a device has the more effective it is with reference to its contraceptive effects.

Large copper IUDs can be used for upto 10 years (5 years in cases of relatively smaller copper IUDs).

ii) Hormone releasing IUS

Mirena is a famous hormone releasing IUS. It bears a capsule containing Levonorgestrel around its stem which releases approximately 20 µg daily.

As it releases a progestogen, Mirena has benefits for reducing menstrual blood loss dramatically. It is indicated for following uses;

- Contraception;
- Management of Heavy Menstrual Bleeding (HMB);
- Part of Hormone Replacement Therapy (HRT) regimen.

Table. Comparison between intrauterine contraceptives.

Characteristic	**Copper IUD**	**Mirena**
Failure rate in 1st year	0.8%	0.1%
Mode of action	Toxic effect on both sperm and egg, i.e. acting prior to fertilization	Local hormonal effect on the cervical mucus and endometrium
Duration of use	10 years	5 years
Effect on menstrual cycle	Periods can become heavier with more pain	Periods become irregular but much lighter. Women often become amenorrhoeic
Menstrual spotting	Often more days of spotting before and after periods	Erratic spotting very common initially but usually settles
Hormonal side effects	None	May cause greasy skin, acne, breast tenderness, mood swings with time
Therapeutic benefits	None	Helps in cases of HMB. Can be used as part of an HRT regimen
Cost	Cheap	Expensive

iii) Risks

- With intrauterine contraception, it has been shown that risk of pelvic infection is higher in first few weeks after insertion. But in long-term there is no relative higher risk compared to women not using any method of contraception;
- An IUD does not protect against contracting STIs e.g. Chlamydia or Gonorrhea relative to condoms or other barrier methods, which do;
- If intrauterine contraceptive fails and pregnancy occurs, the risk of it being ectopic is higher.

iv) Contraindications

According to UK Medical Eligibility Criteria for Contraceptive Use (UKMEC), category 4 contraindications to intrauterine contraception include;

- Current STI, or PID, including post-abortion and post-childbirth;
- Malignant trophoblastic disease;
- Unexplained vaginal bleeding (if assessment not carried out yet);
- Endometrial and cervical cancer (until assessed and treated);
- Uterine malformation or anatomic pathology e.g. fibroids;
- Copper allergy contraindicates use of Copper T-IUD, however, Mirena can still be safely used.

(IX) Emergency Contraception (EC)

This form of contraception is meant to be used after unprotected sexual intercourse and before implantation has occurred.

Can also be considered in cases where there is probable breach of barrier methods or if oral contraceptives have been forgotten, for added protection.

Generally, there are two types of emergency contraceptives;

i) Hormonal EC

- **Levonorgestrel** in a single dose of 1.5 mg if taken within 72 hours of unprotected intercourse is effective for upto ¾^{ths} of pregnancies that may otherwise have occurred. Its dose can be repeated in a short span of time.
- A progesterone receptor modulator **ullipristal** 30mg is also licensed for use as EC upto 120 hours after unprotected intercourse.
- These disrupt ovulation or corpus luteal function depending on the phase of menstrual cycle it is taken.
- May cause nausea or vomiting but are relatively safe to use.

ii) Intrauterine EC

- A copper IUD can be inserted for EC, either;
    - Upto 5 days after earliest calculated ovulation day, covering multiple unprotected intercourse episodes during the same menstrual cycle; or,
    - Upto 5 days after a single episode of unprotected intercourse at any phase of the same menstrual cycle.
- This emergent insertion of an IUD prevents implantation. Also, the copper ions have embryotoxic effects. Mirena IUS is **not** shown to be effective for EC and *should not be used for this purpose*.
- Depending on risk of sexually transmitted infection, antibiotic cover may be used.
- The Copper IUD can be kept *in situ* or removed once the menstrual period starts.

(X) Sterilization

These are permanent methods of contraception and are highly effective.

Because of their irreversibility, they are offered to those individuals who are sure of their completed families.

i) Male sterilization

- Vasectomy is the male sterilization procedure. It involves ligating and division of vas deferens bilaterally through small incision on scrotal sac usually under general anesthesia;
- Post-procedure, semen analysis is carried out after regular intervals of 12 and 16 weeks to ensure successful completion (azoospermia). Until lab evaluation confirms, alternative contraceptive methods are needed *additionally*;

- It has been shown to be slightly more effective than female sterilization methods;
- The procedure can be reversed with 25% subsequent chance of getting partner pregnant but outcome is unpredictable and complex.

Table. Vasectomy techniques and their features.

Techniques of vasectomy	**Features**
Ligation or clips	Most commonly used Unipolar diathermy
Excision	Allows histological confirmation
No-scalpel vasectomy	Widely used in China Special instruments used which puncture the skin Relatively low incidence of complications
Silicone plugs/ sclerosing agents	Avoids a skin incision

ii) Female sterilization

There are different options for sterilization procedures in women;

- Most famous employed procedure is one that involves *mechanical blockage of fallopian tubes*, preventing sperms from reaching and fertilizing the ovum— using clips, fallope rings, ligation etc;
- Other options involve removal of the uterus (=hysterectomy) with or without removal of bilateral fallopian tubes (=salpingectomy) and ovaries (=oophorectomy);
- In women, these sterilization procedures can be performed with minimal access, as in **laparoscopically** or with **mini-laparotomy** or through posterior vaginal fornix *per vaginum* (**colpotomy**);
- For postnatal mothers, mini-laprotomy is the procedure of choice which involves a small transverse suprapubic incision to access and block the fallopian tubes.

Table. Techniques of female sterilization and features.

Technique of tubal occlusion	**Features**
Clips	Technique of choice for majority. However, occasionally may not occlude whole tube.
Fallope rings	Easy to apply but damage 2–3 cm of tube, thereby making subsequent reversal more difficult.
Ligation	Suitable for postpartum mini-laparotomy. Has a relatively higher failure rate.
Electrocautery/ diathermy	May damage surrounding structures, e.g. bowel and bladder. Relatively higher long-term failure rate.
Essure	Inserted via hysteroscope under local anaesthetic. Expanding metal springs placed into Fallopian tubes proximally.
Chemical agents, e.g. ***quinacrine***	Inserted via hysteroscope under local anaesthetic.

iii) Consent

Consent for such procedures should clearly indicate;

- Irreversibility of this procedure;
- Risk of failure of procedure;
- Complications associated with each approach and procedure.

iv) Complications

- With male sterilization (vasectomy) procedure;
    - Bleeding;
    - Wound infection;
    - Haematoma;
    - Sperm granulomas can result from local inflammation and may require surgical excision;
    - Sometimes, anti-sperm antibodies can develop, major cause of continued infertility even if vasectomy is reversed;
    - Chronic scotal pain or discomfort but is very rare (6-8% by 1 year post-procedure);
    - Possible association with prostate cancer and testicular cancer (unproven).
- With female sterilization methods;
    - In procedures with invasive access to pelvis, there is potential to cause damage to surrounding structures;
    - Obesity or adhesions may affect visualization of structures during procedure and may require on-table conversion of a laparoscopic intervention to mini-laparotomy;
    - If there is failure of procedure and preganancy occurs, it is more likely to be ectopic.

(XI) Abortion

Abortion of a pregnancy is a process whereby a gestation is terminated.

i) Laws

- In western countries, it is legal to be performed up until the age of viability of a fetus (20 weeks or 24 weeks). However, consent of both mother or father may be taken into consideration as per local law.
- **According to Pakistan Penal Code 338**, based on Islamic values, the act of terminating a pregnancy is an act of crime (includes a woman who causes herself harm with the intention to miscarry);
    - **Isqat-i-Haml** is a punishable offence when the unborn baby's organs have not been formed;
    - **Isqat-i-Janin** is a punishable offence when the unborn baby's organs have been formed.
- Though PPC 338 does not describe a gestational age cut-off, however, it does describe situations where terminating a pregnancy is not an act of crime;
    - If such miscarriage is caused in good faith for the purpose of saving life of the woman, or;
    - Providing necessary treatment to the woman.

ii) Prerequisites

- Confirmation of pregnancy by a sensitive test;
- Medical history to determine contraindications to surgery or anesthetic complications, drug reactions or allergies;
- Assessment of gestational age by ultrasound or abdomen/pelvic examination;
- Screening for genital tract infections including STIs such as HIV and Hepatitis B;
- Blood typing;
- Administration of anti-D immunoglobulin at the time of procedure if rhesus-negative mother;
- Cervical pap smear (if screening is due).

iii) Techniques

Abortion is safest when it is performed between the 6^{th} and 12^{th} gestational weeks.

However, the choice of technique for inducing abortion is primarily centered around the gestational age.

a) First Trimester Abortion

- The medical technique available for abortion upto 9 weeks of gestation;
    - Involves use of Mifepristone (an antiprogestogen) *combined with* Gemeprost (a prostaglandin E_1);
    - This combined technique carries out complete abortion in >95% first trimester gestations;
    - A 600mg **mifepristone RU486** tablet orally is taken, followed 48 hours by a **gemeprost** 1mg vaginal pessary insertion *once*;
    - Women usually stay in the hospital for 4-6 hours after Gemeprost pessary insertion during which passage of fetus occurs.
- The surgical techniques available for first trimester abortion require dilatation of the cervix through which a plastic cannula is inserted to remove the gestational sac from the uterus;
    - Dilatation of cervix can be carried out by instruments or by priming agents e.g. intravaginal or oral prostaglandins.
    - Manual vacuum aspiration (MVA) is the technique of providing manual suction to plastic cannula by means of an ***MVA syringe*** (of 50 mL).
    - With larger gestational age fetus aged 7-15 weeks, an electric pump can be used instead to provide suction termination under cover of general anesthesia.

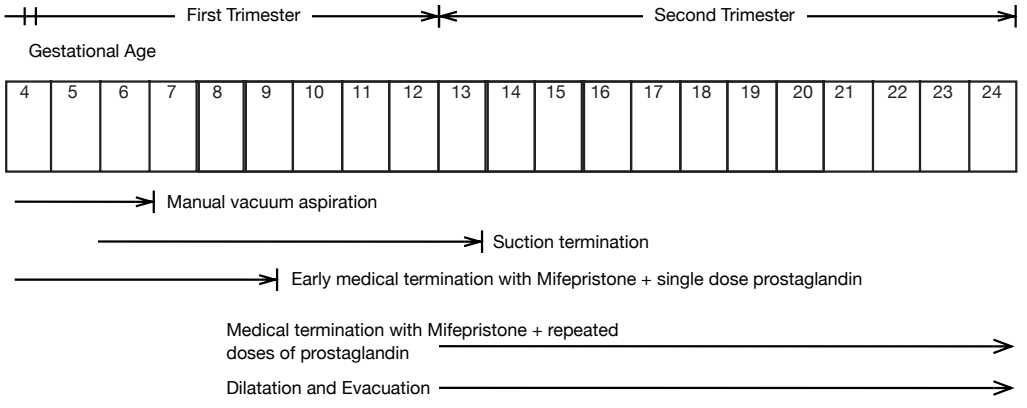


Figure. Choice of abortive techniques with respect to gestational age.

Table. Characteristics of early abortion methods

Characteristics	**Surgical**	**Medical**
Effectiveness	Highly	Highly
Average blood loss	Around 80 mL	Around 80 mL
Completeness	95%	95%
Duration	Brief	Takes several days
Anaesthesia	Usually GA, but can be done under sedation or local anesthethic	None
Analgesia	May be required following procedure	Oral or intramuscular analgesia
Number of visits required	1	2
Setting	Hospital/clinic	Usually hospital/clinic
Contraindications	None	Asthma, cardiac disease
Possible complications	Haemorrhage, infection, uterine perforation, cervical damage, failure to remove pregnancy	Haemorrhage, infection, failure to pass products

b) Late Abortion

Mid-trimester abortions are associated with more complications. Often these may be requested after ultrasound scan for anomalies done at 20 weeks gestation shows fetal abnormalities;

- Medical termination of mid-trimester gestations is carried out with similar combination of RU486 (Mifepristone) and intravaginal prostaglandins as for 1st trimester abortions;
    - A dose of antiprogestogen Mifepristone is followed 36 hours by Gemeprost pessary;
    - The Gemeprost pessary can be repeated once every 3-6 hours until fetus is aborted;
    - In 10 % of cases, women, however, need additional surgical evacuation.
- Surgical termination of mid-trimester gestations utilizes Dilatation and Evacuation (D & E) technique;
    - In comparison to MVA and suction termination methods, this is more a more aggressive intervention;
    - Carries a higher risk of damage to uterus and surrounding structures;
    - Ultrasound has an important role in real-time during the procedure and can recognize failed abortion and retained products for futher management;
    - Recommended to be performed by a skilled and experienced clinician.

iv) Complications of abortion

- Incomplete abortion— this is the major reason for additional surgical termination after a failed or incomplete medical abortion procedure;
- Infection— can present as a febrile illness usually with pelvic pain and vaginal discharge. STIs should always be ruled out before procedure. Prompt administration of antibiotics is vital to prevent secondary complications;
- Subfertility— mechanical damage or post-procedure infection can affect fallopian tubes and surrounding structures to develop fibrosis and adhesions;
- Traumatic injuries— this risk is very low with early abortions, but aggressive procedures can cause bleeding, tears and ruptures. Dilatation can result in cervical incompetence in subsequent gestations.
- Psychological issues, feelings of regret and guilt are commonly expected, and a support system should be offered.

v) Follow-up

Immediately after the procedure, contraception should be instituted. All hormonal methods can be started on the same day.

An appointment should be set up 2 weeks' post-procedure to ensure;

- Completion of abortion on radiologic and biochemical testing (e.g. β-hCG);
- Exclusion of an ongoing pregnancy (pelvic examination should be performed);
- Exclusion of pelvic infection;
- Contraceptive options and advice;
- Assessment of emotional state.

CHAPTER 6 FERTILITY, SUBFERTILITY AND INFERTILITY

(I) Nomenclature

- *Infertility* is defined as the inability of a couple to conceive following 12–24 months of exposure to regular sexual intercourse (i.e. ≥ 2/week).
- Spermatogenesis— mitotic division of spermatogonia, followed by meiotic division to form spermatids.
- Spermiogenesis— transformation of immature spermatids into mature spermatozoa (sperm cells).
- Capacitation— is a process of maturation that allows spermatozoa to bind to the zona pellucida of ovum and undergo the *acrosome reaction* in preparation for fertilization. Capacitated sperms are, in comparison, more active.
- When a capacitated sperm meets the corona radiata layer of an oocyte, the acrosome develops perforations with release of acrosomal vesicles. This is known as the **acrosome reaction**.
- Normozoospermia— normal ejaculate as defined by the reference values (*see parameters below*).
- Oligozoospermia is diagnosed when sperm concentration is < 1million/mL in the ejaculate.
- Asthenozoospermia— sperm analysis showing less than the reference value for normally motile sperms.
- Teratozoospermia— less than the reference value for sperms having normal morphology.
- Oligo-asthenoterato-zoospermia— disturbance of all three variables (i.e. concentration, motility, and morphology).
- Azoospermia— no spermatozoa in the ejaculate.
- Aspermia— no ejaculate.

(II) Preconceptual advice

Couples seeking medical advice preconceptually should be adviced to;

- Stop smoking;
- Stop any recreational drug use;
- Regular sexual intercourse, atleast 2-3 times/week.

In addition, an attentive clinician should;

- Optimize management of medical problems;
- Eliminate drugs not safe for pregnancy;
- Optimize body weight to a BMI in the range of 20-30;
- Commence folic acid supplements;
- Ensure ***immunity to rubella*** in the female.

(III) Male fertility

- In males, the process of spermatogenesis starts at puberty and continues throughout life;
- The activation of hypothalamic-pituitary axis at puberty, sends stimuli to testes to start spermatogenesis via gonadotrophins;
- FSH in males stimulates spermatogenesis, while LH regulates androgens production and subsequent male secondary sexual characterisitics;
- The process of spermatogenesis takes 74 days within the seminiferous tubules;
- The travel of mature sperms up to the epididymis (where they upto 70% of them are stored) takes an additional 10 days;
- From the epididymis, the sperms exit through the vas deferens into the urethra during ejaculation (shown in figure).

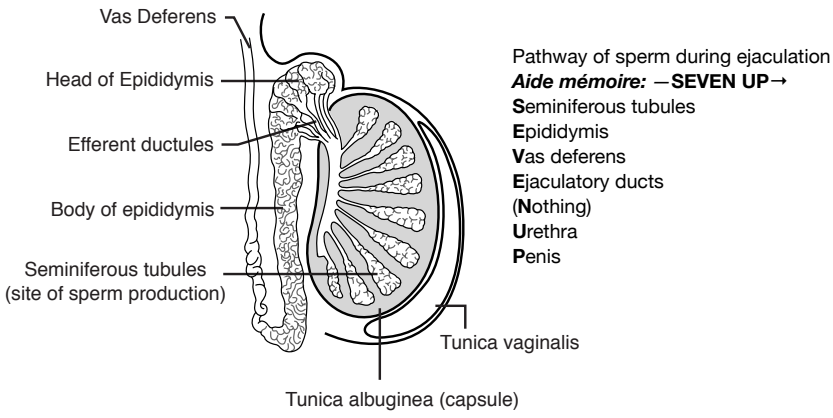


Figure. Anatomy of a testis

(IV) Male subfertility

The causes of male subfertility can be classified as;

- Disorders of spermatogenesis;
- Impaired sperm transport;
- Ejaculatory dysfunction;
- Immunological and infective factors.

i) Disorders of spermatogenesis

- These may arise as a result of;
    - Exposure of scrotal sac to high temperature, as occurs in;
        - Warm innerwear and clothing;
        - Prolonged hot baths;
        - Undescended testes;
        - Varicocele.
    - Chromosomal deletions of Y chromosomes; may lead to impaired spermatogenesis.
    - Certain drugs;
        - Psychotropic medications and recreational drugs;
        - Antiepileptics;
        - Antihypertensives;
        - Antibiotics;
        - Chemotherapeutic medications.

ii) Disorders of sperm transport

These are often seen in men with;

- Congenital malformations of epididymis or vas deferens;
- Infection or inflammation of outflow tract;
- Vasectomy and subsequent reversal.

iii) Ejaculatory dysfunction

This can occur secondary to;

- Drugs;

- Idiopathic;
- Metabolic disease;
- Systemic illness, such as DM and multiple sclerosis, among others.

iv) Immunological and infective factors

- Spermatogonia are kept isolated from blood by means of a specialized blood-testes barrier.
- Sometimes, as it happens in vasectomy, exposure to sperms can trigger immunologic phenomenon that creates antibodies to sperms resulting in sub- or infertility post-procedure.
- Immunologic factor involved with mumps infection (if it occurs after puberty), can result in subfertility.
- Acute epididymitis and other infective processes can have deleterious effects on spermatogenesis and genital tract. STIs and spread of UTIs can also be implicated as causative factors.

(V) Normal parameters of oocytes and factors affecting female fertility

- After ovulation, an oocyte can survive, on average, for 24 hours;
- After ejaculation, male sperms can survive in the female reproductive tract for upto 7 days;
- Factors affecting fertility include;
    - Fertility declines significantly with decreasing age, especially for women after the age of 35;
    - Smoking reduces fertility *in females* and sperm viability *in males*;
    - Alcohol consumption in excessive amounts is harmful to sperm quality;
    - Anxiety, stress and psychiatric illness may affect libido and fertility;
    - Body mass indices (BMI) in its extremes (<19 or >29) also correlates with ↓ fertility;
    - Drugs, e.g;
        - NSAIDs— excessive use can *potentially* negatively affect ovulation;
        - Chemotherapy— inhibits cell division of spermatogonia and oogonia;
        - Cimetidine, sulphasalzine, and androgen injections— affect sperm quality.
    - Radiation exposure is known to cause subfertility;
    - Industrial exposure to dyes and chemicals may also affect male and female fertility.

(VI) Female subfertility

When investigating subfertility, it is best to stay organized and group probable causes as;

- Hypothalamic-pituitary-ovarian (HPO) axis dysfunction;
- Ovulatory disorders secondary to ovarian factors;
- Tubal disease;
- Endometrial disease;
- Other unspecified causes.

i) HPO axis dysfunction

The endocrinologic control of ovulation follows a hierarchy in which hypothalamus, pituitary, and the ovaries play an important role.

- Gonadotrophin-releasing hormone (GnRH) from the hypothalamus stimulates the pituitary to secrete gonadotrophins— FSH and LH;
- FSH and LH have a pivotal role on ovaries where they aid in the maturation of an oocyte and facilitate its release from the ovary, respectively, by means of a feedback regulatory loop;
- Factors that disrupt this endocrinologic control ***anywhere along the HPO axis*** can precipitate down-stream ovulatory dysfunction and subfertility. E.g;

  - Hypothalamic disease, such as Kallman syndrome;
  - Polycystic ovarian syndrome (PCOS);
  - Hyper- or Hypothyroidism;
  - Hyperprolactinemia.
- Women with body mass indices (BMI) in their extremes, either <19 or >29 are often observed to have HPO axis dysfunction.

ii) Ovulatory disorders secondary to ovarian factors

- Polycystic ovarian syndrome (PCOS) is the most common ovarian cause of anovulation.
- Premature ovarian failure and perimenopause can also lead to anovulation. These can be tested for by means of Anti-Müllerian hormone (AMH);
  - AMH is secreted by granulosa cells of ovary;
  - Its levels correlates with ovarian follicle pool of small antral follicles, as a marker of ovarian reserve;
  - Its levels decrease with age and are undetectable in the post-menopausal period.

iii) Tubal disease

The most common cause of an acquired tubal dysfunction comes as sequelae to pelvic infections;

- STIs such as Chlamydia and Neisseria Gonorrhoea have a tendency to cause PID, which often results in inflammatory destruction of fallopian tubes and surrounding structures;
- Endometriosis can spread to fallopian tubes and affect the transport of oocytes down to the uterus.

iv) Endometrial factors

Endometrial abnormalities may prevent implantation of fetus. The abnormalities may be congenital as in bicornuate uterus, or acquired as;

- Uterine fibroids;
- Uterine adhesions;
- Uterine polyps.

(VII) Approach to male- and female subfertility

i) History and examination

Table. History taking and examination focus in subfertility.

	History		**Examination**	
	Female	*Male*	*Female*	*Male*
Infertility	Subfertility duration Previous contraceptive use Fertility in previous relationships as well as current Previous investigation and treatment Fertility in any former partners Previous fertility investigations and treatment		Height, weight, BMI Fat, hair distribution -Acne -Galactorrhoea	-Hypoandrogenism -Gynaecomastia
Medical	*Menstrual history:* -Menarche -Regularity, -Pain, -Menorrhagia, -Intermenstrual bleeding *Previous pregnancies:* -Abortions, -Miscarriages -Ectopic pregnancies *Time to initiate previous pregnancies* *Drug history, e.g.* -Hyperprolactinemics -Chemo- or radiotherapy	***-Recent febrile illness*** -STIs -Epididymitis -Mumps orchitis -Testicular maldescent -Chronic disease -Drug/alcohol abuse -Recurrent UTIs	Abdominal masses or tenderness	-Inguinal hernia -Inguinal masses
Surgical	Previous abdominal or pelvic surgery, Gynaecologic procedures	-Herniorrhaphy -Testicular injury -Torsion -Orchidopexy -Vasectomy ± reversal	-State of hymen -Clitoris and labia -Vaginal infection, septa, endometriotic deposits -Cervical polyps -Uterine size, position, mobility and tenderness -Pap smear, if due	-Site of testicles, -Orchidometer for volume of testis -Epididymis nodularity or tenderness -Varicocele -Penile abnormality, e.g. hypospadias
Work	Toxic substance exposure including chemicals, radiation Time away from home through work			
Sexual	Coital frequency and timing, including knowledge of the fertile period Dyspareunia Postcoital bleeding			

ii) Investigations

Before a more thorough investigation of the female partner is carried out, it can be considered more cost-effective to perform a semen analysis as the first test.

a) Semen analysis

It is recommended to obtain a sample produced after 3-5 days of sexual abstinence.

A second sample should be obtained for confirmation in case of non-satisfactory parameters usually after 1-3 months.

Table. Semen analysis

Volume	> 2 mL
pH	> 7.2
Sperm concentration	> 20 million/mL
Total sperm number	> 40 million/ejaculate
Motility	> 50% grade a and b
Morphology	> 30% normal forms
Liquification time	Within 30 minutes
White blood cells	< 1 million/mL

The potential of sperm to fertilize is indicated by its;

- Progressive motility;
- Morphology, and;
- Agglutination.

For men with azoospermia or oligospermia, it is important to check for gonadotrophins, testosterone and prolactin levels;

- Low levels of FSH and testosterone indicate hypogonadotrophic hypogonadism. Can be treated with FSH and hCG injections;
- High FSH levels suggest **testicular failure**. In such a case, choromosomal karyotyping may reveal Klinefelter's syndrome (47 XXY);
- An obstructive cause may be the reason if FSH is normal. Here, surgical retrieval of sperms may be possible as an approach to management;
- High prolactin levels correlate with hypogonadism. This can occur secondary to pituitary tumors or drugs;
- Retrograde ejaculation is a possibility in those with history of diabetes and prostatic surgery. This is an indication for analysis of ***a post-ejaculation first-void urine sample***.

For men with low progressive motility and/or significant ***agglutination*** on semen analysis, testing for **anti-sperm antibodies** should be carried out. *In-vitro* fertilization (IVF) may help such individuals in management;

If on examination, vas deferens is impalpable then cystic fibrosis screening is warranted. ***Congenital Bilateral Absence of Vas Deferens (CBAVD)*** *is a minor variant of cystic fibrosis.*

b) Post-coital test (PCT)

The couple is asked to have intercourse at a prescribed time during periovulatory phase of cycle of the female, 6-10 hours after which a mucus sample from the cervix is obtained.

Though of limited prognostic value, this test can provide information whether there are adequate motile number of sperms and cervical secretions are receptive.

c) Female subfertility investigations

For investigating the female causes of sub- or infertility, following should be considered;

- Assessment for HPO axis dysfunction, with;
    - Follicular phase levels of FSH, LH, and estradiol (preferably on day 2-5 of cycle).
- Assessment of ovulation, with;
    - Mid-luteal progesterone level (ideally, 7 days before start of next menstrual bleeding).
- Fallopian tube patency, with;
    - Hysterosalpingogram (HSG), or Hysterocontrast synography (HyCoSy) as highly sensitive screening tests, and;
    - Operative laparoscopy and dye test for diagnostic confirmation (gold standard).

For fallopian tube patency, both HSG and HyCoSy are comparable in terms of their sensitivity in detecting pathology— HSG uses radio-opaque dye while HyCoSy utilizes a sono-opaque contrast medium to visualize upper genital tract anatomy (see Figure).

However, neither these tests or any other can test for tubal function which is not equivalent to tubal patency.

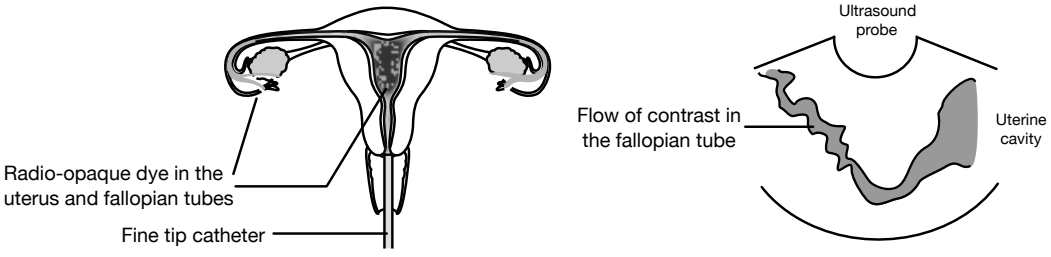


Figure. Schematic representation of HSG (left) and HycoSy (right).

iii) Management of sub- and infertility

Conselling is an important part of management for both male and female partners.

a) Male subfertility

- Hypogonadotrophic hypogonadism can be treated with exogenous gonadotrophins and hCG to restore testicular volume, spermatogenesis, and secondary sexual characteristics.
- Idiopathic oligospermia does not respond to hormonal therapy. In these individuals, intrauterine insemination with ovarian stimulation, or IVF with intracytoplasmic sperm injection (ICSI) are options.
- Obstructive azoospermia and conditions where sperm quality is inadequate can be managed with **Surgical Sperm Retrieval (SSR)** followed by IVF with ICSI treatment to boost chances of a successful pregnancy.
- Men with varicocele can get surgical ligation procedure for it, however, there is no evidence yet to support if it improves fertility.

b) Female subfertility

Management is mainly centered around the cause;

- HPO axis dysfunction may benefit from lifestyle changes/BMI optimization;
- Hypo- or hyperthyroidism to be managed respectively;
- Hyperprolactinemia— *if secondary to tumor may need surgery or dopaminergic agonist therapy*;
- Management of ovulatory dysfunction should be done by addressing the cause. Afterwards, ovulation induction (OI) can be considered with;
    - Ovulation induction with anti-estrogen agent clomiphene citrate (CC); CC blocks feedback inhibitory effects of estrogen on gonadotrophins. FSH levels increase, stimulating the ovary to produce more follicles;

  - Ovulation induction with laparoscopic ovarian drilling (LOD)— may be considered in women who do not respond to CC treatment;
  - Ovulation can also be induced by daily doses of FSH from the beginning of a cycle to stimulate the ovaries and serial ultrasound scans to identify and follow growing follicles. In this case, exogenous hCG can trigger ovulation (because of its binding affinity for LH receptors).
- Aim of management of tubal dysfunction is to restore normal anatomy but depends on severity and location of the damage as well as on the skill of the surgeon.
- Peri-tubal, peri-ovarian and fimbrial adhesions can also attempted to be removed by laparoscopic adhesiolysis.

iv) Assisted conception

Assisted conception techniques have drastically improved treatment of subfertility. The basic concept behind these techniques is to bring the sperm and egg in close proximity to facilitate fertilization.

Table. Acronyms for assisted conception techniques.

Abbreviation	**Definition**
IVF	*In vitro* fertilization
IUI	Intrauterine insemination
ICSI	Intracytoplasmic sperm injection
PGD	Preimplantation genetic diagnosis
DOT	Direct oocyte transfer
PROST	Pronuclear stage transfer
DIPI	Direct intraperitoneal insemination
MESA	Percutaneous epididymal sperm aspiration
TESE	Testicular sperm extraction
GIFT	Gamete intrafallopian transfer

While the use of many of these techniqes has declined because improving success rates of IVF.

Other techniques, such as Preimplantation Genetic Diagnosis (PGD) and Preimplantation Genetic Screening (PGS) have also gained widespread popularity.

a) Intrauterine Insemination (IUI)

This is a procedure whereby a sample of prepared sperm are introduced into the uterine cavity with a fine uterine catheter at the time of ovulation;

- Mild stimulation with FSH may be needed to ensure 2-3 maturing follicles developing in the ovaries increases the success rate by upto 15-20%;
- Serial ultrasound scans ensure under- and overstimulation;
- It is indicated for use in cases of;
  - Unexplained infertility;
  - Mild male factor;
  - Ejaculatory probems;
  - Cervical problems;
  - Ovulatory disorders;
  - Mild endometriosis.

b) *In vitro* fertilization (IVF)

In-vitro fertilization (IVF) can be an alternative to surgery in cases of tubal dysfunction;

- If tubal damage has resulted in hydrosalpinx, it is advisable to remove the affected fallopian tubes prior to IVF treatment as they are thought to affect implantation adversely;
- Because fertilitization occurs in fallopian tube, indications for use of IVF include;
    - Severe tubal disease— tubal blockages;
    - Severe endometriosis;
    - Moderate male factor;
    - Unexplained infertility;
    - *Unsuccessful IUI.*
- Stages of *in vitro* fertilization are (see Figure);
    - Pituitary downregulation;
    - Ovarian stimulation;
    - hCG ovulation trigger;
    - Oocyte retrieval;
    - Fertilization (by means of insemination or ICSI)
    - Embryo culture;
    - Embryo transfer;
    - Luteal support.

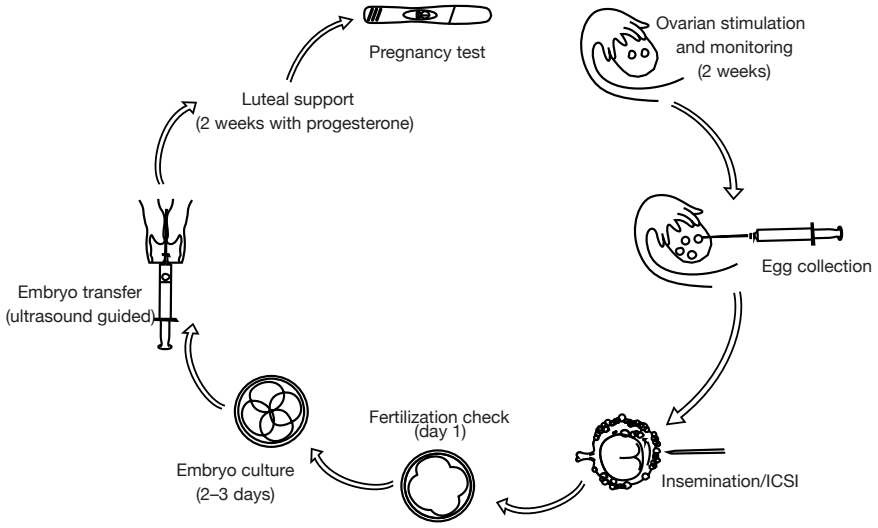


Figure. Illustration of an IVF treatment cycle.

c) Intracytoplasmic Sperm Injection (ICSI)

ICSI is a technique by which a single, *morphologically normal* sperm is immobilized by "***striking***" the tail and is injected into a mature oocyte that has had its surrounding cumulus and corona cells removed.

A very fine glass pipette is used to inject the immobilized sperm into the oocyte by rupturing the oolemma. The oocyte is then incubated under lab conditions to allow fertilization.

Indications for this technique include;

- Severe male factor infertility, including but not limited to azoospermia and oligo-astheno-teratozoospermia; and sperms obtained via;
    - Microepididymal sperm aspiration (MESA);
    - Testicular sperm extraction (TESE), or;
    - Percutaneous epididymis sperm aspiration (PESA).

- Poor or total non-fertilization from previous IVF cycles;
- Preimplantation genetic diagnosis (PGD) cycles.

d) Surgical Sperm Retrieval (SSR)

SSR is an option for male individuals with obstructive azoospermia and inadequate sperm quality;

The procedure can be performed under sedation or general anesthetic. A fine needle is inserted into the epididymis or testicular tissue to obtain a sample;

The sperms obtained can also be cryopreserved or used in IUI or IVF/ICSI cycle.

e) Cryopreservation of gametes

This refers to the cold storage of sperm or oocytes for later use or donations to other subfertile couples;

- This is most useful for individuals undergoing chemo- or radiotherapy for malignancies;
- The cryopreserved gametes can be utilized for donor inseminations, IUI, or even IVF;
- Cryopreservation of gametes is effective with pregnancy rate near to that seen with normal IVF cycles.

f) Preimplantation Genetic Diagnosis (PGD)

This is a special technique that offers the opportunity to select having a pregnancy with an embryo that is unaffected by a certain genetic illness;

It is most useful for couples that carry mutations for disease and are at risk of having a child with an inherited genetic disease;

The technique involves creation of an embryo by IVF followed by genetic testing of the embryo still *in vitro* before transferring it to the uterus. *Sex-chromosome linked diseases can also be determined in the same manner*.

g) Complications of assisted conception

- Ovarian hyperstimulation syndrome;
    - It is more likely to be seen in women with 20 or more follicles maturing rapidly or those with PCOS;
    - Administration of exogenous hCG or natural rise of hCG with conception can trigger this syndrome;
    - Patients typically present with abdominal pain, distention, nausea, bowel disturbance, shortness of breath, and poor urinary output; may require hospital admission and inpatient care.
- Ectopic pregnancy;
- Multiple pregnancy.

CHAPTER 7 DISORDERS OF EARLY PREGNANCY

(I) Ectopic pregnancy

It is defined as the implantation of a conceptus outside of the normal uterine cavity.

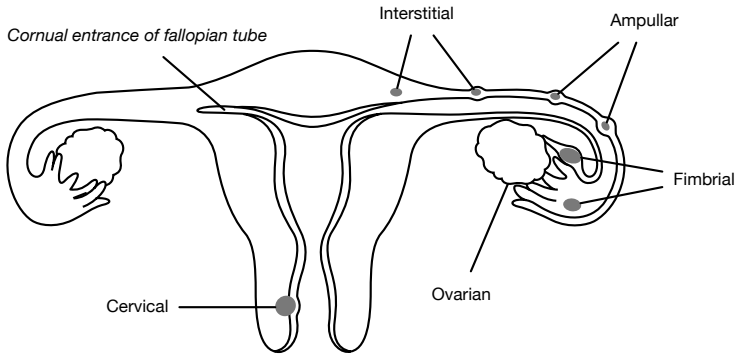


Figure. Possible sites of implantation of an ectopic pregnancy.

i) Clinical Features

Majority of patients present with a subacute onset of abdominal pain, vaginal bleeding (usually dark red, signifying old blood), and occasionally with shoulder tip pain (due to free fluid in peritoneum irritating the diaphragm) and dizziness (secondary to blood-loss anemia).

These symptoms most commonly occur in a background of a missed period. However, even non-specific symptoms should be of high suspicion in any sexually active female, especially those with;

- Tubal disease, e.g. previous pelvic infection with Chlamydia is associated with upto 40% of cases with ectopic pregnancy;
- Previous ectopic pregnancy;
- Previous tubal surgery;
- Subfertility;
- Use of intrauterine device.

Examination may reveal;

- Tenderness of the fornices and cervical excitation on bimanual examination;
- Tense, tender abdomen with rebound phenomenon or other signs of acute abdomen;
- Signs of hypovolemic shock if there is rupture of ectopic pregnancy and ongoing internal bleeding.

ii) Investigations

Following are useful in diagnosing ectopic pregnancies;

- Observing hemodynamic parameters, i.e. BP, pulse, temperature;
- Haemoglobin levels, haematocrit, blood typing and cross matching (in case of emergent need);
- Biochemical tests in context with clinical picture and ultrasound findings;
    - β-hCG levels >25 mIU/mL is diagnostic of pregnancy; *these levels double every 48 hours* in normal developing pregnancies. However, **in ectopic pregnancies**, *the rise observed is often* ***suboptimal***;
    - Transvaginal ultrasound scan (TVUSS); **an intrauterine gestational sac should be visible on sonography at about 4.5 weeks of gestation**. The *corresponding βhCG levels is approximately* **1500 mIU/mL**;
    - If there is discrepancy between βhCG level and ultrasound findings, e.g. an ↑ βhCG level with no intrauterine gestational sac on TVUSS is highly suggestive of an ectopic pregnancy;

  - TVUSS can also *at the same time* detect **free fluid in the pelvis and peritoneum**. Such a finding is highly suggestive of a ruptured ectopic pregnancy;
  - **Heterotopic pregnancy** is a rare occurrence of an intrauterine pregnancy with *simultaneous extrauterine gestation*. This condition may be missed on routine TVUSS.
- Laparoscopy; can be both diagnostic and therapeutic.

iii) Management

Ectopic pregnancy can be managed using an *expectant, medical or surgical approach*, depending on clinical presentation and patient choice.

- Expectant management is based on the notion that a significant percent of all tubal pregnancies abort spontaneously without intervention— this can be considered for otherwise asymptomatic and hemodynamically stable patients. However, as precaution, serial β-hCG levels and ultrasonography need to be performed regularly to detect complications *in time*;
- Medical management is centered around Methotrexate, a folic acid antagonist. A dose calculated of 50 mg/m^2 (of total body surface area) as single intramuscular or divided doses inhibits DNA synthesis in trophoblastic cells;
  - Reasonable indications for methotrexate-based termination of ectopic pregnancy;
    - Cornual ectopic pregnancy;
    - Persistent trophoblastic disease;
    - Patient with only one fallopian tube, and future pregnancy desired;
    - Individuals refusing surgery or cannot undergo surgery due to high risk;
    - Ectopic pregnancy that is adherent to bowel or a blood vessel;
    - Unavailability of facilities for followup with medical management.
  - Medical management is contraindicated in cases of;
    - Chronic liver disease, renal disease or haematological disorder;
    - Active infection;
    - Immunodeficiency;
    - Breastfeeding.
  - Known side effects with medical management include, but not limited to;
    - GI symptoms; nausea, vomiting, stomatitis;
    - Conjunctivitis;
    - Photosensitive skin rash (*avoid sunlight exposure and alcohol during treatment*);
    - Nonspecific abdominal pain.
  - It is recommended that ***additional contraceptive measures be taken for 3 months after medical management*** because of the ***teratogenic potential of methotrexate***.
- Surgical management can be done by means of laparoscopy. Laparotomy may be considered for severely compromised patients;
  - Laparoscopy is the mainstay of treatment as it is less invasive and there is early recovery;
  - Intraoperatively, it is preferred to remove the fallopian tube (=salpingectomy) if possible. This is in contrast to extraction of fetus by a small surgical opening (=salpingotomy) which carries a higher risk of recurrent ectopic pregnancy later.

(II) Miscarriage

Miscarriage is a pregnancy that ends spontaneously before the fetus has reached age of viability (gestational age before or at 24 weeks);

- Sporadic miscarriage of a gestation is a very common complication. It often goes unrecognized as most conceptions are lost during the first month after LMP around the time of expected menstrual period;

- Factors that influence gestation loss include;
    - Advanced maternal age— an independent risk factor;
    - Chromosomal abnormalities;
    - Medical/endocrine disoders;
    - Uterine abnormalities;
    - Infections;
    - Drugs/chemicals.

i) Clinical Features and investigations

- Women with gestational amenorrhea that present with lower abdominal pain with or without vaginal bleeding should be thorough evaluated by means of history taking, and examination. Speculum examination is an important aspect of evaluation as it shows whether the cervix is open or closed.
- Ultrasound scanning for gestational sac, its diameter, fetal pole, fetal heart beat, and fetal/embryonic tissues is of high significance. During non-emergent routine evaluations, if gestational sac is smaller than expected for date, then possibility of incorrect dates should be ruled out by repeat scan after 7 days.
- Individuals presenting with vaginal bleeding should have blood group typing done in addition to haemoglobin and haematocrit levels. Rhesus negative (Rh-ve) women must receive anti-D in cases of vaginal bleeding during pregnancy.
- Placental protein measurements (a specialized test) show that ultrasound is better in diagnostic value and other biochemical tests are often of less value.

Table. Miscarriages, their classification, their presentation and findings.

Clinical presentation	**Ultrasound findings**	**Diagnosis**	
Per vaginal bleeding and pain Speculum: Cervical os closed	Intrauterine pregnancy	*Threatened miscarriage*	
Per vaginal bleeding and pain Speculum: Cervical os open	Intrauterine pregnancy	*Incomplete*	***Inevitable miscarriage***
	Retained products of conception	*Complete*	
Pain and bleeding has resolved Speculum: cervical os closed	Retained products of conception	*Incomplete miscarriage*	
Often light slow vaginal bleeding ± pain before 20 weeks gestation.	Fetal pole present, but no fetal heartbeat identified. Gestational sac present (diameter >20 mm) but no fetal pole seen.	*Missed miscarriage*	
≥ 3 consecutive spontaneous miscarriages	—	*Recurrent miscarriages*	

In cases of missed miscarriage, when an ultrasound scan shows a gestational sac > 25mm in diameter but without identifiable embryonic/fetal parts. This is often wrongfully termed as "*blighted ovum*" and "**anembryonic pregnancy**"— *in actuality, lack of fetal parts indicates early death, and resorption of the embryo with persistence of placental tissue*.

ii) Management

Patients presenting with a miscarriage can have expectant, medical or surgical management. However, emergency surgery may still be needed in those opting for expectant and medical management. The risk of loss of gestation is high in all types ***except threatened miscarriage***;

- Expectant management is often chosen by women who like to be in control of situation and avoid risk with surgical intervention and side effects of medical management;
- Prostaglandins are the cornerstone in medical management of miscarriages, especially safe for those with minimal residue in uterine cavity on ultrasound. Single or divided doses misoprostol can be administered orally or vaginally used in combination with mifepristone (progesterone antagonist);

- Evacuation of Retained Products of Contraception (ERPC) is a surgical option for miscarriages with high success rate (95-100%). It involves mechanical dilatation and curettage of the uterus. Risk of complications is low but ERPC can potentially cause;
    - Cervical trauma, uterine perforation, post-op infection, late cervical incompetence and intrauterine adhesions;
    - Intrauterine adhesions that develop as a result of ERPC can predispose to subfertility later.

iii) Follow-up

- Having suffered a loss of gestation, patients should also be referred to counselling services and support groups for their psychological well-being.
- For couples with recurrent miscarriages (≥ 3 consecutively), investigations should include;
    - Parental and fetal karyotyping;
    - Gynaecological examination/evaluation to exclude uterine abnormalities;
    - Screening for diabetes;
    - Thyroid function tests;
    - Antiphospholipid antibodies, lupus anticoagulant and anticardiolipin antibodies.

(III) Gestational trophoblastic disease (GTD)

Gestational trophoblastic disorder is a term commonly applied to a spectrum of inter-related diseases originating from the placental trophoblast.

i) Aetiology, pathophysiology and types

Gestational trophoblastic disease occurs when a spermatozoon enters an ovum that has lost its nucleus, or if two sperms enter the ovum.

Further development these pathologic cells is thought to be due to a defective maternal immune response to the invasion by the trophoblastic cells.

In consequence, the villi become distended with nutrients. The primitive vasculature within each villus does not form properly, with the result that the fetus (***if any***) starves, dies and is absorbed— whereas the trophoblast continues to thrive and, in certain circumstances, invades the maternal tissues.

The increased syncytiotrophoblast activity leads to an increased production o human chorionic gonadotrohpin (hCG), chorionic thyrotrophin and progesterone. The raised hCG levels may induce the development of thecaluteal cysts in the ovaries.

The main categories of GTD are benign gestational trophoblastic neoplasia and persistent gestational trophoblastic neoplasia;

- Benign gestational trophoblastic neoplasia— mostly benign, and can be subtyped into;
    - Complete hydatidiform mole;
    - Partial hydatidiform mole;
    - Hydropic degeneration of the trophoblast.
- Persistent gestational trophoblastic neoplasia— mostly malignant. These may be apparently confined to the uterus (invasive mole) or with extra-uterine spread (choriocarcinoma).

a) Complete hydatidiform mole

Also referred to as the *classical hydatidiform mole* is described as a generalized swelling of the villous tissue, diffuse trophoblastic hyperplasia and no embryonic or fetal tissue.

In over 90% of complete moles only paternal genes are found, and in 10% the mole is heterozygous.

b) Partial hydatidiform mole

This is characterized by *focal swelling of the villous tissue, focal trophoblastic hyperplasia and embryonic or fetal tissue*. These localized abnormal villi are scattered within macroscopically normal placental tissue which alt-

hough tends to retain its shape— hence the term 'partial' mole.

Unlike complete moles, partial moles usually have a biparental genetic make-up— triploid, or rarely tetraploid chromosomal constitution, with *two sets of paternal haploid genes and one set of maternal haploid genes. There may also be a concurrent* ***fetal gestation***.

c) Hydropic degeneration of the trophoblast

Similar to partial moles, hydropic degenerations of the trophoblast also have focal trophoblastic changes and biparental genetic make-up, but the distinguishing factor here are ***relatively smaller villi (< 3mm)*** on histology.

d) Invasive mole

Invasive moles are those *that invade surrounding structures— but confined within the uterus.*

In the invasive mole the trophoblast-covered villi penetrate the myometrial fibres and may extend to other organs, but the appearance of the villi remains that of a benign tumour.

Invasive moles *that also spread* ***extra-uterine*** *or* ***through blood vessels*** are termed '**choriocarcinomas'**.

e) Choriocarcinoma

Here, the tumorous lesion *of trophoblastic epithelium* is characterized by sheets of trophoblastic cells, both syncytio- and cytotrophoblasts, with few or no villi formed;

- These are highly malignant and tend to metastasize to the lungs, liver and brain;
- Around 50% of choriocarcinomas arise from a molar pregnancy as **invasive moles** *that invade bloodstream* while 30% occur after a miscarriage and 20 per cent after an apparently normal pregnancy.

Choriocarcinomas can occur after an extrauterine pregnancy and affected individuals present with signs and symptoms similar to those of ectopic pregnancy.

f) Risk factors

Evidence-based established risk factors for GTD include;

- High maternal age;
- Maternal blood group A— observed to be at a greater risk than blood group O women;
- Previous history of GTD.

ii) Clinical features

Patients with a GTD most commonly present with;

- Persistent vaginal bleeding;
- Uterine enlargement greater than expected for gestational age;
- An abnormally high level of serum hCG— consequent hyperemesis may also be observed.

Absent fetal heart sounds on pinard's stethoscope or doppler are also observed with complete moles.

Because choriocarcinomas can occur after an apparent normal pregnancy, affected individuals may present with symptoms due to metastates— dyspnea, abdominal pain and/or neurological symptoms. Rarely, this may occur *upto 10–15 years after last pregnancy*.

Symptoms from complications including *pregnancy-induced hypertension*, *hyperthyroidism*, *hyperemesis*, *anemia* and the development of ovarian *theca-lutein cysts* (see Chapter 9: Ovarian diseases and malignancies) may also be observed.

The ovarian hyperstimulation and enlargement of both ovaries predisposes to ovarian torsion or rupture of theca lutein cysts.

iii) Investigations and diagnosis

Serial measurement of hCG levels is the gold standard for diagnosis and monitoring the therapeutic response;

- Molar changes can now be detected as early as the 2nd month of gestation by ultrasound, which typically reveals a uterine cavity filled with multiple sonolucent areas of varying size and shape (classically

called '*snow-storm appearance*') without associated embryonic or fetal structures.

- Confirmatory diagnosis is with histological examination of lesions— *showing trophoblastic hyperplasia*.

Because of propensity for metastasis of choriocarcinomas, a chest X-ray is indicated to exclude lung metastasis.

Arteriography was first previously used for *in-utero* diagnosis of GTD. But this has mainly been replaced by ultrasound imaging. In women with persistent GTD or with chemotherapy-resistant disease, angiography has a proven role in diagnostic work-up of myometrial invasion and surgical management.

iv) Management, treatment and follow-up

Key points to note here are;

- Uterine contractions and the expulsion of grape-like vesicles material may occur naturally;
- Suction evacuation may be considered in other cases on presentation. The administration of prostaglandins or oxytocics to induce contractions should be avoided as these may lead to the intravascular dissemination of trophoblast;
- Gentle curettage may be performed later to remove any residual trophoblastic tissue;
- If bleeding persists > 21 days, a 2nd curettage is indicated to prevent dissemination of trophoblastic cells.

Complete disappearance of β-hCG takes 12–14 weeks on average and *β-hCG levels should be followed at 7-10 days intervals*;

- If the level falls serially no drug treatment is needed;
- When β-hCG level has been normal for 3 consecutive weeks, test monthly for 6 months;
- If the assay shows normal β-hCG levels for 6 consecutive months, follow-up can be discontinued;
- During the follow-up period pregnancy should be avoided— *oral contraceptives are safe in this period*;
- If the serum β-hCG level plateaus for more than 3 consecutive weeks, or rises, or if metastases are detected, treat with **methotrexate**;
- For other high-risk individuals or those with persistent GTD, ***multi-agent therapy*** is indicated.

Women over 40 years of age, or those who have completed their families, may prefer to have a hysterectomy, to avoid potential malignancy.

(IV) Other early pregnancy disorders

Table. Summary of some other early pregnancy disorder

Disorder	Epidemiology	Risk factors	Clinical presentation	Management
Hyperemesis gravidarum	Occurs in about 1-2% of pregnancies	- Non-caucasian population; - Multiple gestation; - GTD.	- Severe and intractable vomiting in pregnancy; - Abdominal pain.	- Fluid and electrolyte replacement; - Ultrasound scan; - Antiemetics and multivitamin replacement.
Urinary Tract Infection (UTI)	6% of pregnant women have asymptomatic bacteriuria. Can progress to symptomatic UTI in upto 30% cases.	- Pregnancy; - Previous UTI; - History of renal stones.	- Pyrexia; - Dysuria; - Hematuria.	- Antibiotics.

CHAPTER 8 BENIGN DISEASES OF UTERUS AND CERVIX

(I) Uterus

Table. Terminology of aberrant endometrial and myometrial tissue.

Terminology	Description
Adenomyosis	An extension of endometrial tissue into the uterine myometrium leading to abnormal bleeding and pain. The uterus becomes soft, globular.
Adenomyoma	A well-circumscribed collection of endometrial tissue within the uterine wall. They may also contain smooth muscle cells and are *not encapsulated*. Adenomyomas can also prolapse into the endometrial cavity similar to a classic endometrial polyp.
Endometriosis	The presence of endometrial cells outside the uterine cavity. The hallmark of this chronic disease is cyclic pelvic pain.
Endometrioma	A cystic collection of endometrial cells, old blood, and repeated accumulation of menstrual debris on the ovary; also known as "chocolate cysts."
Leiomyoma (uterine fibroids)	Local proliferations of smooth muscle cells within the myometrium, often surrounded by a *pseudocapsule*. Also known as fibroids, these benign growths may be located on the intramural, subserosal, or submucosal portion of the uterus.

i) Endometrial polyps

These are discrete benign outgrowths of endometrium, moving with flow of the distention of medium;

- They may be sessile or pedunculated (attached by a pedicle);
- With increasing age, the *most common abnormality* is endometrial hyperplasia, which can be present localized to endometrial polyp tissue;

Clinically, they may present with;

- Menorrhagia;
- Dysmenorrhea;
- Intermenstral bleeding.

Management is guided by following recommendations;

- Endometrial polyps in women <40 years of age, only require treatment by removal if symptoms persist for ≥3 months;
- Women >40 years of age and pre-menopausal, polyps detected on ultrasound or hysteroscopic testing should be considered for removal;
- Post-menopausal women that develop endometrial polyps should have them removed because of ↑ risk of hyperplasia and malignancy;
- Surgical removal remains the mainstay of treatment of endometrial polyps (see Figure).

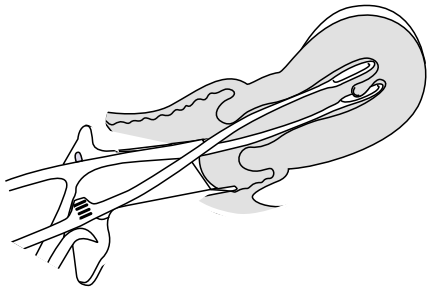


Figure. Illustration of surgical removal of endometrial polyps using polyp forceps.

ii) Asherman syndrome

When endometrium is damaged upto its basal layer, regeneration (as seen with normal endometrial cycle) *does not* occur, and instead there is fibrosis and adhesion formation. This complication is called **Asherman's syndrome**.

Sometimes, damage to endometrium may be carried out as part of a therapeutic approach to menorrhagia—controlled endometrial ablation using a diathermy loop or laser reduces menstrual blood loss significantly in those with menorrhagia (*discussed later)*.

Other causes of Asherman's syndrome include;

- Excessively aggressive curettage during evacuation of retained placental tissue after miscarriage or secondary post-partum haemorrhage;
- Tuberculosis;
- Schistosomiasis.

Lippes loop is a relatively large inert IUD that is used to prevent adhesion formation by maintaining separation of uterine walls.

On the other hand, once formed, adhesions can be lysed hysteroscopically, *thereby improving fertility*.

iii) Leimyomas

Leimyoma is a benign tumor of uterine myometrium. It consists of uterine smooth muscle appearing as a firm and whorled mass surrounded by a thin **pseudo-capsule** through which blood vessels enter the fibroid.

The typical whorled appearance may be altered by different forms of **degeneration**;

- **Red degeneration**— this follows *an acute disruption* of blood supply *during active growth*. Although rare, it is classically seen during mid-second trimester of gestation where it presents as sudden onset pelvic pain, mild fever and leucocytosis. The symptoms improve in a few days and intervention is not required;
- **Hyaline degeneration**— occurs where there is *gradual* outgrowth of fibroid relative to its initial blood supply;
- **Cystic degeneration**— progression of hyaline degeneration can lead to central necrosis in the central portion of fibroid, leaving behind cystic spaces. Over long term, these can get calcified and be incidental findings on Xrays in postmenopausal women.

Although the exact pathophysiology is unknown, risk factors for development of fibroid include;

- Nulliparity;
- Obesity;
- Family history of fibroids;
- African racial origin (3 times higher risk relatively).

It can be found at many locations at or around the uterus (see Figure);

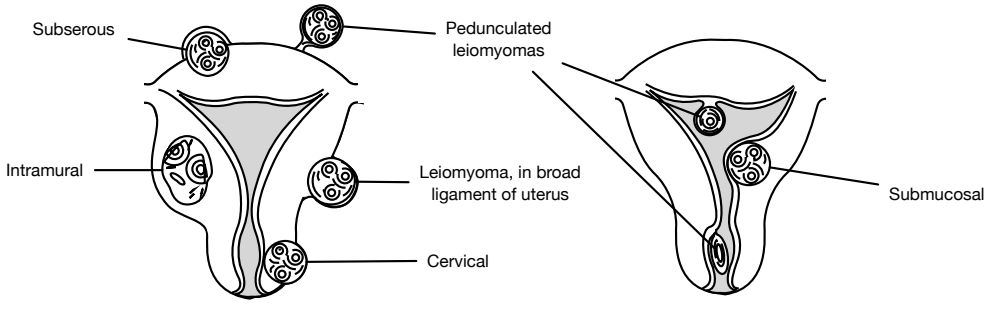


Figure. Location and types of uterine fibroids.

- Submucous fibroid— bulging into the endometrial cavity;
- Intramural fibroid— located centrally within the muscular myometrium wall of uterus;
- Subserosal fibroid— at the outer border of the myometrium;
- Pedunculated fibroid— fibroid attached to the uterus by a narrow pedicle containing blood vessels;
- Cervical fibroids can arise from myometrium surrounding the cervix;
- Fibroids can also arise in the broad ligament. These are thought to be due to embryonal remnant tissue.

a) Clinical Features

Fibroid are **estrogen dependant**. Commonly seen in 20% women >30 years of age. Often asymptomatic, they can, however, present with;

- Menstrual disturbance;
    - Menorrhagia— indicate presence of a submucous fibroid because of its distortion of endometrial surface;
    - Pressure symptoms— urinary frequency, etc.
- Pain symptoms— especially with occurrence of ***degenerations*** (described above);
- Subfertility and difficulty conceiving— due to mechanical distortion of anatomy preventing implantation (the risk of miscarriage, however, *does not* increase once a pregnancy has established);
- Rarely, malignant transformation of leimyoma into **leimyosarcoma** may occur which presents as a *rapidly enlarging abdominopelvic mass and weight loss.*

b) Investigations

Haemoglobin and haematocrit levels may be carried out if there is a history of menorrhagia, but ultrasound scanning remains the **test of choice**. It aids in;

- Distinguishing fibroid from other periadnexal masses, e.g. ovarian mass;
- Pressure effect on surrounding structures from fibroid, e.g. hydronephrosis.

c) Treatment

- Asymptomatic fibroids detected incidentally may be managed with a wait-and-watch approach. This employs repeat examination and ultrasound at 6-12 months' interval to determine the growth rate.
- In other cases, options for medical *management* are;
    - Ovarian suppression with GnRH agonists is the only available treatment, as NSAIDs and COCs *tend to be* relatively ineffective for symptoms;
    - Ovarian suppression shrinks the fibroid size and improves symtoms. This facilitates surgical treatment by *decreasing the bulk and vascularity* if used over a 3-month period;
    - The fibroids, however, regrow to previous size on stopping medical therapy.
- Surgical *treatment* options include;
    - Hysteroscopic removal of fibroid— improves menorrhagia drastically;
    - Uterus-conserving myomectomy— for larger fibroids can relieve pressure effects on surrounding structures while preserving fertility;
    - Hysterectomy— is an option for those that do not require fertility;
    - Interventional radiological techniques— **uterine artery embolization (UAE)** is a less invasive technique that embolizes both uterine arteries. The result is shrinkage of fibroid due to decreased blood supply and menorrhagia improves drastically.

d) Complications

In addition to subfertility, the mechanical distortion from fibroids may cause;

- ↑ risk of an abnormal lie of fetus in later trimesters of pregnancy;
- ↑ risk of post-partum haemorrhage— due to inefficient uterine contractions.

iv) Endometriosis

Endometriosis is the *most common benign gynaecological condition*, estimated to be present in 10-15% of women. It is a condition in which endrometrial tissues is deposited outside the endometrial cavity.

The uterosacral ligaments are common sites, but ovaries, pelvic walls, pouch of Douglas, intestines, umbilicus, abdominal scars, nasal passages and pleural cavity can all be involved (see Figure).

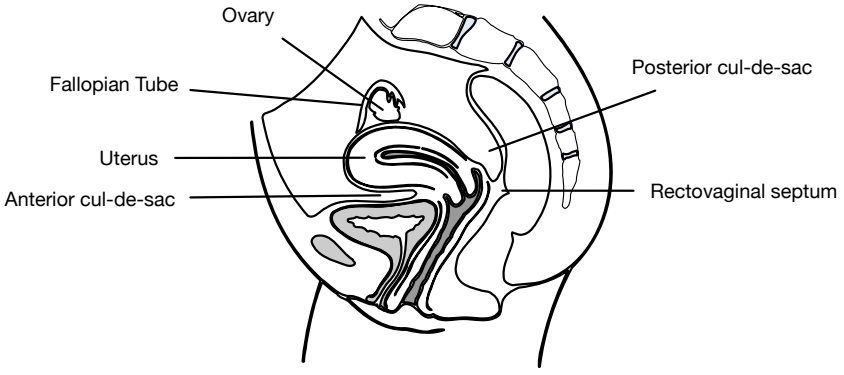


Figure. Common sites of endometriosis deposits.

The extrauterine endometrial tissue deposits undergo cyclical bleeding under hormonal control. Pain, inflammatory reaction occurs that heals with fibrosis and adhesion formation between associated organs.

a) Aetiology

Table. Aetiological theories of endometriosis.

Sampson's implantation theory In animal studies, experimental endometriosis can be induced by placement of menstrual fluid or tissue in the peritoneal cavity. This has lead to this widely accepted theory that suggests that endometriosis in human results from retrograde menstrual regurgitation menstrual fluid and subsequent implantation on the peritoneal surface.	**Meyer's coelomic metaplasia** Because there is a common origin for cells lining the Müllerian duct, ovaries and peritoneum, it has been proposed that endometriosis results from de-differentiation of these lining epithelia into their primitive form and then transforming into endometrial cells. This transformation may be influenced by biochemical factors, however, yet to be identified.
Genetic and immunological factors Endometriosis is seen more commonly in oriental women and less so in those from Afro-Caribbean origin. There appears to be an increased incidence in first-degree relatives as well. It is therefore suggested that genetic and immunological factors play a role in development of endometriosis.	**Vascular and lymphatic spread** Vascular and lymphatic embolization of endometrial tissue has been demonstrated and explains endometriosis is seen at distant sites outside peritoneal cavity, such as joints, skin, kidney and lung. It is certainly a complex interaction of more than one theoretical processes in development of endometriosis.

b) Histological subtypes

Based on appearance during laparoscopy and histological features, endometrial deposits can be classified as shown in Table;

Histological subtype	Components	Hormonal response	Laparoscopic appearance
Free	Surface epithelium, glands and stroma	Proliferative, secretory and menstrual changes	Hemorrhagic vesicle/bleb
Enclosed	Glands and stroma	Variable proliferative changes, secretory changes, but no menstruation.	Papule and (later) nodule. May present as wedge-shaped extensions of stroma (**Ramification**) deep in tissues.
Healed	Glands only	No response	White nodule or flattened fibrotic scar

c) Clinical Features

Clinical presentation is with non-colicky pelvic pain during menses, as the extrauterine endometrial deposits under hormonal control undergo similar changes as endometrial lining of the uterus with each menstrual cycle.

Intensity of symptoms does not correlate with extent of disease; however, site of pain may give insight to the spread. e.g;

- Deep dyspareunia (pain with intercourse) may occur if endometriotic tissue seeds the pouch of Douglas;
- Cyclical rectal bleeding episodes with bowel deposists;
- Cyclical epistaxis (nose bleeds) with nasal passage deposits;
- Cyclical hemoptysis ± hemopneumothorax with lung deposits (rare).

Physical examination may reveal;

- Thickening or nodularity of uterosacral ligaments;
- Tenderness in the pouch of Douglas;
- An adnexal mass/swelling;
- Fixed retroverted uterus (see Figure).

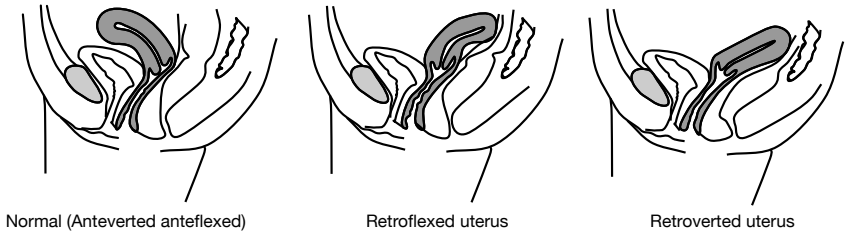


Figure. Normal uterine position, retroflexion and retroversion seen in endometriosis.

d) Investigations

- Transvaginal ultrasound scanning— detects relatively large lesions of endometriosis involving the ovaries (as endometriomas or chocolate cysts). The role of ultrasound is limited with smaller lesions;
- MRI scanning can detect lesions >5 mm in size in deep tissues like rectovaginal pouch— useful for presugical planning;
- Laparoscopy is the gold-standard for diagnosis. The advantage of this test lies in its diagnostic and therapeutic potential;
    - Staging of extent, biopsy and treatment with diathermy or laser can be performed altogether with this approach;
    - Can visualize endometriotic lesions under direct vision. Ovarian lesions are often seen as superficial hemorrhagic red vesicles or blue-black '**powder-burn**' lesions;
    - Identification of endometriotic lesions, however, can be missed by an inexperienced laparoscopist.
- CA-125 levels are often seen elevated with severe endometriosis. Though not of diagnostic value alone, these levels can be followed to see fall and rise with treatment and recurrence, respectively.

e) Treatment

Endometriosis is difficult to treat and is known to be a recurrent disorder spanning throughout reproductive life. In a significant proportion of patients, there is little progression of the disease.

Because these endometriotic deposits are estrogen dependant, a regression is seen with menopause. Similar resolution can be seen when treatment is directed to induce a *pseudomenopausal state*.

Medical treatment of endometriosis *does not improve fertility and should not be given to patients wishing to conceive.* However, surgical ablation/excision of minimal and mild endometriosis *does improve fertility chances;*

- Drug therapy;
    - Analgesics/NSAIDs— improve dysmenorrhea and pelvic pain;
    - COCs— these can be used for both diagnostic and therapeutic purposes; these are forst prescribed ***continuously*** for 6 months initially to render the patient amenorrheic;
        - If symptoms of cyclical pelvic pain regress— a diagnosis of minimal/mild endometriosis is made (in the absence of gross endometriosis on ultrasound);
        - If bowel symptoms persist— there may be coexisting irritable bowel syndrome (IBS) which may require assessment;
        - Continuous use of COCs can be extended indefinitely for several years or until pregnancy is desired, if there is success initially.
    - Progestogens— these are options for individuals with contraindications to COCs use;
        - Inducing therapeutic amenorrhea shows alleviation of symptoms;
        - Levonorgestrel IUS after surgical intervention is shown to be effective long-term.
    - Danazol/gestrinone— ovarian suppressive agents;
        - They are effective, but their use is limited due to their adverse effects profile;
        - Side effects include weight gain, greasy skin, acne (***with use >6 months***), changes in lipid profile and liver function.
    - GnRH agonists— effective as they induce a pseudo-menopausal state;
        - Available as intranasal sprays and slow release depots;
        - Side effects seen are similar to those seen with menopause— osteoporosis, hot flushes, night sweats, etc;
        - **Add-back therapy** with hormone replacement therapy (HRT) can prevent some adverse effects seen with ↓ estrogen levels.
- Surgical treatment— endometriotic cysts should not just be drained but **the inner cyst lining should be excised or destroyed**. This can be performed by;
    - Laparoscopic diathermy, laser vaporization or excision— standard of surgical management.
    - Women who have completed their families may be offered hysterectomy and bilateral salpingo-oophorectomy. Removal of ovary is essential for long-term symptom relief but concomitant *post-surgery HRT should not be started* for upto 6 months to prevent activation of any residual disease.

f) Complications

- Endometriomas on ovaries— affecting fertility;
- Pelvic adhesions (see Figure);
- Difficulty conceiving is seen in upto 30-40% patients affected with endometriosis due to complex processes (shown in Figure).

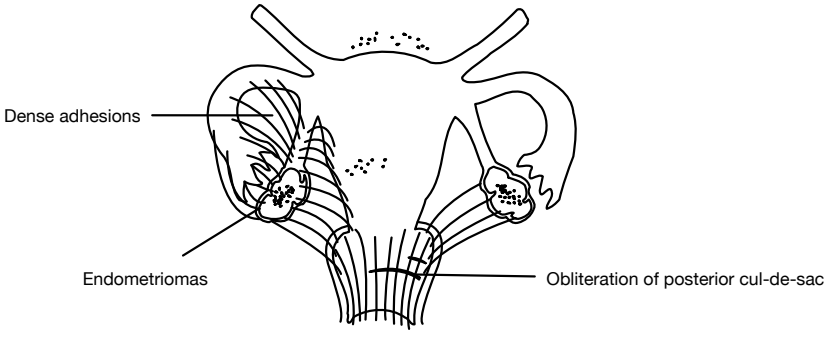


Figure. Schematic of endometriomas and periadnexal adhesions as seen in endometriosis.

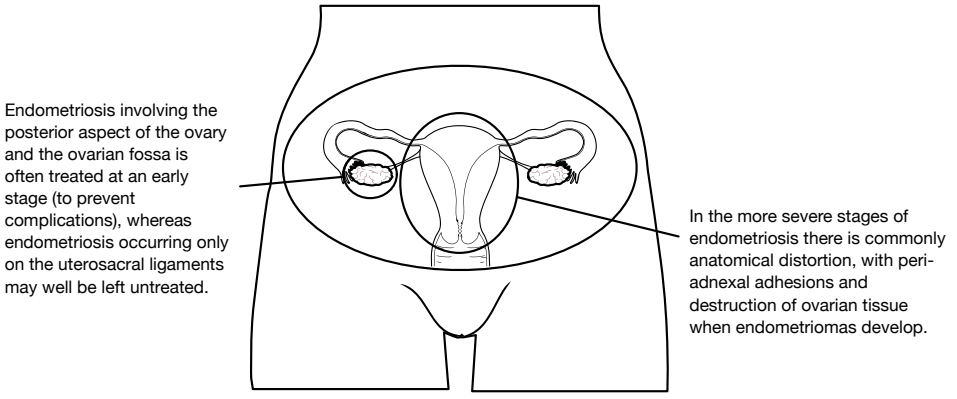


Figure. Endometriosis and infertility.

v) Adenomyosis

Adenomyosis is said to have occurred when endometrial tissue is found deep within the myometrium.

Though aetiological factors are not well understood, women affected with adenomyosis are usually multiparous, diagnosed in their thirties to fourties.

a) Clinical Features

- Clinical presentation is with severe ***secondary*** spasmodic dysmenorrhea and menorrhagia;
- Uterus is enlarged and often described as being '**boggy**' when examined perimenstrually.

b) Investigations

- Ultrasound examination may be useful— shows haemorrhage-filled, distended endometrial glands of altered echogenicity;
- MRI is the investigations of choice as it provides good imaging of soft tissues.

c) Management

- The management options are mainly palliative;
- Medical management options that induce amenorrhea are helpful in alleviating pain and bleeding, but symptoms rapidly return on discontinuation of said treatment. These include;
    - Danazol/gestrinone;
    - GnRH agonists.
- The only definitive option for cure is hysterectomy.

(II) Uterine cervix

a) Cervical ectopy (also known as cervical ectropion or cervical erosion)

The uterine cervix increases in size in response to estrogens. Because the cervix is anchored at the fornices, enlargement results in **eversion** to expose the columnar epithelium of the endocervical canal to lower genital tract (see Figure). This is termed **cervical ectopy** or **ectropion** or inappropriately as '**erosion**'.

It is particularly remarkable during (***Aide mémoire:*** *the 3 P's: Puberty, pills and pregnancy*);

- Neonatal period— under the influence of maternal estrogens;
- Puberty;
- Use of COCs;
- The first pregnancy.

In contrast, only squamous epithelium is visible on per vaginal examination in a postmenopausal woman that is not taking HRT.

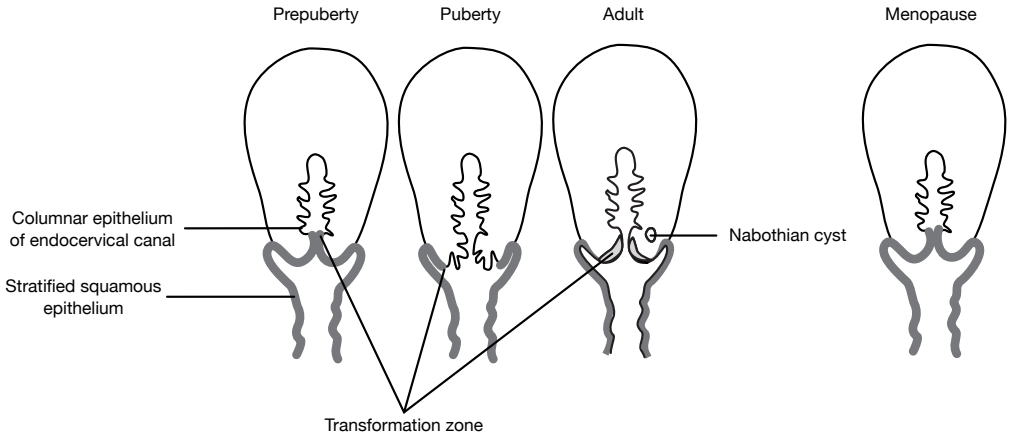


Figure. Transformation zone of the squamocolumnar junction.

Cervical ectropion is associated with;

- Excessive vaginal discharge which may vary from clear-to-mucoid (but non-purulent)— due to ↑ surface area of columnar epithelium;
- Post-coital bleeding— fine blood vessels in the columnar epithelium are easily traumatized.

b) Nabothian follicles

The exposed columnar epithelium in the ectocervix undergoes squamous metaplasia. The mucus glands within the columnar epithelium may become roofed over the squamous cell within the transformation zone. The result is formation of small (2-3 mm) mucus filled cysts visible on ectocervix— termed **Nabothian cysts.**

They can get larger overtime (up to 10 mm) and be detected incidentally on ultrasound scanning but are of no pathologic significance and do not require treatment.

c) Cervical stenosis

Stenosis of the cervical canal is usually iatrogenic;

- Cone biopsy, loop diathermy, ablation procedures (involving the internal os) are all associated with the incidence of cervical stenosis;
- The condition usually presents with dysmenorrhea but with relatively little or no menstrual bleeding because of hematometra (blood accumulating within the cervix);
- Treatment is with hysteroscopy-guided dilation of cervical canal, however, the recurrence rates are high and procedure may need to be repeated or hysterectomy performed to relieve pain.

CHAPTER 9 OVARIAN DISEASES AND MALIGNANCIES

The ovaries contain germ cells surrounded by specialized cells. It is under a complex endocrinologic control and releases an oocyte every month completing an ovarian cycle.

(I) Ovarian cysts

Most cysts of the ovary are due to overgrowth of its cells and can be classified as;

- Functional ovarian cysts;
- Inflammatory ovarian cysts.

i) Functional ovarian cysts

Also known as physiological cysts, these are relatively larger versions of follicles that normally form during ovarian cycle. *Uncomplicated functional ovarian cysts* appear as unilocular cysts on ultrasound scanning, and the cut-off of size between a maximally sized *normal* follicle and a cyst is a diameter of 3 cm (see Figure).

There is an association between ovulation induction and occurrence of these functional cysts. Other associations also include premature female infants and women with gestational trophoblastic disease (GTD).

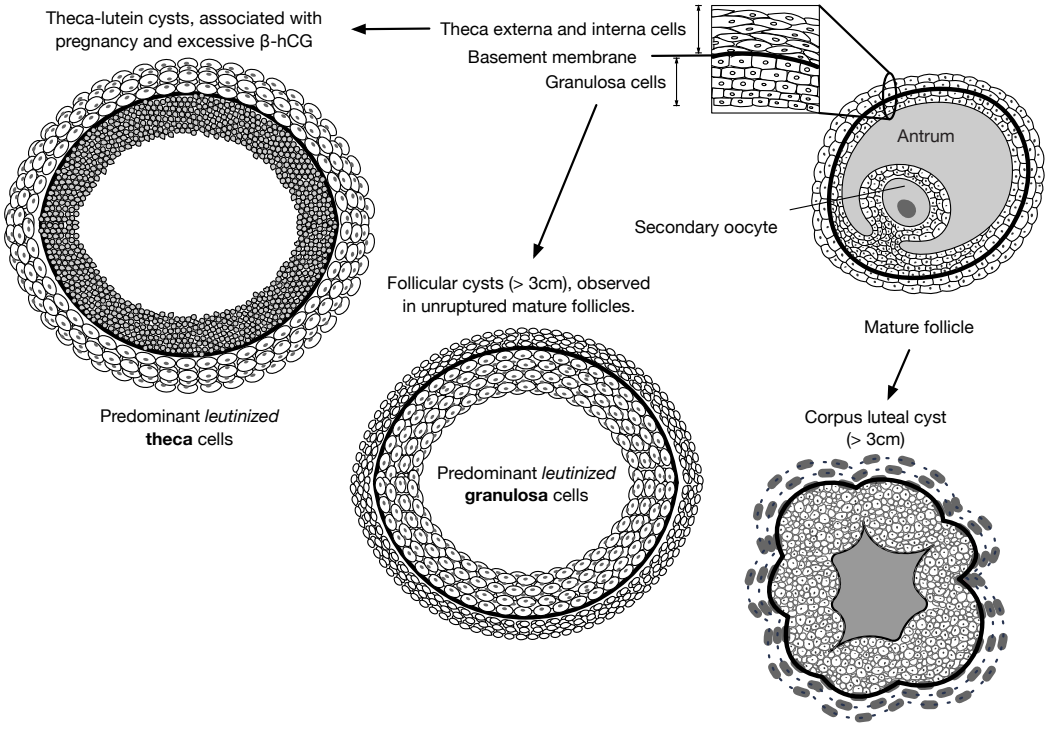


Figure. Illustration of ovarian cyts.

a) Follicular cysts

Follicular cysts are the **commonest benign ovarian tumor**;

- The originate from non-rupture of a dominant follicle, lined by **granulosa cells *predominantly***, and can persist for several menstrual cycles before finally involuting;
- Incidently discovered on ultrasounds, invervention is not needed unless the woman develops symptoms, or they *do not regress spontaneously by 8-16 weeks*;
- Ocassionally, they may be active and produce estrogen and result in menstrual disturbances and endometrial hyperplasia.

b) Corpus luteal cysts

A corpus luteal cyst is, ***by convention***, *a corpus luteum that exceeds a normal size of ~3 cm*;

- These are observed more commonly on the right side— attributed due to ↑ intraluminal pressure secondary to ovarian vein anatomy;
- Luteal cysts tend to rupture and/or hemorrhage. This rupture has a relatively higher risk of occurring on days 20-26 of the menstrual cycle;
- Occasionally, laparoscopic cystectomy may be considered if these cysts do not regress.

c) Theca luteal cysts

These cysts are lined by **lutenized theca cells *predominantly***. Often associated with pregnancy, these occur after ovulation in a corpus luteum;

- A higher incidence is seen with multiple pregnancy and gestational trophoblastic disease (GTD) where the levels of β-hCG are higher.
- While most resolve spontaneously during pregnancy, laparoscopic cystectomy is an option for others.

ii) Inflammatory ovarian cysts

These are cysts on the ovaries seen in association with pelvic inflammatory disease (PID);

- These can be a mass of blood collection (endometriomas) or an abscess in women affected with PID;
- Ultrasound shows characteristic ground-glass appearance in cases of an ***Endometrioma***;
- Treatment is centered around causative infection which improves chances of spontaneous resolution.

iii) Management approach to ovarian cysts

For follicular cysts;

- A normal follicular cyst up to 3cm in diameter requires no further investigation;
- A clear unilocular cyst of 3–10cm identified by ultrasound should be re-examined 12 weeks later for evidence of diminution in size— if the cyst persists, such women may be followed with 6-monthly ultrasound and CA-125 levels (described below);
- If the cyst does enlarge, laparoscopy or laparotomy may be indicated.

Ovarian cysts are very rarely malignant before the age of 35, especially when less than 10cm in diameter. Conservative management appropriate for *most young women*:

- Observation of cystic lesions 10 cm,
- Unilateral oophorectomy (even for solid lesions).

In older age group (>50 years), simple, unilateral cysts <6 cm in diameter with CA-125 levels <35 mU/mL and normal vascular resistance patterns are likely to be benign and may safely be *managed conservatively*. Here;

- If there is no change in the cyst at the second ultrasound at 3 months, follow-up with 6-monthly ultrasound and CA-125 levels is safe.
- Most will resolve in 3 years, but some can persist *for up to 7 years*.

Women over 45 years of age with a unilocular ovarian cyst greater than 6cm or with any other type of ovarian tumour should usually be advised to have a total abdominal hysterectomy and bilateral salpingo-oophorectomy.

(II) Benign ovarian tumors

The cells of the ovary can give rise to these benign growths;

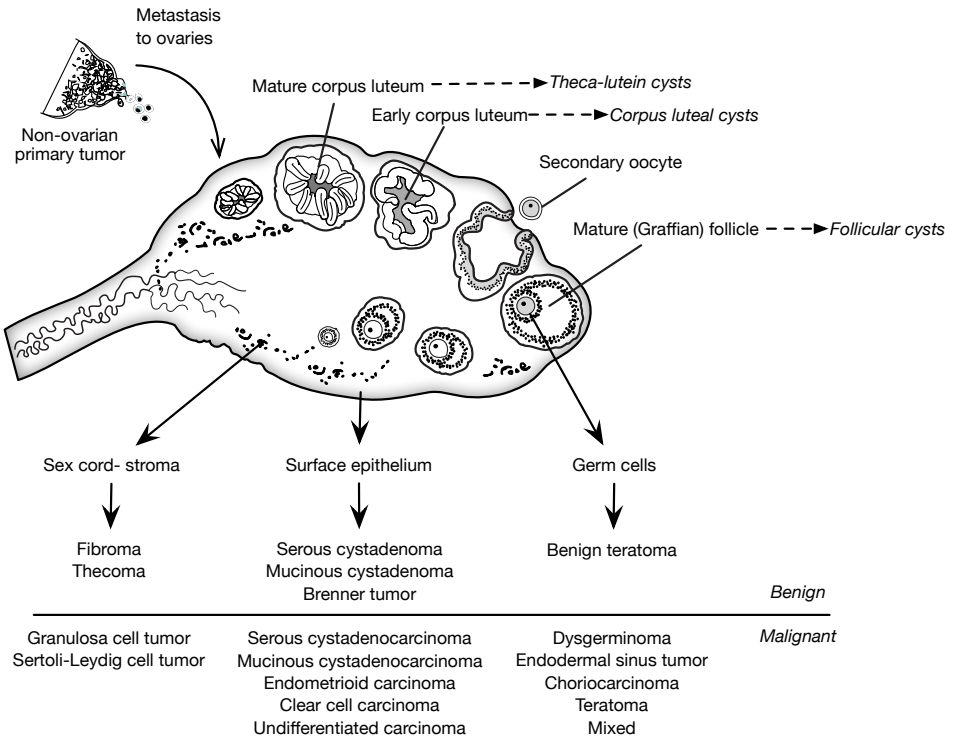


Figure. Ovarian cysts, tumors and their origins.

i) Surface epithelial cell tumors

These are *most commonly* seen in women between 35-55 years of age.

These originate from mesothelial cells of the coelom overlying the gonadal ridge. Because Müllerian and Wolffian structures are also derived from these cells, the neoplastic process can lead to development along fallopian tubal (serous cystadenoma), endocervical (mucinous cystadenoma), endometrial (endometrioid), or uroepithelial pathways (*Brenner tumor*). This explains its subtypes based on histological features;

- Serous cystadenomas— unilocular and unilateral;
- Mucinous cystadenomas— large multiloculated and bilateral;
- Brenner tumors— benign urothelial tumors, may be active and secrete estrogen;
- Endometrioid **carcinomas** (*malignant*)— difficult to differentiate from ovarian endometriomas;
- Clear cell (mesonephroid) **carcinomas** (*malignant*)— typical histological appearance of undifferentiated serosal "*hobnail*" cells (see below).

Serous cystadenomas and mucinous cystadenomas and account for 40% of all benign ovarian tumours. Diagnosis is often made on characteristic appearances on ultrasound and confirmation on histopathology;

Serous cystadenomas are the most commom epithetial ovarian tumors. They are typically unilocular and unilateral but can occur bilaterally;

- These tumors secrete thin, watery fluid inside them, but more characteristic feature of these tumors are intracystic *in-growing* papillomata (without **psammoma bodies** on histopathology, *see below*);
- Without management, these tumors carry potential for malignant transformation later in life.

In contrast, mucinous cystadenomas are usually **large and multilocular**;

- These tumors tend to secrete mucin inside them, resulting in a tenser wall (relative to serous tumors);
- Occasionally the tumor may rupture, releasing mucinous cells, which may become attached to the peritoneum and omentum, leading to an intraperitoneal accumulation of mucin— referred to as ***pseudomyxoma peritonei*** **secondary to primary ovarian cystadenoma**;

- In contrast, pseudomyxoma peritonei can also develop secondary to primary tumor of **the appendix** that metastasizes to the ovary and seeds the peritoneal surface— *pseudomyxoma peritonei secondary to primary appendiceal cystadenoma*.
- Malignant transformation is rare but can occur.

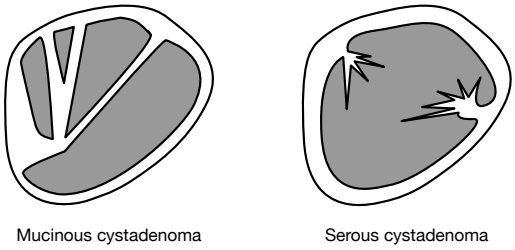


Figure. Illustration of gross appearance on cross sections of common epithelial cells tumors.

Brenner tumours are small benign tumours often found incidentally within the ovary— these contain ***urothelial-like*** epithelium and in rare cases, may secrete oestrogen.

Management of these tumors involves ovarian cystectomy or unilateral salpingo-oophrectomy.

ii) Germ cell tumors

Germ cell tumors are **the most common** ovarian tumors in young women aged 20-40 years;

- **Mature dermoid cyst** (or mature cystic teratoma)— **most common benign germ cell tumor of ovaries**;
    - These belong to *teratoma class of germ cell tumors*— compared to immature teratomas (which predominantly have malignant undifferentiated cells), these are well-differentiated.
    - Usually unilocular and can be bilateral in a few cases;
    - Theoretically any tissue type present in adults may be observed in ***mature teratomas***— mesenchymal, epithelial and/or stromal e.g. hair, muscle fibers, cartilage, bone or teeth may be noted. If a dermoid cyst contains only one tissue type, it is termed **"monodermal teratoma"**. e.g;
        - Struma ovarii— hormonally active thyroid tissue in dermoid cyst;
        - Carcinoid tissue— hormonally active serotonin secreting tissue in dermoid cyst.
- On the other hand, dysgerminomas, endodermal sinus-yolk sac tumors, and **immature teratomas** malignant germ cells tumors (see below in Malignant tumors of ovary).

Diagnosis is with pelvic ultrasound, althouh MRI is also *particularly useful in diagnosis*— because of high fat content in dermoid cysts;

Treatment is by laparoscopic or open excision (cystectomy) of the tumor. Acute torsion, haemorrhage, or rupture may, however, necessitate oophorectomy.

iii) Sex cord-stromal tumors

Sex cord-stromal cells form the connective tissue of ovaries. Sex cord-stromal cells are **solid** ovarian tumors and can attain a large size;

- Subtypes include;
    - Ovarian fibroma— most common sex cord-stromal tumor; these are hard and lobulated tumors with a *glistening white surface* on gross examination;
    - Thecoma— a benign, **solid,** estrogen-secreting tumor; can result in endometrial hyperplasia and post-menopausal bleeding.
- These sex cord-stromal tumors can present with pressure effects on surrounding structures, ***acute torsion***, or complications due to hormonal secretions.
- Ocassionally, a fibroma may present with **Meig syndrome**, which is a triad of *pleural effusion, ascites and ovarian fibroma.*

Surgical excision is the mainstay of treatment for these tumors.

iv) Clinical features

- Bening tumors are observed to follow a predilection for age groups;
    - Germ cell tumors— more commonly seen in young women;
    - Beningn epithelial cell tumors— more common in older women.
- They are brough to attention by symptoms such as discomfort/pain, or incidentally on radiologic testing. Larger size growth can result in additional symptoms;
    - Pressure on bowel— altered bowel habits;
    - Pressure on bladder— urinary frequency.
- Ovarian growths also tend to get affected by torsion, rupture, or haemorrhage into it— an acute severe pelvic pain is clinically correlated with these complications;
- Consistency of growth, whether cystic or solid, may also be appreciable— on bimanual examination (see Figure).

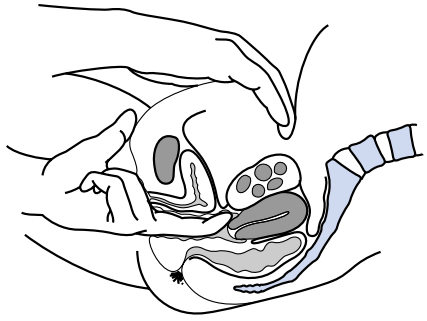


Figure. Illustration of bimanual examination for a peri-adnexal mass.

v) Investigations

In evaluating any pelvic or adnexal mass, a gestation should always be ruled out first by βhCG levels.

Other tests include;

- Hormonal levels of estrogen, androgens, thyroid— depending on clinical picture;
- Tumor marker levels— may be suggestive of, but are not diagnostic;
- Radiologic tests— Ultrasound (with color Doppler), CT scan, and MRI scans may be helpful;
    - Chest Xray may show pulmonary metastatic changes;
    - Abdominal Xray may show calcifications, particularly in cases of benign cystic teratomas.
- Ultrasound-guided cyst aspiration— has some role in diagnosis but carries high false-negative rate. It is uncertain whether it is associated with risk of disseminating malignant cells along the needle track.

vi) Approach to management of benign ovarian tumors

If the patient presents with severe, acute pain or signs of intraperitoneal bleeding, an emergency laparoscopy or laparotomy may be required— as this may be secondary to ovarian torsion.

Asymptomatic, simple ovarian cysts often resolve spontaneously;

- The use of a combined oral contraceptive is unlikely to accelerate the resolution of a functional cyst;
- However, ovarian cysts more than 10 cm in diameter are unlikely to be physiological or to resolve spontaneously.

Table. Criteria for observation of an asymptomatic ovarian tumour.

• Unilateral tumour. • Unilocular cyst without solid elements.

- Premenopausal women – tumour 3–10 cm in diameter.
- Postmenopausal women – tumour 2–6 cm in diameter.
- Normal CA 125 levels.
- No free fluid or masses suggesting omental cake or matted bowel loops.

Solid ovarian tumours are often malignant— in young women these solid tumors are usually germ cell or sex cord-stromal tumours. Young women aged < 35 years are, however, **less likely** to have a malignant epithelial tumour *but certain tumors may warrant surgical removal*;

- A clinical diagnosis may, however, not be possible without a laparotomy and even then, a histological examination is essential for a confident conclusion;
- Frozen section is seldom of value in this situation, as a thorough examination of the tumour is required to exclude invasive disease;
- A sample of peritoneal fluid or peritoneal washings should be sent for cytological examination at the beginning of the operation. It is essential to explore the whole abdomen and both ovaries.

In **prepubertal girls**, teratomata and follicular cysts are the most common. Theca and granulosa cell tumours may secrete hormones with resulting precious puberty;

- Management depends upon the relief of symptoms, exclusion of malignancy and conservation of maximum ovarian tissue without jeopardizing fertility;
- Therapeutic ultrasound-guided cyst aspiration has a limited role in treatment;
    - Cytological assessment of the aspirated fluid is performed routinely but cannot be relied upon to exclude malignancy;
    - The best candidate is a young woman with a unilateral, unilocular, anechoic, thin-walled cyst less than 10cm in diameter;
    - The recurrence rate is ↓ if the fluid is clear and ↑ if it is bloodstained;
    - A tumour in a young woman that appears to be largely solid on ultrasound is *likely to be a germ cell tumour* and requires **surgical removal**.

In a **young woman < 35 years of age**, an ovarian tumour is still *very unlikely to be malignant*.

- Even if the mass is a primary ovarian malignancy, it is likely to be a germ cell tumour that is responsive to chemotherapy. Thus, ovarian cystectomy or unilateral oophorectomy is a sensible and safe treatment for unilateral ovarian masses **in this age group;**
- It is sometimes said that the contralateral ovary should be sampled for histology in case the tumour is malignant. Even when the lesion is bilateral, every effort should be made to conserve ovarian tissue.

Since epithelial cancer is so much more likely **in a woman > 44 years of age** with a unilateral ovarian mass;

- It is probably best advised to have a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy, **or**;
- Unilateral oophorectomy in selected cases of epithelial carcinoma confined to one ovary may give equally good results as the traditional radical approach.

It would seem **reasonable to individualize the treatment of women aged 35–44 years** where there are greater benefits to the patient from a conservative approach and where the risks may well be less.

- If conservative surgery is planned, preliminary hysteroscopy and curettage of the uterus are essential to exclude a concomitant endometrial tumour;
- A thorough laparotomy is especially important, and an appropriate plan of action must be decided in advance if more widespread disease is found.

In **pregnant females;**

- Acute pain due to torsion or haemorrhage into an ovarian tumour— surgical intervention *should be undertaken* regardless of the stage of the pregnancy (under cover of tocolytic drugs in a centre where intensive neonatal care facilities are available);
- If an asymptomatic cyst is discovered, it is prudent to wait until after 14 weeks' gestation before removal. This avoids risk of removing *a corpus luteal cyst* upon which pregnancy might still be dependent;

- On the other hand, in the 2nd and 3rd trimester, the management of an asymptomatic ovarian cyst may be either conservative or surgical depending on risk and benefit;
- Cysts < 10 cm in diameter that have a simple appearance on ultrasound are unlikely to be malignant or to result in a cyst accident, and may therefore be followed ultra-sonographically;
    - Many will resolve spontaneously— if the cyst is unresolved 6 weeks postpartum, surgery may be undertaken then. The role for cyst aspiration in pregnancy, either diagnostically or therapeutically, is small.
    - The tumour marker CA-125 is not useful in the pregnant woman, since elevated levels occur frequently as an apparently physiological change.

Cyst aspiration may be considered in women in whom surgery is considered to be high risk, either because of coexisting medical problems or because dense pelvic adhesions envelop the ovaries.

Laparoscopic surgery is best reserved for young women, under 35 years of age, in whom the likelihood of malignant disease is small and in whom conservation of ovarian tissue is more important;

- The advantages are those of laparoscopic surgery in general— *less postoperative pain, shorter hospital stay and quicker return to normal activities*. Risk of post-op adhesions is also lower;
- However, the consequences of spillage of cyst contents, incomplete excision of the cyst wall and an unexpected histological diagnosis of malignancy are considerable disadvantages.
- Dermoid cysts are ***better removed by laparotomy*** because of risk of serious consequences if there is leakage of the cyst contents;
- Prior to any laparoscopy or laparotomy for a suspected ovarian tumour, it is prudent to perform a bimanual examination under anaesthesia to confirm the presence of the mass.

Table. Indications for laparoscopy.

Uncertainty about the nature of the mass.
Tumour suitable for laparoscopic surgery;
– Age < 35 years;
– Ultrasound shows no solid component;
– Simple ovarian cyst;
– Endometrioma.

vii) Complications

- Acute pain— from torsion, rupture, haemorrhage or infection; most commonly seen with luteal cysts which may mimick an ectopic pregnancy.
- Homonal effects;
    - Estrogen secretion— seen with granulosa cell tumors, theca cell tumors,
    - Androgen secretion— seen classically with *Sertoli-Leydig cell tumors*;
    - Thyroid hormone secretion— seen with mature dermoid cysts that have islands of thyroid cells formed in them.
- Pseudomyxoma peritonei— a rare complication seen with mucinous cystadenoma (also seen with mucinous tumors of the appendix). The mucus secreting tumor cells can seed the surrounding peritoneum and structures with continued secretions.
- Ocassionally, may a fibroma may present with **Meig syndrome**, a triad of *pleural effusion, ascites and ovarian fibroma.*
- Pressure effects from tumor can compress surrounding structures, potentially leading to;
    - Bowel and bladder effects with- or without uterine prolapse;
    - Edema of legs;
    - Varicose veins;
    - Hemorroids.

(III) Malignant ovarian tumors

Solid fixed ovarian masses on bimanual examination or ultrasound, are more likely to be malignant than cystic.

i) Aetiology and risk factors

Upto 80% of **malignant** ovarian cancers are of epithelial cell origin.

- These are often associated with relatively *a greater number of years of active ovulation*. E.g. nulliparity, early menarchal age, and late menopausal age. This is termed the '**incessant ovulation**' theory.
- A reduced incidence has also been observed in those subjects who take OCPs— which inhibit ovulation.
- '**Excess gonadotrophin secretion**' theory suggests that ↑ gonadotrophins and subsequent ↑ estrogens may proliferate the ovarian epithelium to neoplasia.

Table. Summary of factors affecting risk of ovarian cancer

↓ risk of ovarian cancer	↑ risk of ovarian cancer
Multiparity	Nulliparity
OCP use	Intrauterine device insertion
Tubal ligation	Endometriosis
Hysterectomy	Cigarette smoking—*particulary mucinous tumors*
	Obesity
	Genetic mutations (*outlined below*)

Mutations in certain genes are strongly linked to development of familial and sporadic ovarian cancers;

- *Loss-of-function* mutations in **tumor suppressor genes p16 and/or p53**;
- *Loss-of-function* mutations in **tumor suppressor genes BRCA-1 and BRCA-2** gene mutations— familial breast and ovarian cancers;
- *Loss-of-funtion mutations in* ***DNA mismatch repair genes*** **MSH2 or MLH1**— HNPCC (hereditary non-polyposis colorectal cancer, also called Lynch syndrome).
- *Overexpression* of **oncogenes: HER2/neu**— certain sporadic epithelial ovarian cancer;

Research also suggests a link between ovarian cancer and prolonged attempts at induction of ovulation.

ii) Classification

Table. Types of ovarian malignant tumors and their origin-cells.

Origin of neoplastic sells	Types of cancer
Epithelial cell tumours (can be benign, borderline or malignant)	• Serous tumours— serous cystadenocarcinomas • Mucinous tumours— mucinous cystadenocarcinomas • Borderline tumors (BOTs) • Endometrioid tumours • Clear cell (mesonephroid) tumours • Transitional epithelium— Brenner tumours
Sex cord stromal tumours	• Granulosa stroma cell tumour • Androblastoma/ Sertoli–Leydig cell tumour
Germ cell tumours	• Dysgerminoma • Endodermal sinus tumour (yolk sac tumour) • Embryonal cell tumour • *Choriocarcinoma* • Teratoma • Mixed tumours

iii) Epithelial cell malignant tumors

These include the malignant counter-parts of epithelial cell tumors;

- Serous cystadenocarcinomas;
    - Serous tumors can be benign as serous cystadenomas, high-grade undifferentiated cystadenocarcinomas or relatively well-differentiated borderline tumors (BOTs),
    - High-grade undifferentiated subtypes are the most common epithelial cell malignant tumors (upto 70% cases);
    - **Psamomma bodies** if seen on histopathology are pathognomonic (***if seen***)— refers to concentric rings/spherules of ***dystrophic calcification***;
    - Other malignant tumors that can have psammoma bodies include *papillary carcinoma of thyroid, meningioma and malignant mesothelioma*;
- Mucinous cystadenocarcinomas— generally large multiloculated malignant tumours, often associated with pseudomyxoma peritonei. These can also arise as relatively well-differentiated borderline tumors (BOTs);
- Endometrioid tumours— similar in histological appearance to endometrial cancer and often associated with **endometriosis** and/or a synchronous endometrial cancer in some cases;
- Clear cell carcinomas— these *can also arise from* **endometriotic deposits** but are characterized by clear cells resembling renal cell carcinomas (RCCs). A typical histological appearance of undifferentiated serosal "*hobnail*" cells is also seen.

Primary peritoneal carcinoma (PPC) is also a high-grade undifferentiated pelvic (*not always ovarian*) serous carcinoma.

- Although it is similar in histology to serous cystadenocarcinomas of ovary, but affected individuals present without an ovarian mass;
- There are obvious morphological differences on clinical findings at laparotomy. Criteria for diagnosis of PPC includes;
    - Normal sized or slightly bulky ovaries;
    - More extraovarian disease than ovarian disease;
    - Low volume peritoneal disease.
- The clinical behaviour, prognosis and treatment is the same as for high-grade serous cystadenocarcinomas of ovary, but primary chemotherapy is often used first for management as complete surgical debulking is difficult.

Approximately, 10% of epithelial cell tumors can also be borderline— ***borderline ovarian tumors*** (BOTs);

- These are relatively well differentiated, with some features of malignancy (nuclear pleomorphism and cellular atypia) but **do not invade the basement membrane**;
- The majority of BOTs are serous and mucinous tumors;
- Distinguishing between high-grade serous carcinomas and borderline subtypes is important because of differences in disease progression, response to chemotherapy and prognosis.
- A theory has also been proposed which suggests that these tumors arise from inclusion cysts of ovarian surface epithelium and/or endometriosis.

a) Clinical features

Due to vague symptoms, it is not uncommon for ovarian malignancies to be detected late. Common symptoms on presentation include;

- Increased abdominal girth/bloating;
- Persistent pelvic and abdominal pain;
- Decreased apetite.

Other symptoms such as persistent changes in bowel habits, urinary symptoms, back ache, irregular bleeding and fatigue may also be observed.

Physical examination may reveal;

- A fixed, hard mass arising from the pelvis on pelvic and abdominal examination;
- This, together with the presence of ascites is likely for ovarian malignancy especially in older age;
- The lymph drainage of ovaries is to para-aortic node— however, enlarged inguinal lymph nodes may still be suspicious for metastasis;
- Chest examination can also reveal pleural effusion— suspicious for **Meig's syndrome**.

b) Investigations and diagnosis

A pelvic ultrasound is better with transvaginal approach to delineate pelvic pathology— size, consistency, loculations, the presence of solid elements, bilaterality and extraovarian disease ± ascites, should be documented.

Levels of tumor marker CA-125 need to be checked;

- Although not dianostic for ovarian malignancies, these are raised in upto 80% of epithelial cell type ovarian malignancies;
- False-positive raised levels associated with benign conditions such as pregnancy, endometriosis and alcoholic liver disease ***should be ruled out***;
- Other tumor markers e.g. CA19-9, inhibin, hCG and AFP, however, do not hold potential in immediate diagnostic workup but are commonly used pre-op and for follow-up to treatment (see Table).

Table. Tumor markers used in ovarian cancer diagnosis and follow-up.

Tumor marker	**Tumor type**	**Uses**
CA-125	Epithelial ovarian tumors, and ***serous*** BOTs	**RMI calculation**, pre-operative use, and follow-up
CA 19-9	Epithelial ovarian tumors, and ***mucinous*** BOTs	Pre-operative use and follow-up
Inhibin	Granulosa cell tumours	Follow-up
hCG	Dysgerminoma and choriocarcinoma	Preoperative and follow-up.
AFP	Endodermal yolk sac and teratoma	Preoperative and follow-up

The Risk of Malignancy Index (RMI) is thereby calculated from aforementioned investigations (see Table). RMI is of great significance in triaging affected individuls for low-, intermediate- or high-risk of malignancy.

Table. Risk malignancy index for ovarian tumours.

<table>
<tr><th colspan="2">Characteristics</th><th>Score</th><th>RMI score</th></tr>
<tr><td rowspan="2">Ultrasound features (U)
Multilocular cyst;
Solid areas;
Bilateral lesions;
Evidence of metastases;
Presence of ascites.</td><td>None</td><td>0</td><td rowspan="5">RMI score = U x M x CA125 level
RMI < 25— low risk
RMI= 25-250— moderate risk
RMI > 250— high risk</td></tr>
<tr><td>≥ 2 features</td><td>3</td></tr>
<tr><td rowspan="2">Menopausal status (M)</td><td>Pre-menopausal</td><td>1</td></tr>
<tr><td>Post-menopausal</td><td>3</td></tr>
<tr><td>CA-125</td><td colspan="2">Level in units/mL</td></tr>
</table>

Pelvic pathology at intermediate or high risk of malignancy is an indication for imaging using computed tomography (CT) and/or magnetic resonance imaging (MRI) scans;

- The CT scan is particularly useful for assessment of extrapelvic disease and for staging;
- The MRI scan helps define tissue planes and operability;

Other investigations required for preoperative work-up include chest X-ray, electrocardiography (ECG), full blood count, urea and electrolytes, and liver function tests.

c) Staging

Ovarian cancer staging is based on clinicopathological assessment and, like other gynaecocolocial cancers, uses the FIGO staging system (see Table).

Table. FIGO staging for ovarian malignant tumors.

Stage		Description
1	*Tumour confined to ovaries*	
	1a	Limited to one ovary, no external tumour, capsule intact, no ascites
	1b	Limited to both ovaries, no external tumour, capsule intact, no ascites
	1c	Either 1a or 1b, but tumour on surface of ovary or with capsule ruptured or with ascites positive for tumour cells
2	*Tumour confined to pelvis*	
	2a	Extension and/or metastases to uterus or tubes
	2b	Extension to other pelvic organs
	2c	As 2a or 2b, but tumour on surface of ovary or with capsule ruptured or with ascites positive for tumour cells
3	*Tumour confined to abdominal peritoneum or positive retroperitoneal or inguinal lymph nodes*	
	3a	Tumour grossly limited to pelvis with negative nodes. but histologically confirmed microscopic peritoneal implants
	3b	Abdominal implants <2 cm in diameter
	3c	Abdominal implants >2 cm diameter or positive retroperitoneal or inguinal lymph nodes
4	*Distant metastases. Must have positive cytology on pleural effusion, or liver parenchyma*	

Most affected females on presentation have stage 3 disease;

- Metastatic spread is by direct spread to peritoneum and other organs and by lymphatic spread to pelvic and para-aortic nodes.
- A high percentage of women with advanced disease have evidence of peritoneal disease on the diaphragmatic peritoneum.

d) Treatment and management

A surgical approach is used for staging, diagnosis, and treatment. This should be best carried out at gynecologic-oncology department.

Laparoscopy or laparotomy may be carried out to gain wide-access;

- This aids in re-staging and biopsy of suspicious deposits;
- Ascites or peritoneal washings are sampled and a total abdominal hysterectomy and BSO performed along with an omentectomy;
- Lymph node resection is important, to detect occult metastatic disease in lymph nodes.

In young patients wishing fertility, **fertility-sparing surgery** may be carried out in *early stage epithelial ovarian cancer*—this involves;

- Unilateral salpingo–oophorectomy;
- Omentectomy;
- Peritoneal biopsies;
- Pelvic/para-aortic node dissection, and;

- Endometrial sampling (to exclude a synchronous endometrial tumor, as seen in endometrioid tumors).

Fertility-sparing surgery may also be performed in patients with BOTs if fertility is an issue, otherwise pelvic clearance should be performed.

In other cases, **debulking surgery** is used to remove tumor and deposits— this involves **possibly** additional;

- Resection of bowel;
- Peritoneal stripping, or;
- Splenectomy.

The aim of surgery is complete or optimal cytoreduction (aiming to leave behind <1 cm of residual macroscopic disease)— tumour deposits on *the bowel, spleen, peritoneal surfaces and diaphragm are usually amenable to resection*, while disease involving the **porta hepatis and bowel mesentery are not**.

If complete debulking is unlikely to be achievable in pre-op assessment, primary chemotherapy may be offered instead— this involves 3 cycles of chemotherapy, then interval surgery, last 3 cycles of chemotherapy afterwards and finally the so-called '**second-look surgery**' as;

- The 3 cycles of chemotherapy (out of a total 6) aims to reduce tumor burden;
- The interval debulking surgery after these first 3 cycles of chemotherapy aims to re-assess if debulking surgery can be successfully carried out;
- Whether debulking surgery is carried out or not, a second-look surgery is a planned laparotomy at the end of the 6 cycles (*in total*) of chemotherapy— aiming to assess and resect any residual disease.

Three cycles of neoadjuvant chemotherapy followed by interval debulking surgery *is not inferior to upfront surgery* and has been shown to be associated with less morbidity. On the other hand, more recent research suggests that a 'second-look' surgery' offers **no survival benefit**. In some centers, a repeat CT scan may be used instead.

Chemotherapy can be given as;

- Primary treatment ***or*** as neoadjuvant chemotherapy with surgical approach;
- As an adjunct following surgery— adjuvant chemotherapy;
- For relapse of disease— where its use-case scenarios include;
    - Prolonging clinical remission;
    - Prolonging survival;
    - In palliative approach to management.

For advanced ovarian cancer at presentation, surgery combined with platinum-based chemotherapy is the mainstay of treatment.

First-line treatment is usually a combination of a platinum compound (e.g. carboplatin, highly effective for ovarian cancer) with paclitaxel;

- Carboplatin is a platinum compound that is highly effective against ovarian cancer with relatively less side-effects than ***cisplatin***. Its mode of action includes cross-linkage of DNA strands arresting cell replication in actively dividing cancer cells;
- Paclitaxel prevents cell replication and division but has adverse effects like neuropathy, neutropenia, myalgias, and causes loss of all body hair;
- **Bevacizumab**, a monoclonal antibody against vascular endothelial growth factor (VEGF)— inhibits angiogenesis. Although not a first choice due to side effects, but it is effective at improving recurrence free intervals and overall survival when used in combination with carboplatin and paclitaxel in **advanced ovarian cancer**.

Following completion of chemotherapy, a repeat CT scan is necessary to assess response to treatment.

Follow-up of patients includes clinical examinations and CA125 measurement at regular intervals;

- Levels of CA-125 start to rise prior to onset of clinical evidence of disease recurrence;
- When disease recurs or re-recurs, treatment is mainly with a palliative approach;
- If the duration of remission is more than 6 months, chemotherapy may be employed again in some.

e) Prognosis

A multidisciplinary team approach with gynecologic oncology has improved progrosis. However, prognostic factors, in general include;

- Stage of disease (5-year survival for stage 1 disease is over 90% vs. 30% for stage 3);
- Volume of residual disease post surgery;
- Histological type and grade of tumour;
- Age at presentation.

iv) Germ cell malignant tumors

Malignant germ cell tumours occur mainly in ***young women*** and account for approx. 10% of ovarian tumours.

They are derived from *primordial germ cells* within the ovary and because of this may contain any cell type;

Dysgerminomas are the ***most common*** *germ cell tumors* accounting for 50% *of all germ cell tumours*— these can be bilateral in upto 20% of cases and occasionally secrete human chorionic gonadotrophin (hCG);

Endodermal sinus-yolk sac tumours are the *second most common germ cell tumours*, accounting for 15% of germ cell tumors;

- They are mostly bilateralt and associated with secretion of α-fetoprotein (AFP);
- They present with a large solid mass that often causes acute symptoms with torsion or rupture. Spread of endodermal sinus tumours is a late event and occurs usually to the lungs.

Immature teratomas, in contrast to mature cystic teratomas, are uncommon tumors but account for 15-20% of malignant germ cell tumors of the ovary;

- These belong to *teratoma class of germ cell tumors*— compared to mature teratomas (which predominantly have benign well-differentiated cells), these have **additional** undifferentiated immature cells;
- The immature elements in immature teratomas almost always consist of immature neural tissue in the form of small round blue cells focally organized into rosettes and tubules;
- In addition, solid teratomas carry a higher risk of dissemination and metastasis (in comparison to **cystic** teratomas, which tend to be benign— *mature cystic teratomas/dermoid cysts*). Occasionally, there can also be malignant transformation of a cell type within a mature teratoma;
- About one-third of teratomas secrete AFP.

a) Clinical features and investigations

The most common presenting symptom is a pelvic mass— and due to the age incidence, these are not uncommon to be detected during pregnancy— essentially any young woman presenting with a growing solid ovarian mass should be suspected of germ cell tumor;

- MRI is helpful to assess morphology, particularly within teratomas.
- Torsion or haemorrhage may be the cause of acute presentation;
- Metastasis of germ cell tumors is primarily by lymphatic or blood;
- Tumour markers should be measured pre-op as these influence the need for post-op chemotherapy.

Table. Tumor markers associated with germ cell tumors.

Tumor marker	Tumor type(s)	Uses
hCG	Dysgerminoma and choriocarcinoma	Preoperative and for follow-up
AFP	Endodermal yolk sac and teratoma	Preoperative and for follow-up

Given the common sites of metastasis, CT abdomen and CXR are recommended investigations to rule out metastasis in cases of germ cell tumors.

Non-gestational choriocarcinomas are very rare germ cell tumors, usually presenting in young girls with irregular bleeding and very high levels of hCG.

b) Treatment

Most women presenting with malignant germ cell tumours are of reproductive age— here, a fertility-preserving surgery and chemotherapy approach takes precedence over a gross debulking surgery. However;

- Spread of tumor to the contralateral ovary should be ruled out pre- or intra-operatively;
- Peritoneal biopsies and intraoperative frozen sections may be required to assess metastasis;
- If metastatic disease is found, it should be debulked at surgery;
    - For dysgerminomas confined to ovaries (stage 1) surgery alone is effective;
    - For other tumors, adjuvant chemotherapy is often used— this often employs **b**leomycin, **e**toposide and *the platinum-based compound* **c**isplatin (abbreviated as BEP chemotherapy) given over a course of 3-4 treatments.

The BEP chemotherapy regime gives long-term cure rates of over 90% and also preserves fertility if needed.

If the patient has recurrent disease, 90% will usually present in the first year following diagnosis— salvage chemotherapy at this point carries good success rates.

v) Sex cord-stromal cell malignant tumors

These tumours ***also*** account for approximately 10% per cent of ovarian tumours. Their characteristics include;

- Peak incidence ***around the age of menopause***;
- Relatively low malignant potential with a good long-term prognosis;
- Almost 90% cent of these tumors are functional (*i.e. hormone-producing*) tumours with downstream hormonal effects;
    - Estrogen producing tumors— ***granulosa cell-, theca cell- and Sertoli cell-tumors***;
    - Androgen production is seen with ***Sertoli-leydig cell or steroid cell tumors***.
- Granulosa cell tumours are the most common subtype, accounting for over 70% of sex cord stromal tumours.

Granulosa cell tumor is a solid malignant tumor of the ovary.

- Although malignant, these tumors are generally confined to the ovary on presentation.
- **Call-Exner** bodies on histology are pathognomonic for these tumors but may be seen in only half of the cases.
- These carry a good prognosis.

Juvenile granulosa cell tumours are rare granulosa cell tumors that affect pre-pubertal girls.

Sertoli-Leydig cell tumors are low-grade relatively differentiated tumors;

- Mean age of occurrence is 30 years;
- In many cases, these are unilateral and secrete androgens— and thus are also called ***androblastomas***.
- Androgen production is, however, not universal and seen in upto 50% cases.

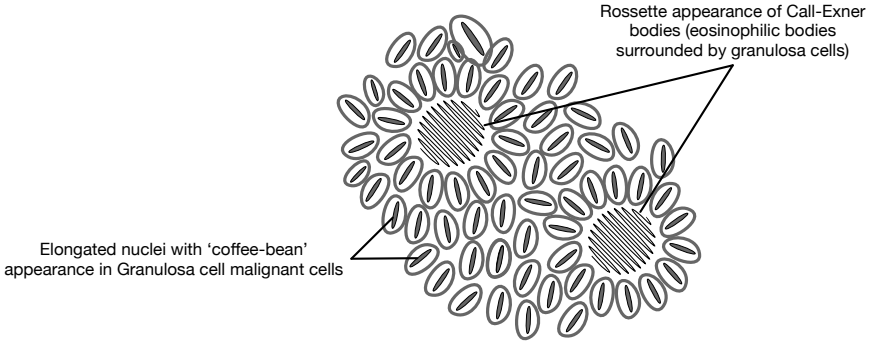


Figure. Illustration of Call-Exner bodies, pathognomonic for granulosa cell tumors on histopathology.

a) Clinical features

Early presentations in individuals affected by sex cord-stromal cell tumors includes secondary effects of hormone production.

Most sex cord stromal tumours present later as unilateral ovarian masses, measuring up to 15 cm in diameter. Macroscopically, the tumour is often solid with areas of haemorrhage.

Granulosa cell tumours may also present as a large pelvic mass or with pain due to torsion/haemorrhage in addition to estrogenic effects;

- Irregular menstrual bleeding;
- Postmenopausal bleeding.

Sertoli–Leydig cell tumours present with a pelvic mass and signs of virilization— common symptoms are *amenorrhoea, deep voice and hirsutism.*

The **rare** juvenile granulosa cell tumors present with precocious puberty in young girls.

b) Treatment

Treatment is based on the patient's age and wish to preserve fertility;

- Unilateral salpingo-oophorectomy, endometrial sampling and staging is sufficient in relatively young;
- In the older group, full surgical staging and debulking is recommended.

Surgery remains the mainstay of treatment for sex cord stromal tumors as there is no effective chemotherapy regime yet.

c) Follow-up

Granulosa cell tumours can recur many years after initial presentation and longterm follow-up is required.

Granulosa cell tumours also tend to produce inhibin— its levels can be used pre-operatively and for follow-up surveillance but are of little value in diagnostic workup.

d) Preventive surveillance

Screening general population has not proven effective using tumour markers or TVUSS.

However, women with one or more family member affected may be offered screening starting at age ≥ 35 by— transvaginal ultrasound + CA-125 levels yearly;

Prophylactic bilateral salpingo-oophrectomy may be offered to those women who have completed their families and are known to carry a gene mutation linked with ovarian cancer.

CHAPTER 10 PREMALIGNANT AND MALIGNANT DISEASES OF UTERUS AND CERVIX

(I) Uterine malignancies

The most common type of cancer of uterus is endometriod adenocarcinoma arising from the endometrium.

On the other hand, clear cell carcinomas can also arise from the endometrium.

Stromal cells or myometrial layer of uterus can also undergo neoplastic change to sarcomas, but these are rare.

Although patients can present with malignancy at any time during their reproductive lives, majority of uterine malignancies occur in the post-menopausal age group.

i) Endometrial carcinomas

a) Pathophysiology

Endometrial carcinomas can be of two types (see Figure);

- Type 1, estrogen-dependant— ***endometrioid*** adenocarcinoma, *arising from* ***endometrial hyperplasia***;
- Type 2, **non-estrogen dependant**— includes ***serous*** papillary carcinomas and clear-cell carcinomas, *arising from an* ***atrophic endometrium***.

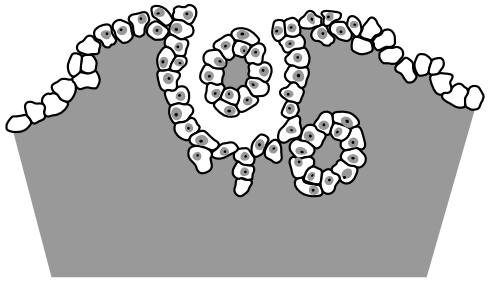


Figure. Illustration of type 2 endometrioid adenocarcinomas.

Type 1 endometrial carcinomas are frequently preceded by endometrial hyperplasia and are characteristically associated with certain risk factors (see Table);

- Tamoxifen, a SERM (Selective Estrogen Receptor Modulator), is also known to increase risk of endometrial cancer up to 2.5 folds (raloxifene, another SERM, does not have this effect).
- **Tobacco** has certain anti-estrogenic effects and associated with *lower incidence* of endometrial cancers;
- Genetic mutations linked with endometrial cancers include— mutations in *DNA mismatch repair genes* MLH1, MSH2, AND MSH6 leading to hereditary nonpolyposis colorectal cancer (HNPCC).

Table. Factors associated with type 1 endometrial carcinomas.

Factors associated with ↑ risk	**Factors associated with ↓ risk**
Obesity	Hysterectomy
Diabetes	COCPs use
Nulliparity	Progestin-based contraceptives
Late menopause	IUDs— i.e. Cu-IUD and LNG-IUS
Unopposed estrogen therapy	Pregnancy
Tamoxifen therapy	Smoking
Family history of colorectal and endometrial cancer	

On the other hand, this does not hold true for type 2 endometrial carcinomas which arise without endometrial hyperplasia. Type 2 carcinomas are also notorious for relatively poor prognosis.

b) Endometrial hyperplasia

Endometrial hyperplasia is an important cause of abnormal uterine bleeding as a precursor lesion in the continuum to endometrial carcinoma.

It refers to ↑ proliferation of endometrial glands relative to the stroma.

As outlined in risk factors above, this hyperplasia is associated with *prolonged* estrogen stimulation of the endometrium as seen with exogenous estrogen administration, anovulation, obesity, polycystic ovarian disease, and functioning estrogen-producing tumors.

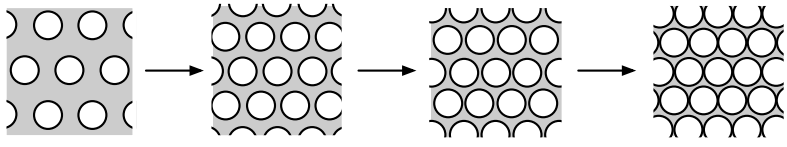
Endometrial hyperplasia is often associated with inactivation of the PTEN tumor suppressor gene (20% of cases), leading to increased cellular proliferation and diminished apoptosis.

Affected individuals commonly present with irregular bleeding or post-menopausal bleeding.

Morphologically, endometrial hyperplasia can simple or complex with or without atypia (see Table).

Table. Morphological classification of endometrial hyperplasia.

Simple hyperplasia without atypia (cystic or mild hyperplasia) exhibits benign cystically dilated glands— these rarely progress to adenocarcinoma.	Simple hyperplasia with atypia is uncommon; besides cystically dliated glands, it exhibits cytologic atypia (e.g., loss of polarity, prominent nucleoli) and 8% progress to malignancy.
Complex hyperplasia without atypia shows closely apposed glands of varying size crowded together into clusters; the epithelium remains cytologically normal and only 3% progress to cancer.	*Complex hyperplasia with atypia* shows glandular crowding and cytologic changes; there is substantial overlap with endometrial adenocarcinoma, highly associated type 1 endometrial carcinomas.



Crowding of glandular cells as seen in endometrial hyperplasia

Figure. Illustration of crowding of glandular cells as seen in endometrial hyperplasia (cellular atypia not shown).

Diagnostic assessment of endometrial hyperplasia is with transvaginal ultrasound (TVUSS);

- In post-menopausal women, endometrial thicknes ≥ 5 mm raises suspicion for endometrial hyperplasia or neoplasia;
- In pre- or perimenopausal women, endometrial thickness can reach upto 15 mm during secretory phase of menstrual cycle. Here, a persistent endometrial thickness ≥ 15 mm is generally considered an indication for further workup to rule out hyperplasia or carcinoma (see Investigations below).

c) Clinical features

Women usually present with abnormal vaginal bleeding. This can manifest as;

- Irregular vaginal bleeding in younger individuals;
- Post-menopausal bleeding in menopausal women (a post-menopausal woman presenting with vaginal bleeding must always be investigated).

Other symptoms, like intermenstrual blood-stained vaginal discharge, heavy menstrual bleeding, dyspareunia, or severe lower abdominal pain may also be observed.

Rarely, women may present with complications of advanced staged cancer. These include;

- Fistula formation;

- Bone or lung metastasis;
- Liver metastasis— affecting liver function.

On examination;

- Enlarged uterus may be observed on pelvic *bimanual examination*;
- Speculum examination may show blood from the cervix.

d) Investigations

Transvaginal ultrasound scan (TVUSS), hysteroscopy and endometrial biopsy— as part of diagnostic workup;

- TVUSS is the best first test in workup— endometrial thickness > 4 mm requires hysteroscopy and endometrial biopsy;
- Hysteroscopy allows direct visualization of endometrial cavity and sampling of endometrium for biopsy;
- The definitive diagnosis of endometrial cancer can only be made on endometrial biopsy. Histological examination can also give information to the **grade** of tumor;

MRI is helpful in **staging** of cancer, and also aids in determining surgical approach.

e) Grading and staging

Endometrioid adenocarcinomas (type 1 endometrial carcinomas) demonstrate glandular growth patterns resembling normal endometrial epithelium. These can be graded into three histologies;

- Grade 1, well differentiated— well-formed glands. These can distinguished from endometrial hyperplasias by *relative lack of intervening stroma*;
- Grade 2, moderately differentiated— well-formed glands mixed with areas composed of solid sheets of cells, which by definition make up 50% or less of the tumor;
- Grade 3, poorly differentiated— greater than 50% solid growth pattern in the tumor.

Type II tumors are by definition poorly differentiated (grade 3) tumors. *Serous papillary carcinoma, clear cell carcinoma and malignant mixed müllerian tumor are also included within this category*.

However, both type I and II endometrial adenocarcinomas can be staged using the FIGO classification.

Table. The FIGO classification for staging of endometrial carcinomas.

Stage		**Description**
1	1A	< 50% invasion of the **myometrium**
	1B	> 50% invasion of the **myometrium**
2		Tumor invading cervical stroma
3	3A	Local ± regional spread of tumor
	3B	Invades serosa of uterus
	3C	Metastases to pelvic ± para-aortic nodes
4		Tumor with metastasis to bladder ***or*** bowel ***or*** distant metastasis

f) Management

Surgery is the mainstay of treatment for endometrial cancer. The extent of surgery depends on several factors including grade and stage of disease and if radio- or chemotherapy is needed;

- Stage 1 endometrial cancer— commonly treated with surgery. However, the extent of surgical intervention depends on grade of cancer, spread, and comorbids.
    - Total hysterectomy and bilateral salpingectomy— most commonly performed. This can be performed by vaginal, laparoscopic or abdominal approaches.
    - If MRI scanning shows involvedment of cervix, a **modified radical hysterectomy** can be chosen instead— removes a cuff of vagina, paracervical and parametrial tissue often involving operative pelvic nodes dissection;

  - High grade undifferentiated tumors have a higher risk of nodal disease. These (e.g. grade 3) may need additional para-aortic nodes chain dissection.

- With stage 2 or higher endometrial cancers are best managed in a gynecologic-oncology department— here treatment strategies include;
  - High-dose radiotherapy (HDR);
  - External beam radiotherapy ± HDR;
  - These may be used in combination, as well as with chemotherapy for distant metastasis.

g) Prognosis

The prognosis of endometrial cancers depends on grade, and type of tumor. Non-favourable prognostic factors include;

- Age >70 years;
- High BMI;
- Grade 3 tumors of papillary, serous, or clear cell histology;
- Lymphovascular space involvement;
- Nodal ± distant metastasis.

h) Prevention

Hormonal contraceptives and intrauterine devices reduce the risk of endometrial cancer. Women with Lynch syndrome are offered prophylactic hysterectomy following completion of childbearing.

There are currently screening strategies for endometrial cancer (unlike CIN) with yearly testing in high-risk groups or the general population.

(II) Uterine sarcomas

These are rare cancers arising from stromal cells or muscle fibers of the uterus.

The **most common** types are carcinosarcomas and leimyosarcomas.

These can be classified into pure sarcomas, heterologous sarcomas or mixed epithelial sarcomas depending on tissue type observed in histological examination.

i) Pure sarcomas

These include ESS and leiomyosarcoma.

- Endometrial Stromal Sarcomas (ESS);
  - Present in perimenopausal women with irregular bleeding, and a *soft,* but *enlarged* uterus;
  - These tend to be low-grade and surgery is often curative.
- Leiomyosarcoma— rare carcinoma of uterine smooth muscle;
  - Can arise as a *malignant transformation of a benign leiomyoma* in rare cases;
  - Usually presents as a rapidly growing *soft* pelvic pelvic mass and pain;
  - MRI is helpful for diagnosis, but histopathology remains the definitive test.
  - Vascular invasion and distant metastasis to lung and brain may be observed.
  - Treatment is mainly centered around surgical removal, but adjuvant treatment may be considered if mitotic count is high (>10 mitosis/high power field).

ii) Carinosarcomas (Mixed epithelial-mesodermal sarcomas, or *previously* Mixed mesenchymal tumors)

These are so-called because they are shown to contain both elements of carcinoma (glandular epithelium) and sarcoma (endometrial stroma, or occasionally bone, cartilage or muscle).

- Women present with abnormal bleeding from uterus;

- Hysteroscopy often reveals a large, flesy mass protruding from the uterine wall into the cavity;
- Treatment is surgery, followed by adjuvant **radiotherapy**;
- Metastasis is common, as well as local recurrence after removal.

iii) Heterologous sarcomas

This rare group of tumors arise from ***sarcomatous tissue*** *which are not usually found in uterus*. These include striated muscle, bone or cartilage;

The most common heterologous sarcoma is **rhabdomyosarcoma** (also known as *Sarcoma botryoides*)— seen in female children;

- A **grape-like mass protruding from the cervix** with watery (often blood stained) discharge is a classical presentation;
- Histolopathology reveals neoplasia of primitive rhabdomyoblast cells;
- It, however, carries a bad progrosis because of high recurrence rates and distant metastasis.

(III) Cervical premalignant disease and malignancy

Human Papillomavirus (HPV) infection leads to premalignant change in the cervical epithelium (cervical intraepithelial neoplasia, CIN).

CIN has potential to transform into a malignancy, if left untreated.

i) Aetiology

Risk factors that have shown to be associated with cervical dysplasia and neoplasia include;

- Smoking;
- HPV infection— spread via skin-to-skin contact; although of no clinical significance, but types 16, 18, 31, and 33 have oncogenic properties;
- Immunosuppression, e.g. patients with AIDS, or those receiving immunosuppressant therapy.

ii) Pathophysiology and grading

The meeting point between columnar epithelium of endocervix and squamous epithelium of the ectocervix is called the **squamocolumnar junction** (SCJ).

Enlargement of the uterine cervix at puberty results in **eversion** to expose the columnar epithelium of the endocervical canal. The **transformation zone** (TZ) is the area where the original SCJ was and current SCJ is located and includes areas of *columnar epithelium undergoing squamous metaplasia*. This is the site where premalignancy and neoplasia develops.

The oncogenesis starts as disordered cell division of basal epithelial cells. This is known as **cervical intraepithelial neoplasia** (CIN). Cancer can arise from CIN if neoplastic cells cross over and spread through the basement membrane.

Regression and progression of CIN may occur, but oncogenesis is multifactorial;

- HPV infection leads to integration of the viral DNA into the basal cells of cervical epithelium— this can result in an uncontrolled cell division and subsequent neoplasia;
- Smoking exposes an individual to carcinogens that can trigger malignancy.

CIN can be divided into low-grade and high-grade disease. Low grade CIN includes grade 1, while high grade CIN includes CIN 2 and 3;

- Low grade CIN refers to minor cytological abnormalities showing mild dyskaryosis or borderline change atypia that is confined to the basal third of the epithelium, whereas;
- High grade CIN (grade 2 and 3) is labelled if there is moderate or severe dyskaryosis extending to 2/3rd (or more) of the epithelial thickness.

Unlike endometrial carcinomas where type II **serous** tumors (*i.e. non-adenomatous predominant cell type*) are by definition grade 3 poorly differentiated tumors, CIN (and also similar VIN and VAIN, *see below*) is still graded

with abovementioned cytologic abnormalities of dyskaryosis and atypia. This is regardless of predominant cell type which may be *squamous cells* or *adenomatous cells*.

For CIN lesions, the Bethesda grading terminology is also used in certain developed countries to distinguish lesions with predominant squamous cells (as ASC— atypical squamous cells) from those with predominant glandular dysplasia (as AGC— atypical glandular cells).

Cervical carcinomas may be;

- Squamous cell carcinomas in upto 80% of cases, or;
- Adenocarcinomas in 15% of cases, or;
- Adeno-squamous mixed carcinomas.

iii) Clinical features

The clinical presentation can be variable;

- Pre-invasive disease is asymptomatic, diagnosed as incidental finding after a loop biopsy of the cervix;
- Cervical malignancies tend to be friable and vascularized. Often, these present as;
    - Post-coital bleeding;
    - Intermenstrual bleeding;
    - Blood stained vaginal discharge;
- Advanced stage malignancies may present with;
    - Spread to spinal cord— pain;
    - Vesicovaginal fistulae— urinary incontinence;
    - Chronic vaginal bleeding— anemia;
    - Ureteric blockage— renal failure;

Pelvic and speculum examination may show cervical growth. In advanced stages, hardness and fixidity of pelvic organs may be observed.

iv) Investigations

All patients with symptoms of post-coital bleeding, or metrorrhagia should have a full pelvic examination;

- Cytology via cervical smears— cytological examination under microscope of scraping from the cervix *can show* ***dyskaryosis*** (i.e. cells in different stages of maturity);
    - This is carried out preferably by liquid-based cytology where a small brush is used to sample cells from the transformation zone and the brush head placed in fixative;
    - This is in comparison to 'Pap' smears where cells are removed from the cervix using a wooden spatula and placed on a glass slide and fixed. Pap smears are still used for cytological assessment in many parts of the world.
- Women between 25 and 64 years of age are recommended to undergo pap smear screening for CIN;
- Patients with high grade smears (moderate → severe dyskaryosis) are referred for colposcopy. While others with low grade smears are followed with repeat testing 6 months later because these often revert back to normal;
    - Application of 5% acetic acid and iodine during colposcopy can aid in identifying areas of increased cell turnover— a biopsy specimen from this site is of relative higher yield;
    - Angiogenesis is apparent in CIN and can also be observed during colposcope.

Because grading of lesions is not adequate enough, staging to confirm the extent of disease;

- Histopathology— helps confirm tumor type. In rare cases, a diagnosis may be missed if the tumor is endophytic (compared to exophytic);
- MRI of the abdomen and pelvis— provides insight into the spread of malignant cells to surrounding structures as well as lymph nodes;
- CXR— helps to exclude lung metastasis;

- Intravenous urogram— integrity of ureters;
- In difficult cases, examination under anesthesia or diagnostic laparoscopy is helpful in staging;
    - Rectovaginal examination under anesthesia— for vaginal and rectal involvement;
    - Cystoscopy— for bladder involvement.

Table. International Federation of Obstetricians and Gynecologists (FIGO) staging of cervical malignancies.

Stage	Description
1	**Carcinoma confined to the cervix** (corpus extension should be disregarded) 1a: Invasive cancer identified only microscopically. All gross lesions, even with superficial invasion, are stage 1b cancers. Depth of measured stromal invasion should not be greater than 5 mm and no wider than 7 mm 1a1: Measured invasion no greater than 3 mm in depth and no wider than 7 mm 1a2: Measured depth of invasion greater than 3 mm and no greater than 5 mm and no wider than 7 mm 1b: Clinical lesions confined to the cervix or preclinical lesions greater than 1a 1b1: Clinical lesions no greater than 4 cm in size 1b2: Clinical lesions greater than 4 cm in size
2	**Carcinoma extending beyond the cervix and involving the vagina** (but not the lower third) and/or infiltrating the parametrium (but not reaching the pelvic sidewall) 2a: Carcinoma has involved the vagina 2b: Carcinoma has infiltrated the parametrium
3	**Carcinoma involving the lower third of the vagina and/or extending to the pelvic sidewall** (there is no free space between the tumour and the pelvic sidewall) 3a: Carcinoma involving the lower third of the vagina 3b: Carcinoma extending to the pelvic wall and/or hydronephrosis or non- functioning kidney due to ureteric obstruction caused by tumour
4	4a: Carcinoma involving the mucosa of the bladder or rectum and/or extending beyond the true pelvis 4b: Spread to distant organs

v) Treatment

a) Treatment of CIN

Aim of treatment is to effectively eradicate CIN;

- CIN-1, Low grade CIN may regress spontaneously in upto 60% cases and are often followed up with a '*wait-and-watch*' approach with a second look colposcopy and biopsy 6 months later.
- High grade CIN requires treatment usually with excision or ablation.

Large Loop Excision of Transformation Zone (LLETZ) by diathermy is the preferred method of removal for higher grade CIN;

- This is carried out using a diathermy wire loop to remove a portion of the cervix which includes trans-formation zone with the area of CIN;

Excision should be up to 10 mm in depth to ensure removal of CIN developing deep in the cervical stroma (see Figure). Advantages of LLETZ include;

- Highly effective— upto 95% cases have negative smears at 6 months;
- Carried out with little risk under local anesthetic;
- Provides sample for biopsy/detailed pathological assessment.

Other methods for removal of CIN include cold coagulation and cone biopsy;

- The term 'cold coagulation' is a misnomer because it **actually** involves placing a hot probe on the cervix under local anaesthesia. It is a destructive treatment, is effective for both high- and low-grade CIN but

does not provide a specimen for pathologic assessment.

- On the other hand, cone biopsy produces a specimen for pathologic assessment as the name suggests by cutting a portion of cervix but ***requires general anesthesia***. Cone biopsy is also notorious for its association with **cervical stenosis or incompetence** in the long term— these have obstetric implications in the fertile age group.

Both cold coagulation and cone biopsy have largely been superseded by loop diathermy.

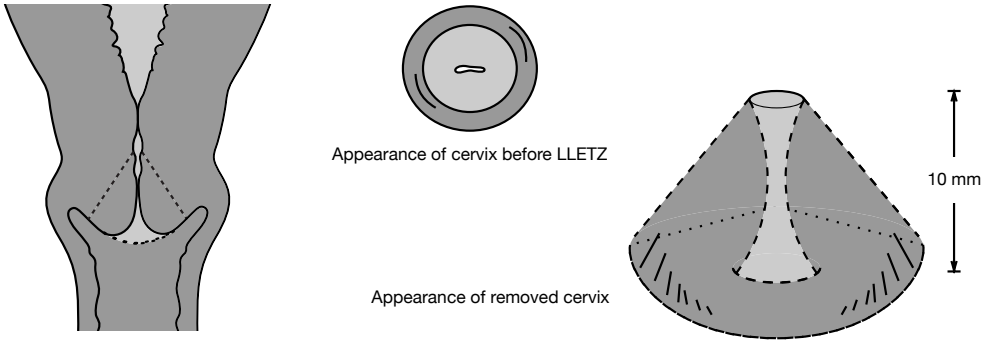


Figure. Illustration of LLETZ using a diathermy wire loop.

Patients who have received treatment for CIN also need **follow-up 6 months later**;

- This follow-up employs a high-risk HPV test and cytological assessment;
- If negative, the woman is returned to routine surveillance— i.e., age-appropriate cervical screening in 3 years time;
- However, if positive, repeat colposcopy is indicated to identify any residual, untreated CIN.

A woman with a history of CIN has an increased life-time risk of recurrent CIN and cervical cancer.

b) Treatment of cervical carcinomas

Treatment of cervical carcinomas, on the other hand, is based on staging of disease and fitness of patients.

Small mobile tumors favour a surgical approach in comparison with radiotherapy ± chemotherapy for larger fixed tumors;

- Stage 1A are preclinical microscopic tumors.
    - These are often diagnosed on histopathology after a loop diathermy.
    - If this pre-invasive disease is not completely excised, then a repeat loop biopsy or knife cone biopsy must be carried out.
    - Hysterectomy is not necessary, and fertility is preserved with this treatment.
- In stage 1B, neoplasia is confined to the cervix— a *Wertheim's hysterectomy* or pelvic radiotherapy should be considered;
    - Radiotherapy is the treatment of choice in **post-menopausal** women, due to tissue fragility encountered during surgical approach post-menopause, or in **pre-menopausal** women that are not fit to undergo general anesthesia;
    - Both radiotherapy and Wertheim's hysterectomy have similar success rates;
    - A radical trachelectomy is a fertility-sparing treatment occasionally chosen for patients with stage 1B1 small volume cancers. This technique involves surgical removal of pelvic lymph nodes, parametrial tissues, and 80% of the cervix.
- For large volume tumors with spread of malignancy beyond the cervix, stages 2-4— radiotherapy ± chemotherapy is the optimal. As a rule, *it is not wise to cut through cancer*.

c) Surgery

For stage 1b tumors, the standard surgical procedure is *Wertheim's hysterectomy,* a **radical hysterectomy and *pelvic* lymph node dissection**— parametrial tissue, uterus, cervix, and upper 1/3rd of vagina along with obtura-

tor, external and internal iliac lymph nodes are removed (ovaries in premenopausal women may be spared).

Compared to total abdominal hysterectomy, this procedure carries a higher incidence of complications;

- Atony of urinary bladder; intermittent self-catheterization may be needed post-operatively;
- Vaginal shortening— sexual dysfunction;
- Lymphedema in lower limbs—due to removal of pelvic lymph nodes;
- Surgery is preferred because it has a higher rate of cure.

d) Radiotherapy and chemotherapy

Radiotherapy serves to deliver a lethal dose focusing on neoplastic tissue.

It can be delivered as **external beam radiotherapy— teletherapy**, or as **internal radiotherapy** (brachytherapy);

- External beam radiotherapy is targeted to administer calculated doses of irradiation (usually 45 Gy units) of irradiation. This is achieved by giving fractions of treatments over several weeks;
- Brachytherapy uses selenium rods inserted into the uterus as the source of radiation and has the advantage of *minimizing* harmful effects on the bladder and bowel. This is because its effects are targeted only 5 mm from the rod.

Ideally, ***cisplatin-based*** chemotherapy is given in conjunction with radiotherapy— to ↑ cure rates.

Radiotherapy is associated with some side effects;

- Erythema-like sunburn over exposed skin;
- Inflammatory effects of radiotherapy— bowel and bladder urgency; can be complicated with bowel perforation in rare cases.
- Radiation treatment can cause fibrosis of surrounding tissues— vaginal stenosis, bladder damage, malabsorption and mucus diarrhea can occur.
- Radiation-induced menopause— this can occur because ovaries are highly sensitive to radiation.

e) Palliative management

Radiotherapy may be considered with a palliative intent, e.g. a one-off treatment with radiotherapy may be used for symptomatic bone metastases. However;

- Malignant pain, rectovaginal, or vesicovaginal fistulae and bleeding may occur.
- Distant spread is often a very late stage of the disease.

vi) Screening and primary prevention

Screening women, in general, has potential to pick up neoplasia early. A standard screening regime is followed in US as;

- Age <21— no cytological assessment or screening for HPV is needed, regardless of sexual activity;
- Age ≥ 21— start with cervical cytology alone without HPV testing; the recommendation is the same whether the individual is HPV vaccinated or not.

The frequency of recommended Pap smear is summarized below;

- Age 21–29— repeat cervical cytology every 3 years with cytology alone; do not perform HPV testing in this age group;
- Age 30–65— repeat Pap every 3 years with cytology alone **or** cervical cytology every 5 years with both cytology and HPV testing (the recommended option in this age group).

Pap smears should be discontinued;

- After age 65 if negative cytology and/or HPV tests for past 10 years AND no history of CIN 2, CIN 3 or cervical carcinoma;
- Any age if subject has had total hysterectomy and has no history of cervical neoplasia.

Vaccines against HPV have been developed to prevent primary infections with oncogenic subtypes of HPV viruses.

- HPV vaccines are highly effective against targeted HPV types when given before exposure to the virus. However subjects with prior exposure to HPV should also be vaccinated.
- Gardasil is most commonly available and is a quadrivalent vaccine against HPV types 6, 11, 16 and 18.
- Other vaccines developed are Gardasil-9 and Cervarix. Gardasil and Gardasil-9 also protect against certain forms of HPV-associated genital warts.

For effective protection, vaccination in females may be carried out in females as;

- Two doses of any HPV vaccine if vaccination is initiated before age 15 years— as 0, and 6^{th} or 12^{th} month for second dose
- Three doses of HPV vaccine if vaccination between the ages of 15-26— as 0, 1^{st} or 2^{nd} month and 6^{th} month for dosing schedule.

HPV vaccination can also be carried out in males.

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CHAPTER 11 CONDITIONS AFFECTING THE VULVA AND VAGINA

(I) Anatomy

Vulval vestibule is the area between the lower end of vaginal canal at the hymenal ring and the labia minora.

Both the labia minora and majora are covered with keratinized, pigmented, squamous epithelium, and sebaceous glands. However, the labia minora do not have adipose tissue and hair follicles, unlike labia majora.

Within the vulval vestibule lie;

- Ducts of minor vestibular glands;
- Ducts of major vestibular glands (Bartholin's glands);
- Urethral meatus;
- Periurethral glands of Skene;

The ducts of the Bartholin's glands open into the itroitus just above the fourchette at approximately 5 o' clock and 7 o' clock.

(II) Non-neoplastic disorders of the vulva

i) Vulvodynia

- Vulvodynia is described as pain in the perineal region in the absence of pathology.
- Allodynia— sensitivity to touch may be observed in patients with vulvodynia.
- It can be classified based on anatomical site of pain; either generalized, localized or clitoral.

ii) Pruritus vulvae

This term refers to vulval irritation in the form of itching.

It is a symptom often seen in women > 40 years of age as part of lichen sclerosis or vulvar eczema.

Diabetes, uremia, liver failure, allergic dermatitis, psoriasis, intertrigo, lichen planus, scabies, candidiasis, and trichomoniasis may all cause itching in the perineal area with additional signs/symptoms. Human papilloma is ***not*** thought to cause pruritus vulvae.

iii) Vulvar ulcers

Most vulvar ulcers are benign in nature and transient. If persistent, they should be biopsied to exclude malignancy. Causes include (see Table);

Table. Table. Benign vulval ulcers.

Aphthous ulcers
Herpes genitalis
Primary syphilis
Crohn's disease
Behçet's disease
Lipschutz ulcers
Lymphogranuloma venereum
Chancroid
Donovanosis
Tuberculosis

iv) Lichen sclerosis

- This destructive inflammatory skin condition which affects mainly anogenital area of women.
- There is inflammation in the subdermal layers of skin. This results in– *hyalinization*. The skin appears white, "parchment paper"-like.
- Additionally, lichen sclerosis presents in women as:
    - Itching, soreness
    - Fissuring— skin of the posterior forchette can split, resulting in dyspareunia.
    - Leukoplakia of vulval skin in a "figure of eight" distribution with loss of vulval architecture is characteristic appearance in late lesions.
- This condition can also affect foreskin of penis in men, in which case it manifests as phimosis.
- It associated with;
    - Other autoimmune illnesses, e.g. autoimmune thyroid diseases, and pernicious anemia;
    - Vulvar squamous cell carcinoma is also notoriously associated with long-standing lichen sclerosis as a **potentially** premalignant lesion (see VIN and vulvar cancers below).
- Skin biopsy is confirmatory.
- Treatment with locale application of steroid creams— *e.g. dermovate*.

v) Vulvar eczema

- Eczema in the perineal area may arise due to an allergy or exposure to an irritant.
- Thickening of the skin and whitening— is often not seen because of manual scratching that obscures this classical finding.
- Avoid nylon clothing, and bath water. Simple unperfumed soap should be used for washing innerwear which preferably should be of cotton. Topical steroids may be considered in other cases.

vi) Squamous cell hyperplasia

Squamous epithelium of the vulvar skin may undergo hyperplastic changes in response to itching.

However, it is a diagnosis of exclusion, and other conditions with *pruritus vulvae* must be ruled out and histological evidence of hyperplasia should be present.

(III) Benign tumors of the vulva

The most common epithelial origin tumors of the vulvar region are squamous papillomata, skin tags, lipomas, and fibromas.

The commonest solid tumors of the perineal area are condylomata acuminate— these are sessile outgrowths of the skin occurring due to infection with human papillomavirus type 6, or 11.

The ducts of the major vestibular glands may get blocked, resulting in a retention cyst— Bartholin's cyst.

- A bartholin's cyst is the commonest cystic tumor of the vulvar area;
- Women > 40 years of age should have histological examination of the cyst wall to rule out carcinoma;
- Antibiotics, and "incision and marsupialization" procedure has good success rates. This involves suturing the internal aspect of the cyst wall to outside, such that the cyst does not reform.

(IV) Premalignant conditions of the vulva

The major premalignant conditions of the vulvar region are;

i) Vulvar Intraepithelial Neoplasia (VIN)

- Squamous VIN— the commoner VIN, is analogous in pathologic characteristics to CIN but, as the name suggests, occurs on vulvar epithelium;

- Squamous VIN and squamous carcinomas are associated with two distinct etiologies— HPV-associated and non-HPV associated tumors associated with premalignant lichen sclerosis or squamous hyperplasia.
- HPV types 16, and 33 are most commonly associated with HPV-associated VIN and squamous carcinomas.

- Paget's disease (adenocarcinoma *in situ,* compared to **squamous** VIN);
  - This uncommon condition is similar to that found in the breast. It presents with pruritus in a red, crusted plaque-like lesion with sharp edges;
  - The diagnosis is confirmed by histological examination— a "***cake-icing effect***" due to overlying thick vulvar skin is a classic description;
  - There may be concomitant adenocarcinoma in the apocrine glands, vulval, vaginal, cervical, endometrial, ovarian, and transitional cell carcinoma of the bladder, and these should all be ruled out;
  - Because of the propensity to involve apparently normal skin, the treatment of Paget's disease is *very wide local excision* ± total vulvectomy. Histological examination should be with special care to exclude an apocrine adenocarcinoma.
  - Adenocarcinoma in the underlying apocrine glands, if found, carries *poor* prognosis.

ii) Clinical features, diagnosis and staging

Intraepithelial disease of the vulva often presents as pruritus vulvae, but may be asymptomatic;

- These lesions are often raised, have a rough surface;
- The colour is variable: white, due to hyperkeratinization; red, due to thinness of the epithelium; or dark brown, due to increased melanin deposition in the epithelial cells;

The extent of VIN can be assessed with application of 5% acetic acid. After 2 minutes, VIN turns white and mosaic or punctation may be visible by naked eye in a good light or using a hand lens or colposcope. *Toluidine blue* is also used as a nuclear stain, but has higher false-positives and false negatives;

The gold standard however remains biopsy, a sample for which may be obtained using a disposable 4mm **Stiefel punch biopsy.**

Unlike endometrial carcinomas where type II **serous** (*i.e. non-adenomatous predominant cell type*) tumors are by definition grade 3 poorly differentiated tumors, VIN is still graded with previously mentioned cytologic abnormalities of dyskaryosis and atypia. This is regardless of predominant cell type which may be squamous cells or adenomatous cells (called **Paget's disease** in cases of VIN).

iii) Treatment

- Spontaneous regression of VIN III in women is seen with a variant known as ***Bowenoid papulosis***;
  - These women are young, often present in pregnancy, have dark skin and the lesions are usually multifocal, papular and pigmented.
  - However, progression to invasion does occur in young women.
- Progression of of other untreated cases of VIN III to invasive cancer is well documented in literature.
- If the patient has presented with symptoms, therapy is required. Asymptomatic patients, particularly under the age of 50 years, may be observed closely. Biopsies should be repeated if there are any suspicious changes.
  - If invasion has been excluded carefully, topical steroids offer symptomatic relief for many women. These may not be applied for more than 6 months because of the thinning of the skin that may result.
  - If the lesion is small, an excision biopsy may be both diagnostic and therapeutic. If the disease is multifocal or covers a wide area, a skin graft may improve the cosmetic result of a skinning vulvectomy.
  - An alternative approach used to be to vaporize the abnormal epithelium with the carbon-dioxide laser— but this has variable results.
  - Another alternative is application of immunomodulating cream— imiquimod, but this too

is known to be less efficacious while carrying the risk of skin burning.

- Surgical excision is associated with recurrence— long term observation and retesting on histological examination is necessary post-surgery.

(V) Vulvar cancers

- Most vulval carcinomas are of squamous origin, although adenocarcinomas can arise from the Bartholin's gland and in conjunction with Paget's disease of the vulva.
- Melanoma, basal cell carcinoma and verrucous carcinomas also occur in the vulva.

i) Pathophysiology

- After invading the underlying tissue, vulval cancer spreads predominantly via the lymphatic system.
- Lymphatics drain vulva and lower ⅓rd of vagina to the inguinal and femoral nodes in the groin and then to the external iliac nodes. Drainage to both groins occurs from midline structures of perineum.
- Tumours with < 1mm of invasion beyond basement membrane carry the *lower* risk of lymphatic spread to be considered '*microinvasive*'.

ii) Clinical presentation

A well-demarcated raised or ulcerated lesion that is hard and craggy and bleeds on touch is highly suspicious for vulval cancer;

- Vulvar symptoms common are pain, lumpy feeling, post-menopausal bleeding;
- Usually a cauliflower-like outgrowth on the vulva is observed, which may ulcerate and present as a persistent ulcer;
- Vulvar region is drained by inguinal and femoral lymph nodes and these should be examined to rule out metastatic enlargement;
- Colposcopy and cervical cytology/pap smear is warranted to rule out multifocal involvement.

Table. Staging of vulvar cancer (FIGO 2009 classification).

Stage	Description
1	1-A; Confined to vulva and/or perineum, 2cm or less maximum diameter. Groin nodes not palpable. Stromal invasion no greater than 1 mm.
	1-B; as for 1-A but with stromal invasion > 1 mm.
2	Confined to vulva and/or perineum, > 2 cm maximum diameter. Groin nodes not palpable.
3	Extends beyond the vulva, vagina, lower urethra or anus; or unilateral regional lymph node metastasis.
4	4-A; Involves the mucosa of rectum or bladder upper urethra; or pelvic bone; and/or bilateral lymph node metastasis.
	4B; Any distant metastasis including pelvic lymph nodes.

iii) Investigations

- Biopsy remains the standard for diagnosis;
- Additional investigations may be considered for staging purposes; poor prognostic signs include;
    - Primary tumor > 4 cm in size;
    - Sphincter involvement;
    - Metastasis to inguinal nodes.

iv) Treatment

Surgery is considered a better approach, as these tumors tend to be locally invasive;

- Excision of primary tumor with wide and deep local excision + removal of groin lymph nodes.
    - Radical wide local excision with margins of 1-2 cm is kept ensuring clear surgical margins.
    - Inguinofemoral lymphadenectomy is needed commonly because of early metastasis to groin nodes. It, however, holds risk of post-op lymphoedema— heavy, woden, painful feeling in legs.
    - Sentinel lymph node (SLN) biopsy is an alternative approach whereby a lymph node is identified and removed in isolation with highest suspicion.
    - If node is negative, patient is followed for recurrence. If positive, then *radiotherapy* is given.
- Radical vulvectomy with removal of whole vulva may be considered in extensive cases.
- Advanced stage disease is often treated with a combination of surgical intervention, removal of metastatic nodes, radiotherapy and chemotherapy.

(VI) Vaginal diseases

i) Condylomata acuminata

- These are the *commonest* tumors in the vagina, occurring secondary to infection with Human Papillomavirus (HPV).
- Biopsy is warranted before treatment is initiated by means of surgery or laser— especially if lesions are close to cervix.

ii) Lichen planus

- Lichen planus of vagina is an erosive skin condition that is due to autoimmune inflammatory destruction. If left untreated can result in vaginal stenosis.
- Treatment is with intra-vaginal steroids and vaginal trainers (to stretch narrowing).

iii) Cystic swellings of vagina

- Mesonephric (Gartner's) or paramesonephric cysts may be seen, especially high up near the fornices.
    - If asymptomatic, they may be managed conservatively.
    - However, marsupialization procedure is superior in efficacy than excision for such cysts.
- Vaginal Adenosis *or* Mucus-containing vaginal cysts are a rare condition classically seen in children of women who took diethylstilbesterol during pregnancy. They are benign and are of no significance.

iv) Vaginal intraepithelial neoplasia (VAIN)

The terminology of VAIN is analogous to cervical intraepithelial neoplasia (CIN) to some extent;

- The difference is of histology that vaginal epithelium lacks crypts (in contrast to cervical epithelium). Hence, the intraepithelial neoplasia remains superficial until invasion.
- As discussed for VIN, unlike endometrial carcinomas where type II **serous** tumors are by definition grade 3 poorly differentiated tumors— CIN and here similar VAIN lesions are still graded with previously mentioned cytologic abnormalities. This is regardless of predominant cell type which may be squamous cells or **rarely** adenomatous cells.
- VAIN is rare to be seen in isolation— it is more likely to present as extention of CIN down to the vaginal canal. Thus, further evaluation is indicated to rule out concurrent CIN in affected individuals;
- VAIN can get buried in suture lines *post-hysterectomy* and present later as invasive neoplasia which is difficult to evaluate.
- Local ablation, or excision have high efficacy. *Partial vaginal colpectomy* to remove the vaginal vault. It removes VAIN buried in suture line post-hysterectomy.

(VII) Vaginal cancer

Although very rare, squamous cell carcinoma of vagina is commonest form of vaginal carcinoma. Other forms

that may be seen are clear cell **adenocarcinomas**, malignant melanomas, embryonal rhabdomyosarcomas and endodermal sinus tumors;

- Vaginal cancer is notorious for being asymptomatic in early stages. However, vaginal bleeding and discharge may be observed in some cases as the presenting symptom;
- The upper vagina is commonest site for invasive disease and can extend to surrounding structures and fistulae can form— e.g. rectovaginal fistula and vesicovaginal fistula. It can also infiltrate pelvic nerves— causing pain;
- Lymphatic spread occurs to the pelvic nodes from the upper vagina and to both pelvic and inguinal nodes from the lower vagina.

Table. Staging of vaginal cancer (FIGO 2009 classification).

Stage	**Description**
1	Invasive carcinoma confined to vaginal mucosa.
2	Subvaginal infiltration not extending to pelvic wall.
3	Extends to pelvic wall
4	4A; Involves the mucosa of bladder or rectum
	4B; Spread beyond the pelvis

MRI pelvis— is important for pretreatment assessment. Other helpful investigations incude;

- Examination under anesthesia (EUA) combined with colposcopy;
- A chest Xray and Intravenous pyelogram— to assess metastatsis.

Radiochemotherapy is first line in most cases due to advancing nature of the neoplasia, keeping a higher threshold to approach with surgical intervention;

- External beam radiotherapy or "radical hysterectomy + vaginectomy and pelvic lymphadenectomy"— for stage 1-2 disease;
- Teletherapy— for carcinomas spreading and involving the parametrium;
- Surgery remains the treatment of choice for individuals who have had prior pelvic radiotherapy.

CHAPTER 12 UROGYNECOLOGY

(I) Symptomatology

- Stress incontinence is a symptom and a sign and means loss of urine on physical effort. It is not a diagnosis. Urgency means a sudden desire to void.
- Urge incontinence is an involuntary loss of urine associated with a sudden strong desire to void which is difficult to defer.
- Overflow incontinence occurs without any detrusor activity when the bladder is over-distended.
- Frequency is defined as the passing of urine seven or more times a day, or being awoken from sleep more than once a night to void.

(II) Vesicourethral causes of urinary incontinence

i) Urodynamic stress incontinence (USI)

Previously called, '*genuine stress incontinence*' is a phenomenon noted during **filling cystometry**.

It is the involuntary leakage of urine during instances of increased intraabdominal pressures, but without detrusor muscle contraction. It is due to urethral sphincter incompetence.

A cystourethrocele is often found in women with USI, but there is no causal relationship.

a) Etiology

- Damage to the nerve supply of the pelvic floor and urethral sphincter caused by childbirth;
- Mechanical trauma to the pelvic floor musculature and endopelvic fascia and ligaments. Prolonged second stage, large babies and instrumental deliveries cause the most damage;
- Menopause and associated tissue atrophy may also cause damage to the pelvic floor;
- A congenital cause— altered connective tissue, particularly collagen;
- Chronic causes, such as obesity and COPD— ↑ intraabdominal pressure. Constipation and associated straining may also result in urinary symptoms;
- Abnormal descent of the bladder neck and proximal urethra, so there is failure of equal transmission of intra-abdominal pressure to the proximal urethra, leading to reversal of the normal pressure gradient between the bladder and urethra, with a resultant negative urethral closure pressure;
- An intraurethral pressure < intravesical pressure— due to urethral scarring of surgery or radiotherapy. It also occurs in older women due to oestrogen deficiency;
- Laxity of suburethral support (normally provided by the vaginal wall, endopelvic fascia, arcus tendineus fascia and levator ani muscles).

b) Clinical features

- Stress incontinence or urge incontinence;
- Urinary urgency, frequency;
- Trigger/exaggeration of symptoms during periods of ↑ intraabdominal pressure— e.g. cough, sneezing.

ii) Detrusor overactivity

Previously called, 'detrusor instability' is an abnormality detected on urodynamic studies as— involuntary contractions during the filling phase which may be spontaneous or provoked.

a) Etiology

- Urinary tract infections may be a trigger;
- Other associations include neuropathy, incontinence surgery, outflow obstruction and smoking;

- The idiopathic form of detrusor overactivity is more prevalent after menopause.

b) Clinical features

- The constellation of symptoms— urgency, frequency, nocturia and ± urinary incontinence *in the absence of urinary tract infection* is termed ***Overactive bladder (OAB) syndrome***;
    - OAB wet— with urinary incontinence;
    - OAB dry— without urinary incontinence.
- Affected individuals tend to stay close to a toilet at all times.

iii) Urinary retention with overflow incontinence

Nerve lesions, urethral obstruction or medications can cause the bladder to malfunction. This can lead to retention of urine, increasing residual urine volumes and overflow incontinence.

a) Etiology

- Upper motor and lower motor neuron lesions
- Urethral obstruction secondary to mass lesions or other causes;
- Side-effects of certain pharmacological drugs.

b) Symptoms

- Poor urinary stream, despite straining to void;
- Incomplete bladder emptying;
- Overflow stress incontinence;
- Recurrent UTIs.

iv) Congenital urinary incontinence secondary to epispadias

- Epispadias is the faulty midline fusion of mesoderm, results in a widened bladder neck, shortened urethra, separation of the symphysis pubis, and variable sphincteric control;
    - Stress incontinence, characteristically more noticeable when standing up;
    - Penile examination will show pathognomonic opening of the urethra on the dorsal surface;
    - Symphysial separation may be apparent on Xray of the pelvis PA view;
    - In such a case of congenital urinary incontinence, the preferable approach may be to do urethral reconstruction or an artificial urinary sphincter.

v) Miscellaneous causes

UTIs, constipation, fecal impaction— all can cause transient urinary incontinence. A proper workup in elderly patients is, thus, needed.

A urethral diverticulum presents classically as "**post-micturition dribble**" as the urine collects within the diverticulum during micturition and later dribbles as the patient stands up.

(III) Extraurethral causes of urinary incontinence

i) Bladder exstrophy and ectopic ureter

- Bladder exstrophy is a congenital defect in development of anterior abdominal and bladder walls. Occurs due to failure of mesodermal migration and breakdown of ectoderm and endoderm;
- An ectopic ureter may be single or bilateral. It can present with incontinence if the ectopic opening is in the vagina or perineum;
- Both these conditions require reconstructive surgery for correction of the defects.

ii) Urinary Fistula

- A urinary tract fistula is an abnormal opening between the urinary tract and the outside.
- It can occur as a complication of;
    - Obstructed labor resulting in compression of the bladder between the head of the baby and bony pelvic wall;
    - Pelvic surgery;
    - Pelvic radiotherapy or malignant metastasis.
- Surgical correction of a urinary fistula is a specialized procedure. Initially, surgery may be delayed for 4 weeks till edema and tissue inflammation improve;
- Surgical intervention techniques include;
    - Debridement, suture and closure of each layer separately without tension;
    - Omentum may be interposed to the site of fistula to aid in closure of the defect by bringing additional blood supply.

(IV) Investigations

Cystometry is usually required to make the diagnosis, and bladder ultrasonography or CT Urogram/intravenous urogram— may be needed to investigate the state of upper urinary tract to exclude reflux.

i) Midstream urine specimen

Analysis of a midstream urine sample in helpful in UTIs. Signs suggestive of infection include;

- ↑ WBC count;
- Positivity for nitrates.

Urodynamic studies are considered invalid in patients with concurrent UTIs as these may affect the results.

ii) Urinary diary

A urinary diary is a hand-written record of oral fluids intake and urinary episodes over a period of 3 consecutive days. It can be useful in assessment of;

- Severity of urinary symptoms;
- Functional bladder capacity;
- Response to treatment.

iii) Pad test

The pad test is used to verify and quantify urinary incontinence;

- In sequence, the individual wears a pre-weighed pad, drinks 500ml of water, rests for 15 minutes before she performs a series of defined manoeuvres. The pad is weighed after, and a urine loss of > 1 gram is considered significant;
- 24-hour and 48-hour pad tests are also variants considered more representative, in which pad are worn for longer durations.

iv) Methylene blue test

For women who are unable to differentiate urinary leakage from vaginal discharge, or in cases of possible vesico-vaginal or urethro-vaginal fistula, a methylene blue test can be performed;

- During this test, methylene blue is instilled into the patient's bladder. Gauze swabs are then placed into the upper, mid and lower vagina (as shown in figure) and a pre-weighed pad into the patient's underwear;
- They are then asked to mobilize for 1 hour and perform provocative exercises. At the end of the test, patients are asked to void and then each vaginal swab is removed. Staining on the pad represents urinary leakage;

- Blue on the lower vaginal swab may represent urethro-vaginal reflux or contamination from the test;
- Blue on the mid-vaginal swab may be indicative of a urethro-vaginal fistula;
- Blue on the upper vaginal swab could suggest a vesico-vaginal fistula.

- A heavy vaginal discharge can also be assessed from this test.

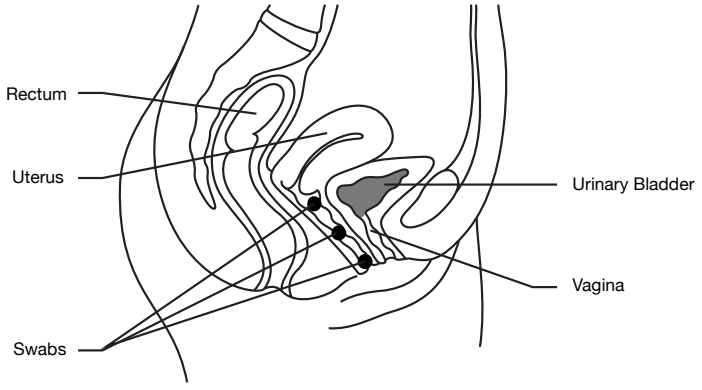

Figure. Methylene blue test.

v) Uroflowmetry

This is a simple, non-invasive investigations for evaluating voiding dysfunction.

It helps asses urodynamic function by measuring urine flow (mL/sec) over time. Together with measurement of residual volume of bladder (e.g. by ultrasound), it can also assess efficiency of micturition;

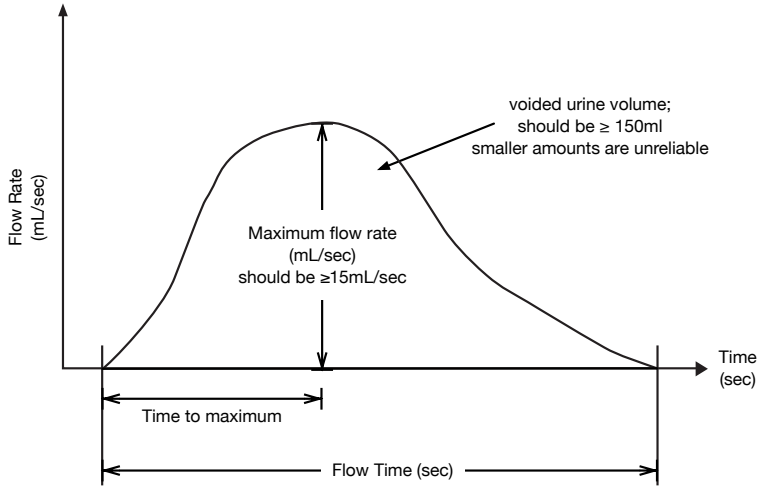

Figure. A normal uroflowmetry– bell shaped curve.

- The flow of urine over a curve can be assessed by gravimetric method; i.e. using rate of change of the weight of the voided urine in the collecting jug.
- Indications for uroflowmetry include;
  - Screening female individuals with voiding difficulty;
  - Pretreatment assessment of urodynamic stress incontinence and detrusor overactivity;
  - Preprocedure assessment; before surgery of bladder neck, or pelvic cancer— to minimize post-procedure deterioration.
- Uroflowmetry can not distinguish between causes of voiding dysfunction. But an abnormal uroflowmetry— non-bell-shaped curve could suggest impaired contractility or outflow obstruction.

vi) Cystometry

Cystometry is an assessment of pressure-volume relationship of the urinary bladder;

- It involves simultaneous monitoring of abdominal pressure as well as intravesical pressure— during bladder filling and voiding phases;
- Cystometric testing in indicated with;
    - Previous unsuccessful surgery for incontinence;
    - Voiding disorder;
    - Neuropathic bladder;
    - Prior to first surgical intervention for incontinence (debatable);
    - Multiple symptoms i.e. urge incontinence, stress incontinence and frequency.
- Pre-procedure, patient voids on a uroflowmeter. Then, a *12 French (size)* specialized urinary cathether is inserted to note residual urine volume. Intravesical pressure is recorded using a 1-mm fluid filled catheter connected to an external pressure transducer. Intra-abdominal pressure is measured using a fluid filled 2-mm catheter inserted into the rectum;
- During the procedure, the bladder is filled with normal saline continuously using a catheter at rates provocative for detrusor instability (~ 10-100 mL/min), and symptoms felt during the filling phase are noted along with detrusor contractions on a computer. After maximal filling, individual is asked to stand and perform provocative activities as well;
- Post-procedure, the individual voids on a uroflowmeter with pressure catheters in place.

Table. Parameters of normal bladder function.

Residual urine of <50 mL.
First desire to void between 150 mL and 200 mL.
Bladder capacity between 400 and 600 mL.
Detrusor pressure rise of < 15 cmH_2O during filling and standing phases.
Absence of systolic detrusor contractions.
No leakage on coughing.
A voiding detrusor pressure rise of <70 cmH_2O with a peak flow rate of >15 mL/sec for a volume >150 mL.

Electronic subtraction of abdominal from intravesical pressure calculates detrusor pressure (see Figure).

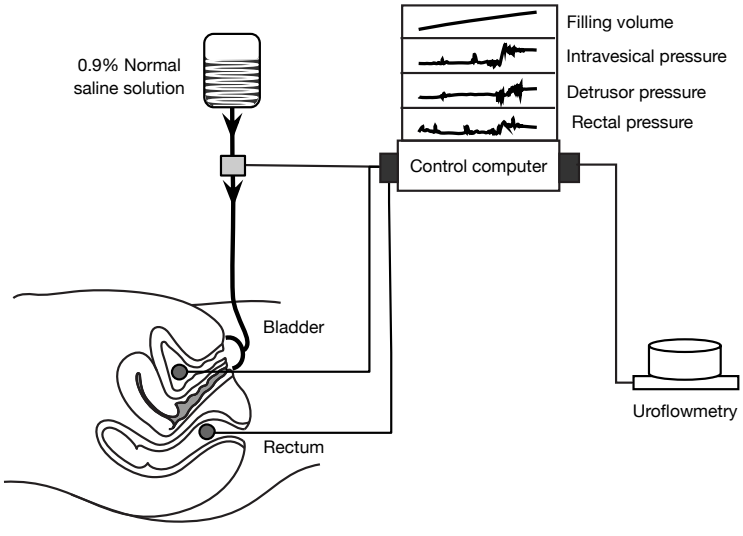

Figure. Illustration of cystometry.

- Spontaneous or provoked *phasic* detrusor contractions which patient cannot suppress— detrusor overactivity;
- Pressure rise during filling phase >15 cmH_2O— low compliance detrusor instability;
- Leakage of urine during standing phase or provocative activities, *without rise in detrusor pressure*— urodynamic stress incontinence.

vii) Videocystourethrography and micturating cystourethrography

Videocystourethrography and micturating cystourethrography can provide more information than a cystometry in some cases;

- In videocystourethrography, a radio-opaque filling medium is used for bladder filling instead of normal saline as in cystometry— and the lower urinary tract can be visualized using Xrays with pressure-flow information (~ videocystourethrography) or using fluoroscopy without pressure-flow monitoring (~ micturating cystourethrography);
- During bladder filling— vesicoureteric reflux can be seen;
- Detrusor contractions, descent of the bladder neck, and base, and leakage of urine can also be visualized as well as diverticulae.

viii) Intravenous urography

This is of little use, and is generally for women with neuropathic bladders, suspected congenital or acquired urinary tract abnormalities (e.g. uterovaginal fistulae), hematuria, or evaluation for ureteric compression from surrounding structures.

This involves the use of intravenous administration of radiopaque dye (in low dose) that is subsequently excreted by the kidneys into the urinary tract to enable visualization.

ix) Ultrasound

Ultrasound pre- and post-void for urinary bladder volume is useful for individuals with voiding difficulties.

Though operator dependent, urethral cysts and diverticula can also be examined.

x) Cystourethroscopy

Cystourethroscopy is helpful for suspected pathology of the urethra or urinary bladder. It is indicated in cases of;

- Reduced bladder capacity;
- Short history of urgency and frequency;
- Suspected urethrovaginal or vesicovaginal fistula;
- Hematuria or abnormal cytology;
- Persistent urinary tract infection.

xi) Urethral pressure profilometry

A voluntary urinary continence is maintained as long as urethral pressure is greater than intravesical pressure.

Urethral pressure profiling can be carried out for this purpose to measure urethral pressure— using catheter tip dual sensor microtransducer.

(V) Treatment

General measures, that improve urinary incontinence symptoms, include;

- Treatment of concurrent urinary tract infection;
- Restriction of fluid intake;
- Modifying medications that ↑ urine output (e.g. diuretics);
- Treating chronic cough and constipation.

i) Urodynamic stress incontinence (USI)

- Treatment is mainly centered around physiotherapy— reinforcement of pelvic floor muscles using pelvic floor exercises;
- Premenopausal women tend to respond better to physiotherapy— with upto 60% individuals noticing significant improvement in symptoms;
- Curative approach involves surgery;
    - Colposuspension— was previously the gold standard operation for stress incontinence associated with highest success rates. Its use is for USI cases associated with cysto-urethrocele prolapses;
    - Tension-free vaginal tape and its modifications are also very effective. The polypropylene tapes courses transvaginally under the midurethra *without tension*;
    - For elderly patients— bladder neck bulking injection is a more appropriate procedure;
    - *If the bladder neck is already adequately elevated and aligned with the symphysis pubis, incontinence may presumably be due to sphincteric function*. Artificial sphincter, periurethral injections and subrethral slings are used to increase outflow resistance in such cases.

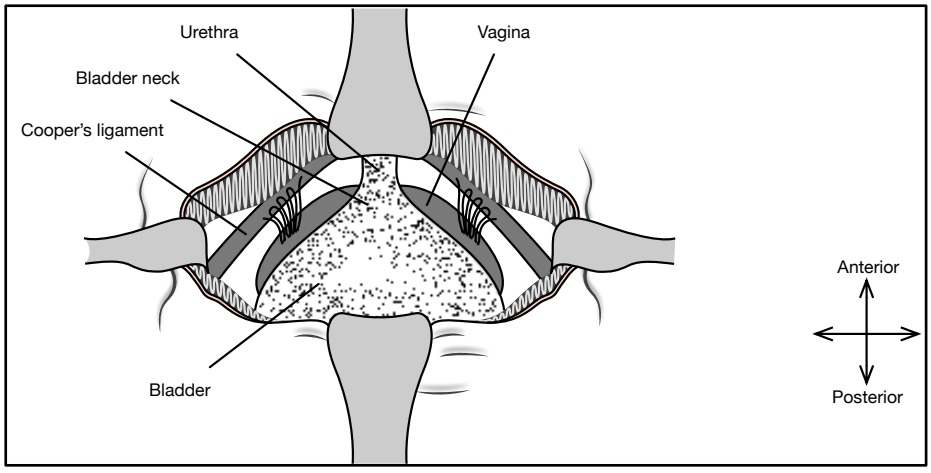

Figure. Colposuspension— Suprapubic view during surgery.

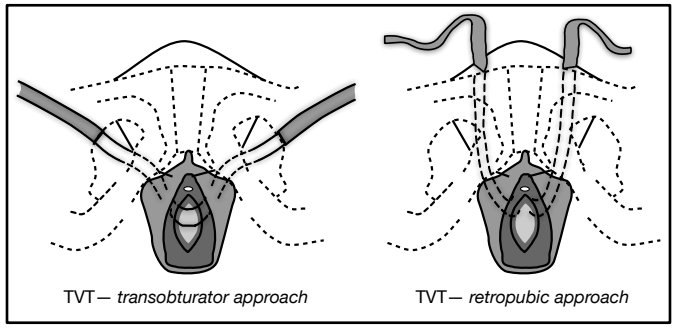

Figure. Illustration of tension-free vaginal tape— inserted by transobturator and retropubic approaches..

Preventative measures can be taken by shortening the 2nd stage of labor *if possible* and reducing traumatic delivery as well.

ii) Detrusor overactivity (DOA)

Evidence-based medicine suggests roles of following in the treatment of detrusor overacitivity;

- Bladder and biofeedback training;
- Pharmacologic options include;
    - Traditional used anticholinergics— Oxybutynin 2.5mg or Tolterodine 2mg orally upto 2

times/day; the latter has lesser side-effects.

- Newer anticholinergics that have shown benefit include, but not limited to;
  - Solifenacin;
  - Fesoterodine;
  - Darifenacin;
  - Desmopressin—an antidiuretic hormone analogue, helps improve ***nocturia;***
  - Imipramine has shown to improve of nocturnal bedwetting episodes.

- Sacral nerve stimulation— electrical stimulation of S-3 nerve root may improve DOA symptoms transiently in some individuals. A permanent implant can also be considered.
- For other cases, intermittent self-catheterization can be taught to the individual.

Preventative measures can be taken as well, by shortening the 2nd stage of labor, and reducing traumatic delivery.

-x-

CHAPTER 13 PELVIC ORGAN PROLAPSE

Pelvic organ prolapse (POP) refers to descent of pelvic organs beyond their normal anatomical confines. These are discussed here in the context of uterovaginal organs.

(I) Classification

These are classified according to their locations and constituent organ;

- Anterior vaginal wall prolapse;
    - Urethrocele— descent of urethra;
    - Cystocele— descent of urinary bladder;
    - Cystourethrocele— descent of bladder and urethra.
- Apical vaginal prolapse;
    - Vaginal vault prolapse—inversion of vaginal apex after a hysterectomy;
    - Uterovaginal prolapse— uterine descent with inversion of vaginal apex.
- Posterior vaginal wall prolapse;
    - Enterocele— descent of, but not limited to, small intestines;
    - Rectocele— descent of rectum.

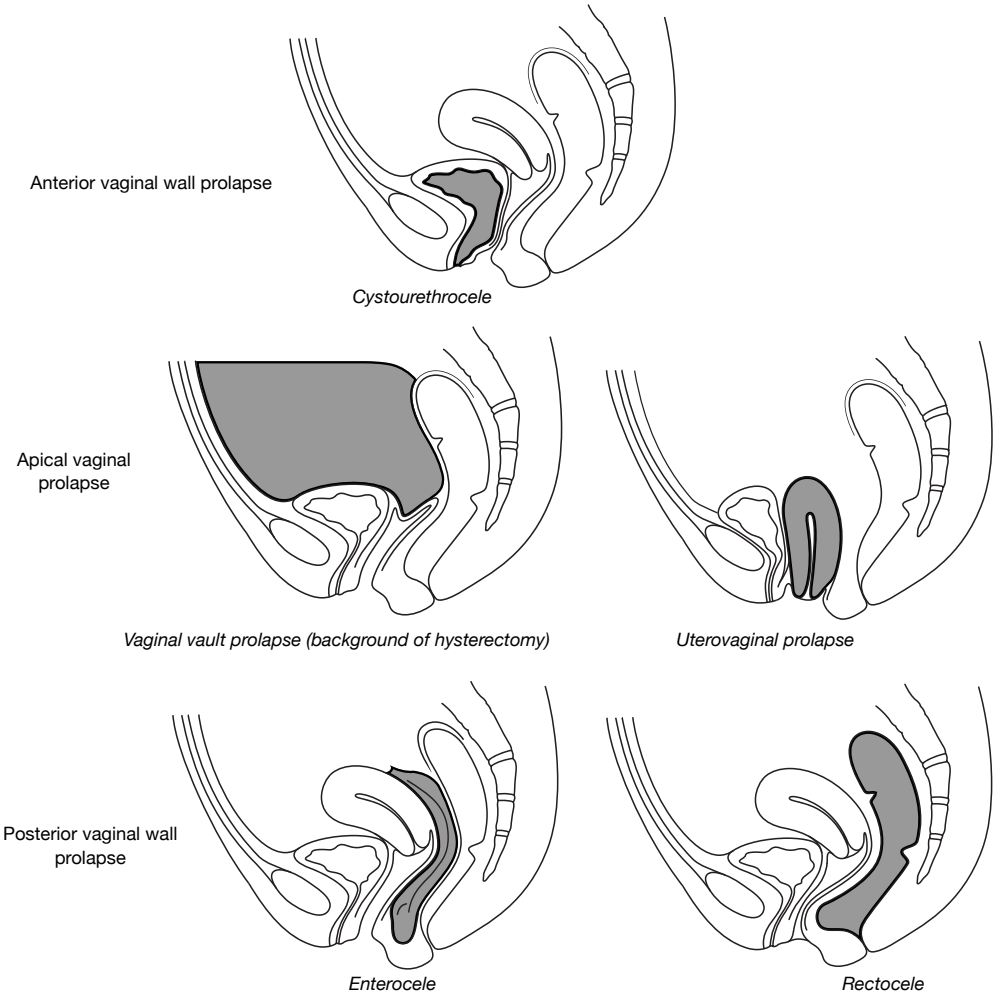

Figure. Illustration of anterior, apical vaginal and posterior vaginal wall prolapses.

(II) Grading

POPs can be graded as;

- First degree prolapse— descent within the vagina. A long cervix may also appear as uterovaginal descent on examination and should be excluded.
- Second degree prolapse— descent to the introitus;
- Third degree prolapse— descent outside the introitus. Also called ***procidentia***, and is usually accompanied with cystourethrocele and rectocele;

(III) Aetiology

The surrounding connective tissues, muscles, and intact nerves maintain pelvic organ positioning. Factor predisposing to POP include, but are not limited to, genetics, aging and childbirth.

- Mechanical stress of childbirth has shown changes in surrounding muscle and fascia;
- Prolapse during pregnancy is thought to be mediated by effects of hormones; progesterone and ***relaxin***;
- Chronic cough, and constipation predispose to POP by ↑ ing intra-abdominal pressure;
- Ageing is associated with loss of collagen and its tensile strength particularly after menopause— estrogen deficiency;
- Iatrogenic surgery may lead to development of POP— coloposuspension mechanically displaces the vaginal wall and may lead to a rectocele or enterocele in few cases.

(IV) Clinical features

- Women usually present with non-specific symptoms— e.g. swelling, local discomfort, bachache, dyspareunia, *apreunia*, bleeding from an ulcerated prolapse.
- Urinary symtoms are common in cystourethrocele— urinary urgency, frequency, recurrent UTIs, and stress incontinence.
- Bowel symptoms— tenesmus, bowel incontinence. Rarely, individuals are noted to ***splint*** their pelvic openings manually during defecation as an apprehensive manoeuvre.
- Ureteric pressure due to extreme prolapse may present with renal insufficiency.
- Pelvic examination— pelvic lump may be observed in some cases.
- Vaginal and rectal examination for diagnosis and grading of prolapse. A rectal examination may help differentiate a rectocele from an enterocele.

Differential diagnosis of an individual presenting with such complains include;

- Anterior wall prolapse— congenital or inclusion dermoid vaginal cyst, urethral diverticulum.
- Uterovaginal prolapse; large uterine polyp.

(V) Treatment

Prior to specific treatment, it is recommended to optimize the general condition by treating (see Figure);

- Obesity;
- Chronic cough;
- Constipation.

Medical management is appropriate for individuals with asymptomatic POP; topical estrogen application should be done for 7-days— for an ulcerated prolapse. Additional consideration include;

- Pelvic floor physiotherapy;
- Pessaries— silicon-rubber-based ring pessaries are famous;
- Shelf pessaries— are useful in those who can not retain a ring pessary.

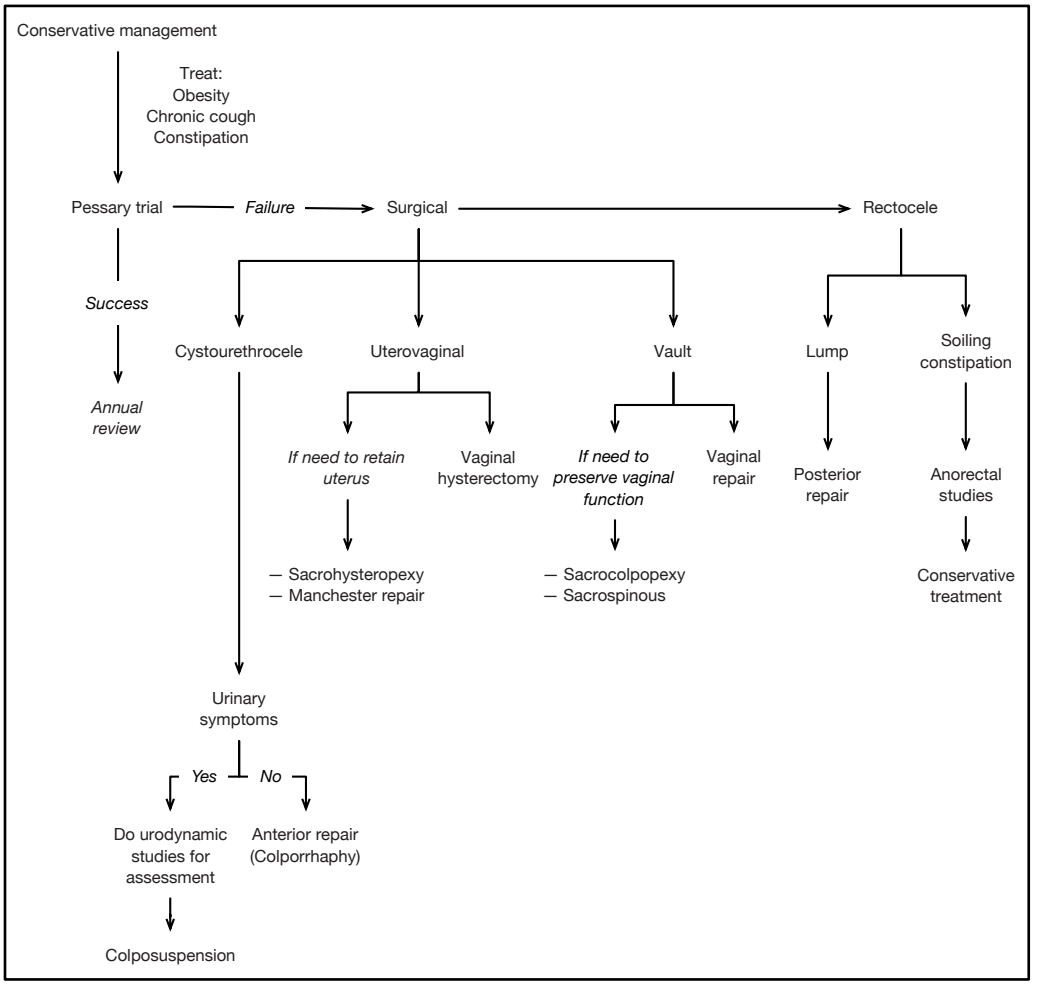

Figure. Algorithmic approach to treatment of POP.

i) Treatment with pessaries

The three commonly used pessaries are shown below (see Figure).

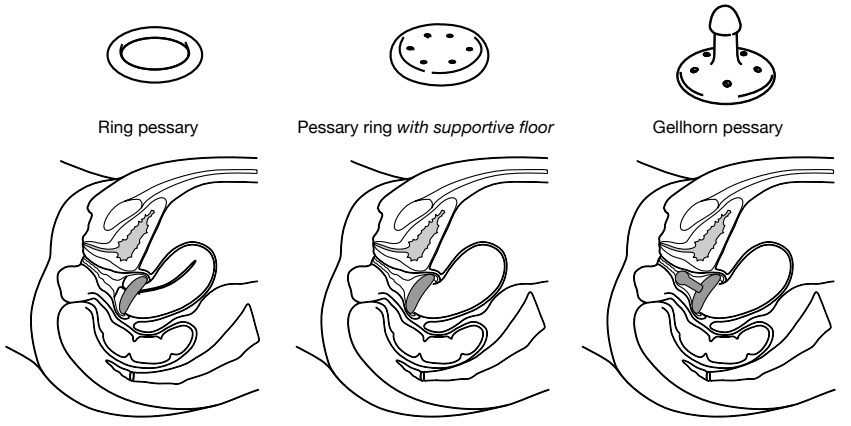

Figure. Illustration of the famous types of pessaries.

A pessary trial is commonly used as first choice of management. Other indications include;

- Patient's wishes;

- As a therapeutic test;
- If childbearing is not complete;
- If medically unfit;
- During and after pregnancy (awaiting involution); a ring pessary is the ***treatment of choice*** in patients with pregnancy and prolapse. It is required till ***18 weeks of gestation***, after which there is generally spontaneous correction of prolapse;
- While awaiting surgery.

ii) Surgical treatment

There are both vaginal and abdominal approaches to surgically correct POP. These are outlined below;

- Cystourethroceles;
    - Anterior repair (colporrhaphy)— most common procedure for cystourethrocele;
        - It should be avoided in cases of concurrent stress incontinence;
        - An anterior vaginal wall incision to identify and close fascial defect is made. Thus, the urinary bladder position is restored.
    - Colposuspension;
        - Is the preferred surgical approach in cases of cystourethrocele with concomitant urinary stress incontinence;
        - Sutures are placed between the paravaginal fascia and the ileopectineal ligaments. These sutures elevate the bladder neck;
        - During exertion, the intra-abdominal pressure rises and presses the urethra against the symphysis pubis, thus controlling the incontinence.

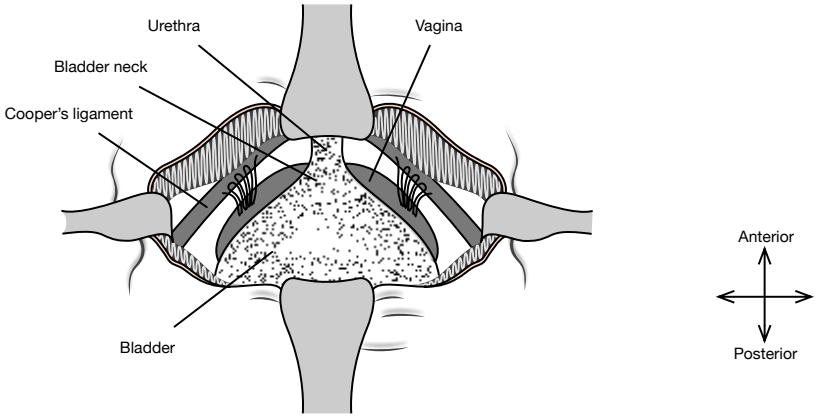

Figure. Colposuspension— suprapubic view during surgery.

- Rectoceles;
    - Surgical intervention may be individualized based on symptoms and clinical assessment which may involve anorectal studies;
    - Posterior repair (colporrhaphy)— is the most common procedure for a rectocele. A posterior vaginal wall incision is made and the fascial defect allowing the rectum to herniate through is identified and closed.
- Enteroceles;
    - If the supports of the proximal vaginal wall are weakened (e.g. after hysterectomy) it may bulge into the vagina, often containing bowel— this is termed an 'enterocele';
    - The intestines may prolapse down filling the pouch of douglas. In these cases, surgery is *also* focused on closing the pouch of douglas;
    - Thus, the surgical approach here is like that of anterior and posterior repair but with additional approximation of peritoneum ± uterosacral ligaments to close the pouch of douglas.

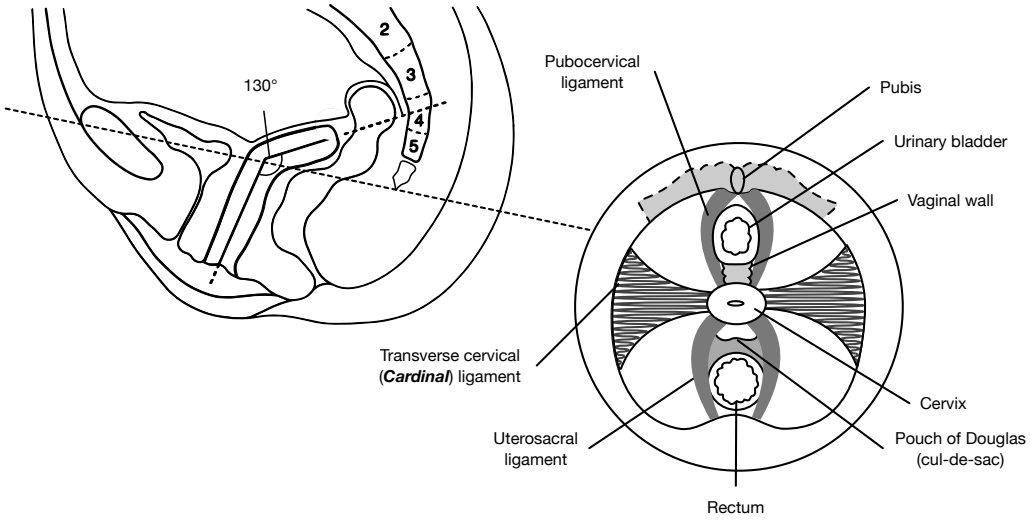

Figure. *Sagittal* and *axial views* of the pouch of douglas, uterosacral ligaments and surrounding structures.

- Uterovaginal prolapses;
    - Uterus can be removed if fertility is not desired. Hysterectomy can be planned via a vaginal or abdominal approach creating support for the vault with uterosacral ligament by;
        - Sacro**colpo**pexy, if total hysterectomy is being performed, or;
        - Sacro**cervico**pexy, if subtotal hysterectomy is being performed.
    - Fertility-conserving approach to uterovaginal prolapse is with Manchester repair or sacro-hysteropexy;
        - Partial amputation of cervix, and approximation of the cardinal ligaments below the retained cervix stump is— **the Manchester operation (or Fothergill repair)**. Often combined with anterior and posterior repair (colporraphy);
        - Sacrohysteropexy involves attachment of a synthetic mesh from the *uterocervical junction to the anterior longitudinal ligament of the sacrum*. The pouch of douglas is also closed;
        - Le Fort colpocleisis— this involves partial closure of the vagina while preserving the uterus. This procedure is usually chosen for elderly frail patients who are unfit for major surgery and are not sexually active.
- Vaginal vault prolapses;
    - Sacrocolpopexy— the *inverted* vaginal vault is attached to the sacrum (sacral promontory) using a mesh and the pouch of Douglas is closed (see Figure);

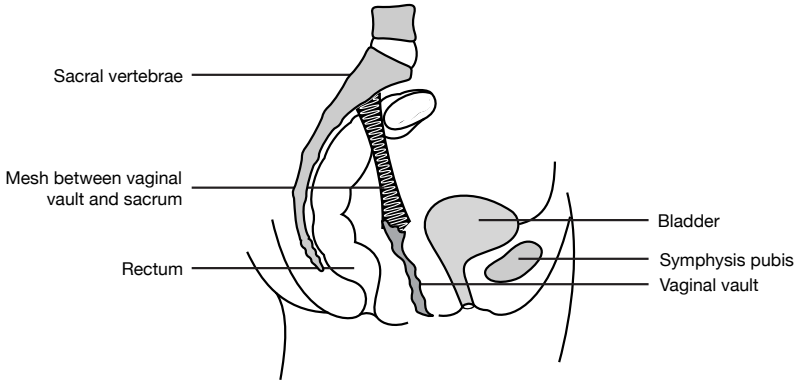

Figure. Sacrocolpopexy.

- **Sacrospinous ligament fixation** is a vaginal procedure in which the vault is sutured to one or the other sacrospinous ligament. But carries a higher incidence of a *cystocele* post-procedure.

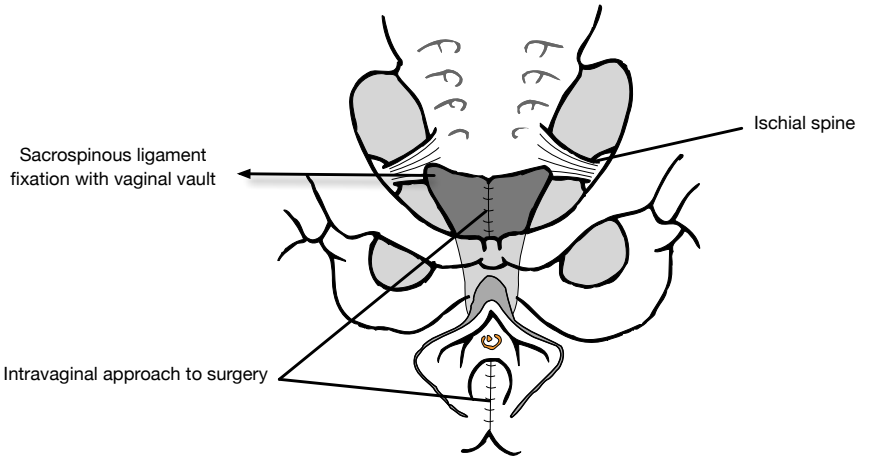

Figure. Sacrospinous ligament fixation. The urinary bladder is *not* shown in the illustration.

(VI) Prevention

The only evidence based-preventive measure against POPs is shortening the duration of second stage of labor— less incidence of prolapse is seen, but this is difficult to employ in-practice.

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CHAPTER 14 MENOPAUSE

The term 'menopause' refers to the cessation of menstrual cycles.

By definition—

- Menopause is defined as the final menstrual period;
- Perimenopause marks the transition from the reproductive to the non-reproductive state, the menopause being a specific event within that phase. Perimenopause is also known as the climacteric;

The average age of the menopause in Western women is approximately 52 years. **Premature menopause** is said to have occured if menopause occurs before the age of 45.

(I) Aetiology

Menopause occurs following loss of ovarian follicular activity leading to a fall in oestradiol levels below the level needed for endometrial stimulation. This is a physiologic change in most cases but may occur secondary to;

- Primary ovarian insufficiency— secondary to pathology of the ovaries themselves e.g. certain chromosomal abnormalities or autoimmune disorders, or sometime secondary insults, e.g. oophorectomy or damage following radio- or chemotherapy;
- A surgical menopause occurs when functioning ovaries are removed—e.g. hysterectomy + oophrectomy. Menopause may also occur iatrogenically by treatments, such as radio, chemotherapy, for malignancy or temporarily during treatment with GnRH analogues for a variety of conditions;
- **Premature** ovarian failure (POF) refers to menopause **before age 40 years**. The cause of spontaneous POF is usually unknown, but there are a number of well-established causes that should be excluded (see Table).

Table. Causes of premature ovarian failure (POF)

Primary causes	Chromosomal anomalies, e.g. Turner's syndrome, Fragile X syndrome;
	Autoimmune diseases, e.g. hypothyroidism, Addison's disease, Myasthenia gravis;
	Enzyme deficiencies, e.g. galactosemia, 17α-hydroxylase deficiency;
Secondary causes	Surgical menopause after bilateral oophorectomy;
	Chemotherapy, or radiotherapy;
	Infections, e.g. tuberculosis, mumps, malaria, varicella;

(II) Clinical features and diagnosis

Menopause is one of the *more common* causes of secondary amenorrhoea and should always be considered in the diagnosis.

Women commonly present with oligo- or amenorrhea and in later cases experience;

- Vasomotor symptoms e.g. 'hot flushes'— characterized by considerably observable flushing of the skin, night sweats, palpitations and headaches;
- Vaginal symptoms of 'burning', dryness and dyspareunia;
- Other less common symptoms include psychic sensations of dyspnea, irritability, fatigue, and anxiety.

The diagnosis is mainly made clinically and often made retrospective. Menopause is said to have occurred *after 12 consecutive months of amenorrhoea.*

There is rarely a need for investigations to confirm menopause but;

- A pattern of ↑ FSH and ↓ estradiol effective reflects loss of ovarian follicular activity associated with ovarian insufficiency (see Table);
- Serum FSH level more than 30 IU/l is highly suspicious of menopause— this can be especially helpful in suspected cases of premature ovarian failure (POF) in relatively younger individuals;

Table. Hormonal changes around perimenopause and menopause.

Hormones	Perimenopause	Early menopause	Late post-menopause
GnRH	↑ pulsatility	Progressive ↓ pulsatility	↓ levels
LH and FSH	↑	↑	Progressive ↓
Estrogen	Slight ↓	Rapid ↓	Sustained ↓ levels
Progesterone	Moderate ↓	*Unpredictable*	↓↓
Inhibin	Slight ↓	Significant ↓	↓↓
Testosterone	Progressive ↓	Progressive ↓	Sustained ↓ levels

(III) Complications

Women who have had a premature menopause are at an increased risk of complications later in life and may need special support;

- Immediate effects (0-5 year);
    - Vasomotor symptoms, (e.g. hot flushes, night sweats);
    - Psychological symptoms (e.g. labile mood, anxiety, tearfulness);
    - Loss of concentration, poor memory;
    - Joint aches and pains;
    - Dry and itchy skin;
    - Hair changes;
    - Decreased sexual desire.
- Intermediate effects (3-10 years);
    - Vaginal dryness, soreness;
    - Dyspareunia;
    - Recurrent urinary tract infections;
    - Urogenital prolapse.
- Long term effects (> 10 years);
    - Osteoporosis;
    - Cardiovascular disease;
    - Dementia.

i) Genitourinary complications

- Urogenital atrophy— risk ↑ with age, especially 3 years after menopause.
    - Vaginal atrophy results in vaginal dryness, itching, dyspareunia, making it more prone to trauma, dryness, spontaneous bleeding and infection.
    - The distal urethra and trigone of the bladder are also prone to atrophy (because of same embryological origin) with oestrogen deficiency— leading to '***urethral syndrome***'— of urinary frequency and dysuria, in the absence of proven infection. This responds well to local estrogen administration.
- Pelvic floor dysfunction leading to weakening of the supporting tissues and ligaments, which may already be damaged by childbirth or other trauma, and thus contributing to the higher incidence of prolapse and urinary stress incontinence.
- Loss of sexual desire or libido around menopause, termed '***female sexual dysfunction***'. This is based on a classification system introduced by the International Consensus Development Conference on Female Sexual Dysfunction.

ii) Skeletal complications

Trabecular bone is continuously undergoing turnover and is estrogen-sensitive. Fall in estrogen levels after menopause leads to ↓ bone density and ↑ risk of osteoporosis and fractures.

The Fracture Risk Assessment tool (FRAX) is a good screening model for postmenopausal women. Individuals found at increased risk undergo DEXA bone scanning (see Table).

Table. Clinical risk factors used in the FRAX tool:

Current age
Gender
A prior osteoporotic fracture— includes a morphometric vertebral fracture, prior clinical vertebral fracture or a hip fracture as strong risk factors
Femoral neck BMD
Low body mass index
Oral glucocorticoids for more than 3 months at a dose of prednisolone of 5mg daily or more (or equivalent doses of other glucocorticoids)
Current smoking
Parental history of hip fracture
Alcohol intake (3 or more units a day)
Rheumatoid arthritis
Secondary osteoporosis e.g. type 1 diabetes, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption etc.

NICE guidelines favour limited role for preventative treatment In women < 75 years of age, except those with already an occurance of fracture.

iii) Cardiac complications

Estrogen has a ***well-established*** protective role against coronary heart disease (CHD).

Menopause (or other ↓ estrogen states) is associated with rise in total and LDL cholesterol and a fall in HDL cholesterol— a change that is reversible to some extent with estrogen administration.

Estrogen also has a direct effect on the cardiac vessel walls— loss of oestrogen is associated with vasoconstriction and atherogenesis, while oestrogen administration stimulates vasodilatation via nitric oxide.

iv) CNS complications

Many women report memory changes during menopause.

Studies suggest use of estrogen around the time of menopause may have a beneficial effect in improving cognitive function.

(IV) Management

For most, menopausal symptoms are relatively short lived and will settle within a few years, but for others long term treatment may be needed.

The assessment of the menopausal woman should follow a systematic approach with direct questioning. It is benefical to inquire about;

- Sexual problems, vaginal dryness, soreness;
- Lower urinary tract symptoms;
- Family history of cardiovascular disease, osteoporosis, breast cancer and ovarian cancer.

Physical examination to rule out coexisting gynaecological problems;

- Breast examination for lumps;
- Abdominal and pelvic *bimanual* examination— assessment for size of uterus, lumps, adnexal mass;
- Pap smear testing.

While HRT is an extremely effective option, it is only one of a number of possible approaches.

It is best to have systematic approach. After lifestyle changes, if a woman's main problem is atrophic vaginitis, oestrogen pessaries or cream may be preferred, at least until the symptoms are relieved.

i) Lifestyle changes

Lifestyle modifications recommended after menopause include;

- Smoking is associated with an earlier menopause and ↑ risk of many post-menopausal complications. It is highly recommended to encourage smoking cessation;
- Body weight increases on average 1 kg per year around menopause. Avoid excessive weight gain— eating a balanced diet;
- Regular physical activity, especially weight-bearing exercises, have positive effects;
    - Reducing hot-flushes and other vasomotor symptoms seen with menopause;
    - Conserve bone density, reducing risk of fractures;
    - Improving risk of coronary heart disease.

ii) Alternative therapy and supplements

Although not widely employed and lack scientific evidence-based outcome, certain alternative therapies may still be considered in women where hormones or HRT is not warranted or contraindicated e.g. previous hormone sensitive malignancies (see Table).

Ingested alternative/herbal supplements, however, still carry risks of hormones because of hormonal properties.

Table. Alterantive and complimentary treatments for symptoms of menopause.

Complementary drug-free therapies	Acupuncture Reflexology Magnetism Reiki
Herbal remedies (designed to be ingested)	Black cohosh (*Actaea racemosa*) Dong quai (*Angelica sinensis*) Evening primrose oil (*Oenothera biennis*) Gingko (*Gingko biloba*) Ginseng (*Panax ginseng*) Kava kava (*Piper methysticum*) St John's wort (*Hypericum perforatum*)
'Natural' hormones (designed to be ingested or applied to the skin)	Phytoestrogens, e.g. isoflavones, red clover Natural progesterone gel Dehydroepiandrosterone (DHEA)

iii) Non-hormonal prescription treatments

- For hot flushes, SSRIs, and gabapentin have shown improvement in symptoms;
- For women > 60 years of age and found at high risk of osteoporosis considerable alternatives include (see Table);
    - Bisphosphonates;
    - SERMs— Tamoxifen and raloxifene;
    - Recombinant parathyroid hormone— reserved for those with a very high risk of fractures.

iv) Hormone replacement therapy (HRT)

Based on Women's Health Initiative (WHI) trial, the risk and benefits of HRT must be weighed before use. It is important to note accepted indications for starting HRT;

- Menopausal symptoms— hot flushes, vaginal dryness, mood swings, irritability, etc;
- Prevention and treatment of osteoporosis;
- Decreased libido.

HRT should not be used for for primary prevention of heart disease.

a) Contraindications to HRT

Table. Relative and absolute contraindications to HRT.

Absolute contraindications	Suspected pregnancy Breast cancer Endometrial cancer Active liver disease Uncontrolled hypertension Known venous thromboembolism (VTE) Known thrombophilia (e.g. Factor V leiden) Otosclerosis
Relative contraindications	Uninvestigated abnormal bleeding Large uterine fibroids Past history of benign breast disease Unconfirmed personal history or a strong family history of VTE Chronic stable liver disease Migraine with aura

b) Modes of treatment

Estrogen and progesterone combination is used for HRT, especially those individuals that have a uterus;

- Conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) are the most common hormone replacements for estrogen and progesterone;
    - The oral estrogen results in a serum estradiol:estrone ratio of 1:2, *opposite of normal premenopausal state*. It also induces certain hepatic enzymes and ↑ production of certain proteins by 1st pass metabolism— thyroid-binding and sex-hormone binding globulins;
    - Transdermal estrogen— avoids first-pass metabolism, and ***theoretically*** does not affect the coagulation profile. This is *relatively useful for women with personal or family history of venous thrombosis or liver dysfunction*. The estradiol:estrone ratio here is of 2:1, similar to a normal premenopausal state;
    - Subcutaneous implants of estrogen are reserved for those who do not respond to standard levels of estrogen, especially younger women in whom ovaries have ***also*** been removed.
- In HRT, progestogens are **also** added for ≥10-12 days/month to mimic normal menstrual cycle and reduce the risk associated with prolonged unopposed estrogen. They can either be given;
    - Cyclically— to mimic natural 28-day cycle and resulting in a regular withdrawal bleed, or;
    - Continuously— to prevent any bleeding, so-called '**no bleed**' treatment.
    - The former is usually prescribed for women who are **perimenopausal**, while the latter is usually recommended for women who are **clearly post-menopausal**.
    - Levonorgestrel-IUS is alternative form for progesterone administration and provides endometrial protection for up to 5 years.
    - Women who have had a hysterectomy ***do not*** need a progestogen.

- Ovaries are also a source of upto 50% of circulating testosterone;
    - Women who undergo surgical or chemoradiation-induced menopause may become *relatively* testosterone deficient;
    - Although, not specifically, but loss of libido, sexual desire and fatigue can be attributed to ↓ testosterone.
- Another treatment regimen is to combine oestrogen, to decrease hot flushes, with a SERM that improves bone and protects against breast and endometrial cancers. Unfortunately, raloxifene alone *does not* relieve hot flushes.
- Tibolone is a synthetic STEAR (Selective Tissue Estrogen Activity Regulator) with weak oestrogenic, progestogenic and androgenic effects;
    - It improves hot flushes (without stimulation of endometrial cells), vaginal dryness, bone density, mood and sexual function;
    - It does carry an increased risk of developing breast cancer but this is less than that associated with combined oestrogen/ progesterone therapies.

Table. Summary of non-hormonal and hormonal prescription treatments for menopause.

<table>
<tr><th colspan="3">Prescription medications</th><th>Targeted effects</th></tr>
<tr><td colspan="4">Non-hormonal prescription treatments</td></tr>
<tr><td colspan="3">alpha-adrenergic agonists e.g. clonidine</td><td rowspan="5">Target mainly vasomotor symptoms</td></tr>
<tr><td colspan="3">β-blockers e.g. propanolol</td></tr>
<tr><td colspan="3">SSRIs e.g. fluoxetine, paroxetine, or citalopram</td></tr>
<tr><td colspan="3">SNRIs, e.g. venlafaxine</td></tr>
<tr><td colspan="3">Gabapentin</td></tr>
<tr><td colspan="3">SERMs e.g. Tamoxifen, or raloxifene</td><td>Target mainly osteoporosis</td></tr>
<tr><td colspan="4">Hormone replacement therapy (HRT)</td></tr>
<tr><td rowspan="6">Oestrogen alone (if uterus removed) or
Estrogen and progestogen combined</td><td colspan="2">Different oestrogens used in HRT
Oestradiol (transdermal, gel or implant)
Oestradiol valerate
Conjugated equine oestrogens
Oestrone sulphate
Oestriol (vaginal only)</td><td rowspan="6">All menopausal symptoms</td></tr>
<tr><td colspan="2">Different progestogens used in HRT</td></tr>
<tr><td>C-19 nortestosterone derivatives</td><td>Norethisterone (transdermal)
Levonorgestrel (transdermal or intrauterine IUS)</td></tr>
<tr><td>C-21 progesterone derivatives</td><td>Dydrogesterone
Medroxyprogesterone acetate
Cyproterone acetate</td></tr>
<tr><td>C-17 derivatives</td><td>Drospirenone</td></tr>
<tr><td>Progesterone</td><td>Micronized progesterone (vaginal gel, pessary, or suppository)</td></tr>
<tr><td colspan="4">STEAR (Selective Tissue Estrogen Activity Regulator)— tibolone, targets certain menopausal symptoms. Also conserves bone mass and improves libido.</td></tr>
</table>

c) Side-effects

Side-effects of HRT may be estrogen or progesterone related (see Table).

Table. Estrogen- and progesterone-related side effects of HRT.

Oestrogen related	**Progestogen related**
Breast enlargement Nausea Headaches Leg cramps Dyspepsia	Fluid retention Breast tenderness Increased appetite Constipation and bloating Headaches Mood swings Irritability or depressive symptoms Acne

d) Risks and benefits of HRT

Table. Risks, benefits and uncertainities surrounding HRT.

Benefits	**Risks**	**Uncertainties**
↓ vasomotor symptoms ↓ urogenital symptoms Improved sexual function ↓ risk of osteoporosis	Breast cancer Endometrial cancer VTE Stroke	Cardiovascular disease Alzheimer's disease Ovarian cancer

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CHAPTER 15 COMMON GYNECOLOGICAL PROCEDURES

(I) Hysteroscopy

Hysteroscopy is the inspection of the endometrial cavity through the cervix by means of a telescopic hysteroscope. High quality images can be obtained.

Diagnostic and therapeutic procedures possible via hysteroscopy include, but not limited to;

- Sampling of endometrium for histopathological examination;
- Removal of endometrial polyps, submucous fibroids, intrauterine adhesions and septae;
- Endometrial ablation.

Endometrium can be visualized even if there is active bleeding by circulating fluids through the hysteroscope.

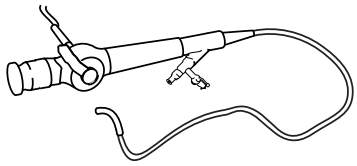

Figure. Illustration of a *flexible* fibreoptic hysteroscope.

i) Indications

Any abnormal uterine bleeding from the uterus;

- Postmenopausal bleeding;
- Irregular menstruation, intermenstrual bleeding and post-coital bleeding;
- Persistent menorrhagia;
- Persistent discharge;
- Suspected uterine malformations;
- Suspected Asherman's syndrome;

ii) Complications

- Perforation of the uterus;
- Damage to cervix may occur if cervical dilatation is necessary;
- Ascent of endometrial infection;

(II) Laparoscopy

Laparoscopy allows the visualization of the peritoneal cavity.

It involves puncture of peritoneum using a Verees needle followed by insufflation of carbon dioxide into the peritoneal cavity. This enables insertion of small ports with mounted cameras (in diagnostic laparoscopy) or operative instruments (operative laparoscopy).

i) Indications

- Suspected ectopic pregnancy;
- Undiagnosed pelvic pain;
- Tubal patency testing;
- Sterilization procedures.

Nowadays, a wide varity of operative procedures can also be performed. These include, but not limited to;

- Ovarian cystectomy or oophorectomy;

- Cautery of endometriotic deposits;
- Reversal of sterilization procedures;

ii) Complications

- Damage to intraabdominal structures— bowel, major vessels;
- Damage to bladder— this risk can be reduced by preoperative emptying of the bladder.
- Incisional hernia.

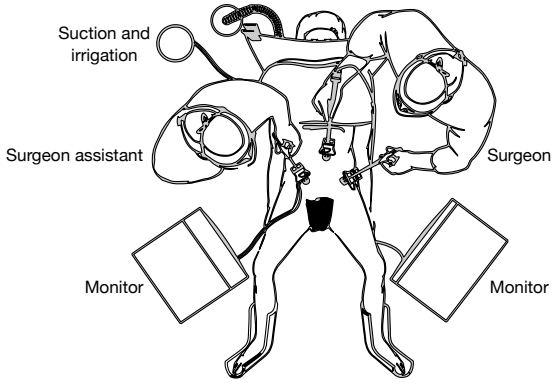

Figure. Laparoscopy— operative setup.

(III) Hysterectomy

Hysterectomy involves removal of the uterus while ligating the left-over three pedicles;

- The infundibulopelvic ligament, which contains the ovarian vessels.
- The uterine artery.
- The angles of the vault of the vagina, which contain vessels ascending from the vagina; the ligaments to support the uterus can be taken with this pedicle or separately.

i) Indications

Indications for hysterectomy include, but not limited to;

- Severe menorrhagia when other treatments have failed;
- Severe endometriosis or adenomyosis where other treatments have failed;
- Uterine, ovarian or cervical cancer;
- As an emergency life-saving procedure in certain postpartum situations, e.g. placenta accreta or severe postpartum haemorrhage;
- Prophylactic treatment along with oophorectomy and salpingectomy for those at risk of cancer.

ii) Types

Hysterectomy can be subclassified into (see Figure);

- Total hysterectomy ± bilateral salpingo-oophorectomy— uterine body and fundus are removed along with the uterine cervix;
- Subtotal hysterectomy— uterine body and fundus are removed leaving uterine cervix *in situ* and additional advantage of preserved pelvic floor support with cardinal and uterosacral ligaments remaining intact.

Hysterectomies be carried out by any of the abdominal, vaginal or laparoscopic approaches (see below).

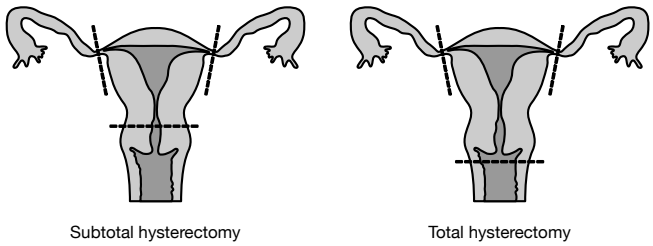

Figure. Illustration of subtotal (left) and total hysterectomy (right).

iii) Abdominal hysterectomy

Abdominal hysterectomy is usually performed through a Pfannenstiel (suprapubic transverse) incision. For larger masses or concurrent malignancy, a midline incision may be used.

If the uterus is greater in size than that of a 12-week pregnancy— abdominal hysterectomy is safer and preferred here.

Abdominal hysterectomy is also indicated when there is malignancy, as the ovaries and lymph nodes may need to be examined and sampled.

iv) Vaginal hysterectomy

Vaginal hysterectomy is associated with a faster recovery. Vaginal approach often takes precedence over abdominal approach in individuals with;

- Older age;
- Significant comorbidities.

Vaginal hysterectomy involves ligation of the same three pedicles as abdominal or laparoscopic hysterectomy, but the sequence of ligations is reversed.

Laparoscopy is often used to aid vaginal surgery, termed *laparoscopic-aided vaginal hysterectomy (LAVH)* in which the first two steps are completed laparoscopically and the third vaginally.

In surgery for pelvic organ prolapse (POP), hysterectomy is commonly performed vaginally as part of the correction of anatomical prolapse, although this is not necessary in all cases.

Total ***vaginal*** hysterectomy with bilateral salpingo-oophorectomy remains a relatively specialized procedure.

v) Laparoscopic hysterectomy

Total laparoscopic hysterectomy (TLH) is an alternative to abdominal and vaginal hysterectomies.

Here, the uterus removed through the vagina and the open vault closed with laparoscopic sutures.

TLH is associated with a considerably longer procedure time, but post-operative pain and recovery times are lesser.

vi) Complications of hysteretomy

Though complications vary with procedure used, complications include, but not limited to;

- Haemorrhage (intra- or immediate postoperative);
- Deep vein thrombosis (pelvic surgery);
- Thromboembolism;
- New bladder symptoms (both overactive bladder and stress incontinence);
- Higher incidence of vaginal prolapse after hysterectomy for any cause;
- Immediate onset of menopausal symptoms (if ovaries removed in a premenopausal woman).

Uncommon and rare complications include;

- Bladder injury (uncommon);

- Ureteric injury (rare);
- Rectal injury (rare);
- Vesicovaginal or rectovaginal fistula (consequence of injury) (very rare);
- Risk of *cervical cancer* in cases of **subtotal hysterectomies** (surveillance with cervical cytology is indicated in these individuals);
- Risk of later *ovarian cancer* if ovaries not removed.

(IV) Cystoscopy

Cystoscopy involves passing a small-diameter telescope through the urethra into the bladder;

- A cystoscope may be flexible or rigid;
- Excellent images of both these structures can be obtained;
- A cystoscope with an operative channel can be used to biopsy any abnormality, perform bladder neck injection, retrieve stones and resect bladder tumours.

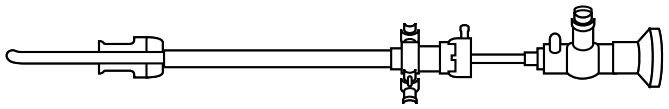

Figure Illustration of a *rigid* cystoscope.

Indications for cystoscopy include;

- Haematuria;
- Recurrent urinary tract infection;
- Sterile pyuria;
- Short history of irritative symptoms;
- Suspected bladder abnormality (e.g. diverticulum, stones, fistula);
- Assessment of bladder neck.

Complications associated with cystoscopy include, but not limited to;

- Postoperative urinary tract infection;
- Bladder perforation (rare).