Preface

All you need to know to ace the exams—in one place!

This book serves as a rapid review of *high yield* gynecology, obstetrics and neonatology-oriented topics for MBBS students, FCPS parts, USMLE step 2, PLAB, and other board exams. The book is an assimilation of gynecology, obstetrics and neonatology, as are scattered throughout multiple chapters in **bullet-points format** to facilitate quick easy reading and memorization without getting bogged down on too much unnecessary details. Additionally, the book features;

- More than 200 high-contrast and easy-to-understand and memorize illustrations and numerous tables scattered throughout a total of 35 chapters;
- Numerous mnemonics or *aide mémoires* (*memory aides*) spread throughtout the text to help easy memorization of difficult to remember factual knowledge;
- Illustrated chapters to help memorize difficult concepts. The heavily illustrated topics of normal and abnormal labour particularly help in perfecting clinical examination skills, and impressing OBGYN academic clinicians during clinical postings;
- Pathophysiology illustrations with practically useful knowledge— intended to help students and postgraduate trainees alike for easy memorization and quick review of such complex topics.

It is recommended that the reader studies the book thoroughly and cover-to-cover to ensure all topics are covered which may be dispersed for easier contextual learning. A sequentially descriptive writing style has been chosen throughout the book— which is not only easy to ***read, learn and remember in the same order***, but also resonates with clinical teaching approach of academic clinicians.

All facts, figures and illustrations are as per the latest edition textbooks' standards (as of 2018) and correct to the best of my knowledge. Books referenced in writing include *Ten teachers' 20th ed., Llewellyn-Jones' 10th ed., and William's* among countless others. No copyright infringement is intended.

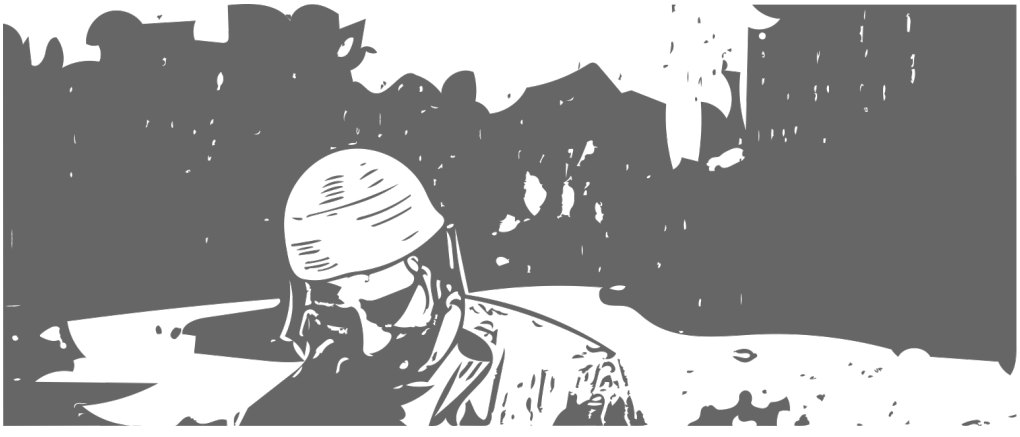
Use e-mail if there are any any queries. We value original illustrations, mnemonics and memory aids among other tools for studies. Kindly report suggestions or mistakes for future editions.

Dr. Syed Wajid Ali.

21st October, 2018.

dr.ali92@outlook.com

Acknowledgements



The *credit* goes to God, mum, dad, my sister, my computer and all those who belived in me and helped me through this journey.

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).

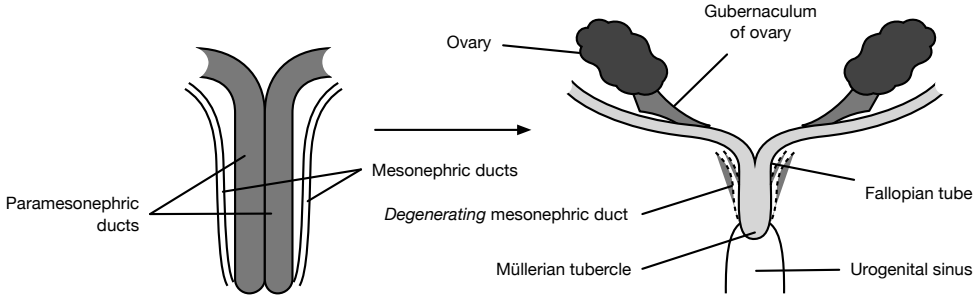


Figure. Development of the mesonephric and paramesonephric ducts.

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.

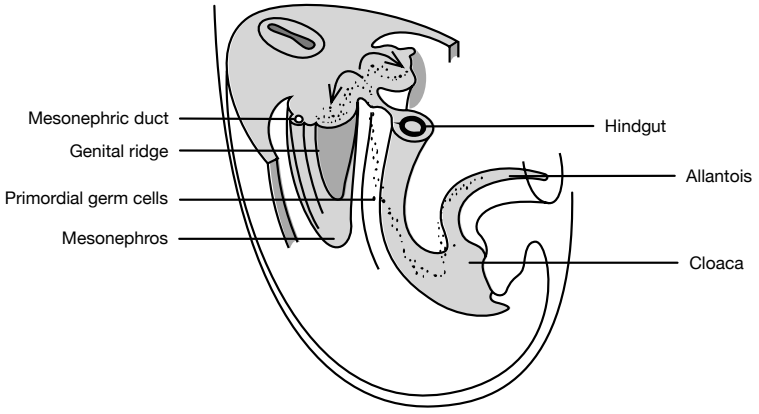


Figure. Cross section of posterior abdominal wall showing genital ridge and migration of primordial germ cells.

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.

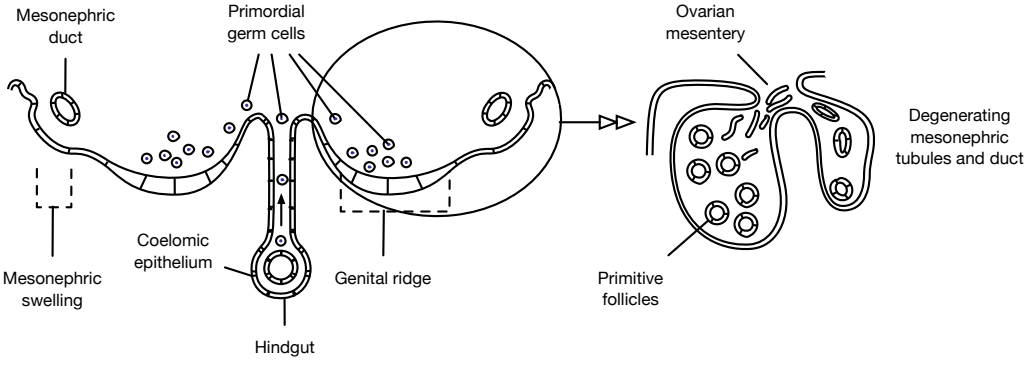


Figure. Development of the ovary.

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.

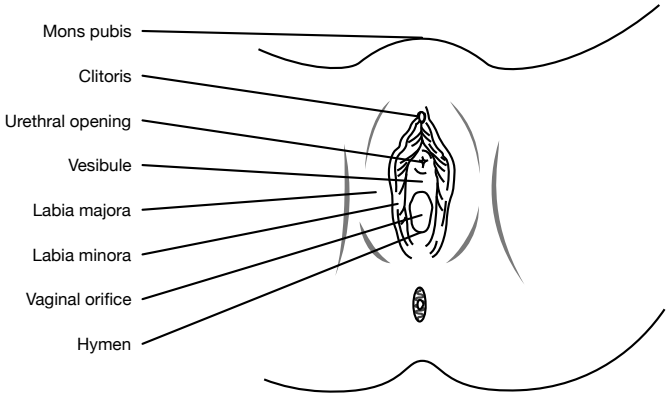


Figure. The female external genitalia.

- 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.

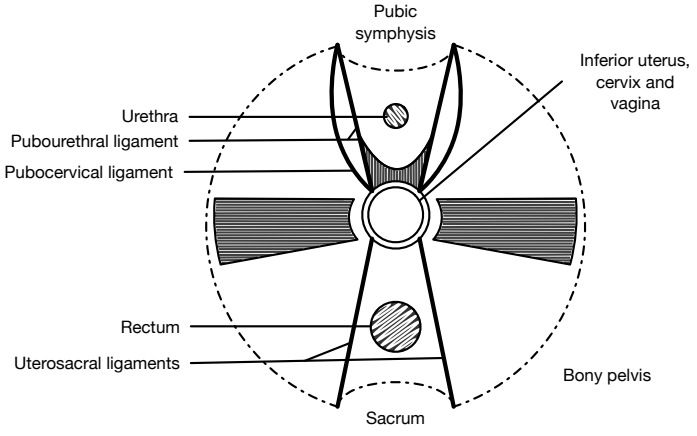


Figure. Figurative illustration of ligamental support of lower part of uterus, cervix and upper vagina.

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).

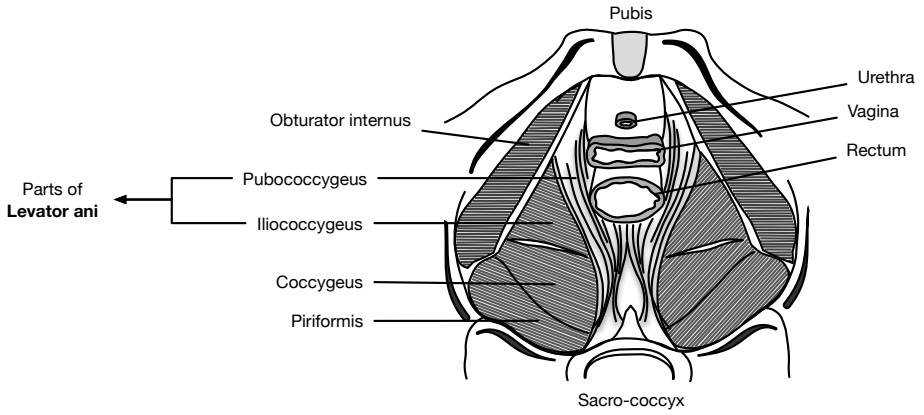


Figure. Pelvic floor musculature— *superior view*.

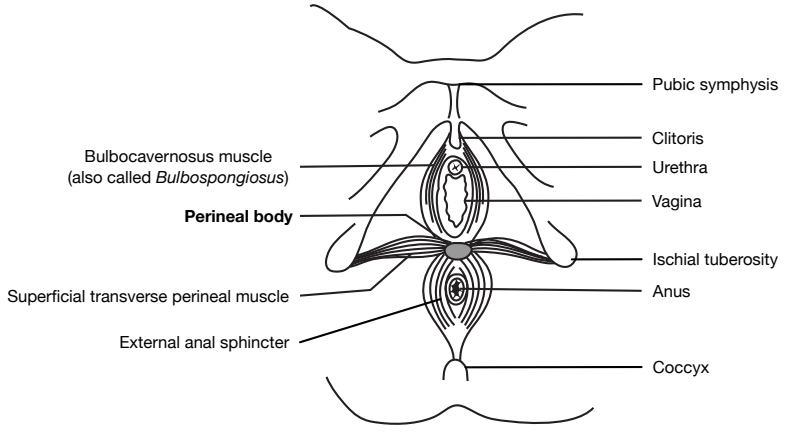


Figure. Perineal body and the perineum— *inferior view*.

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.

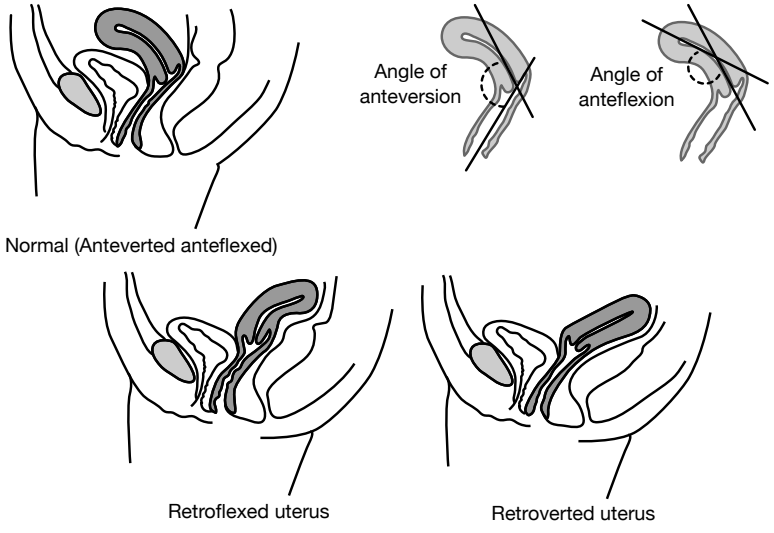


Figure. Illustration of long axis uterus, cervix and vagina with variations.

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'.

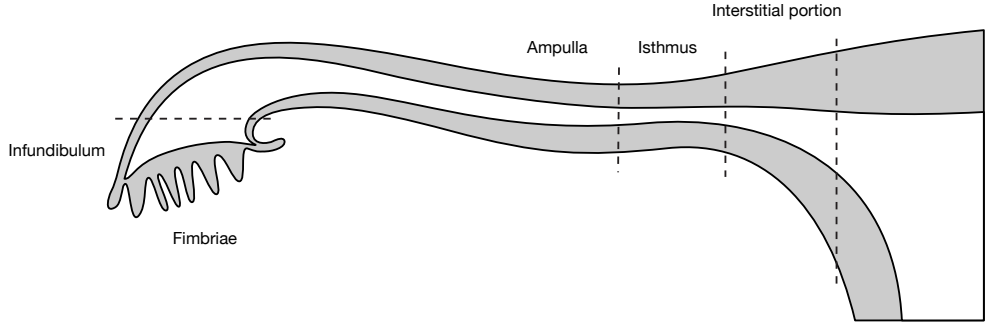


Figure. Illustration of parts of a fallopian tube.

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*).

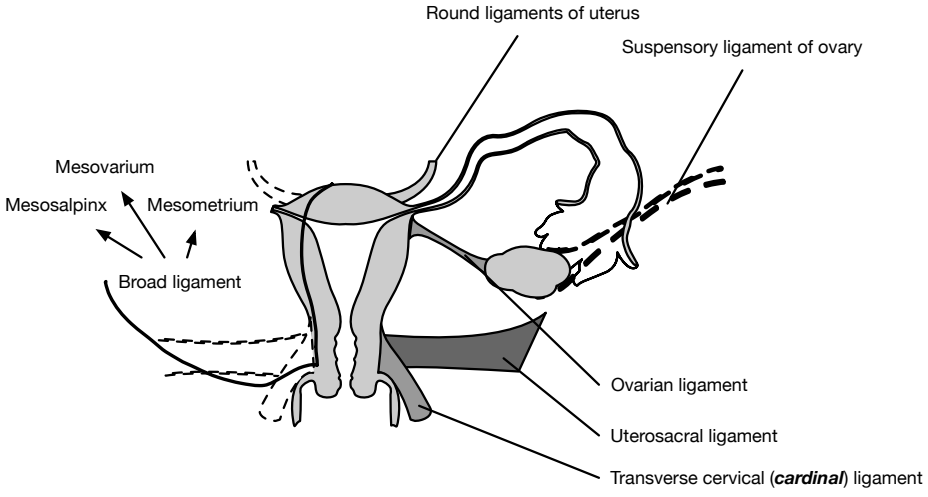


Figure. Illustration of ligamental support of internal genital organs.

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*).

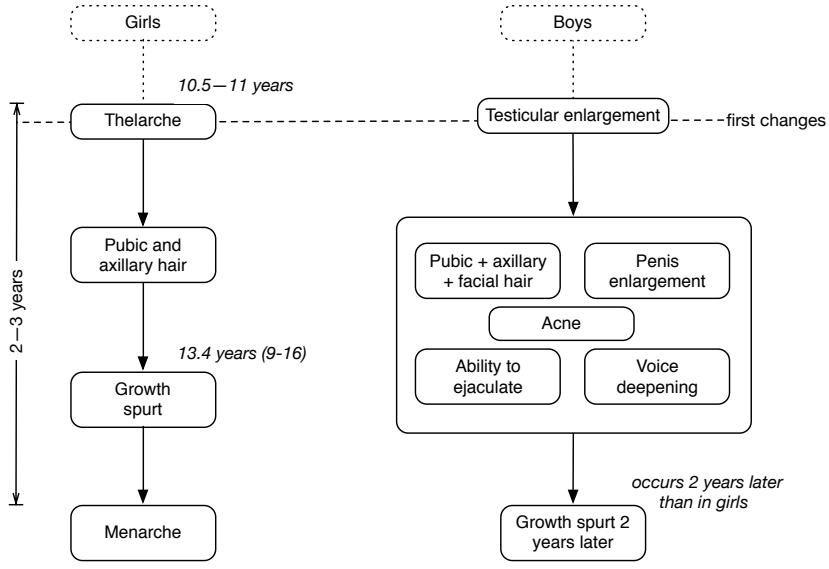


Figure. Puberty in males and females.

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.

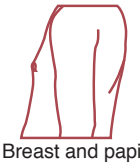
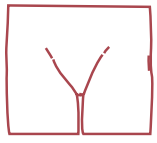
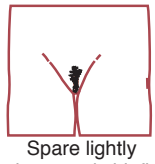
	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Breast					
		Breast and papilla are elevated as small mound. Areolar diameter increases	Further enlargement of the breast bud with loss of the contour seperation between breast and areola	Aerolar and papilla form a secondary mound	Mature areolar is part of the 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)

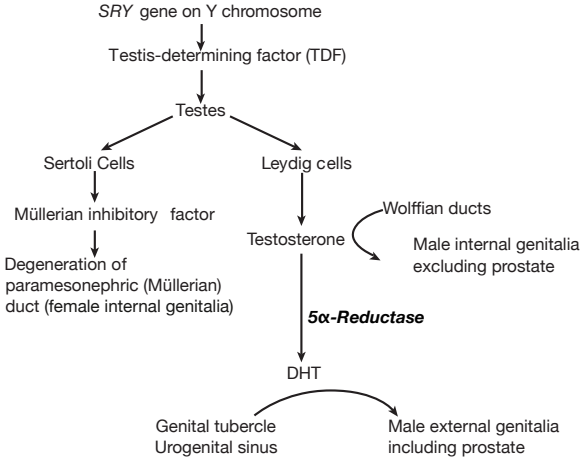


Figure. Schematic of enzymes involved in embryologic development of genotypic males (46, XY).

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.

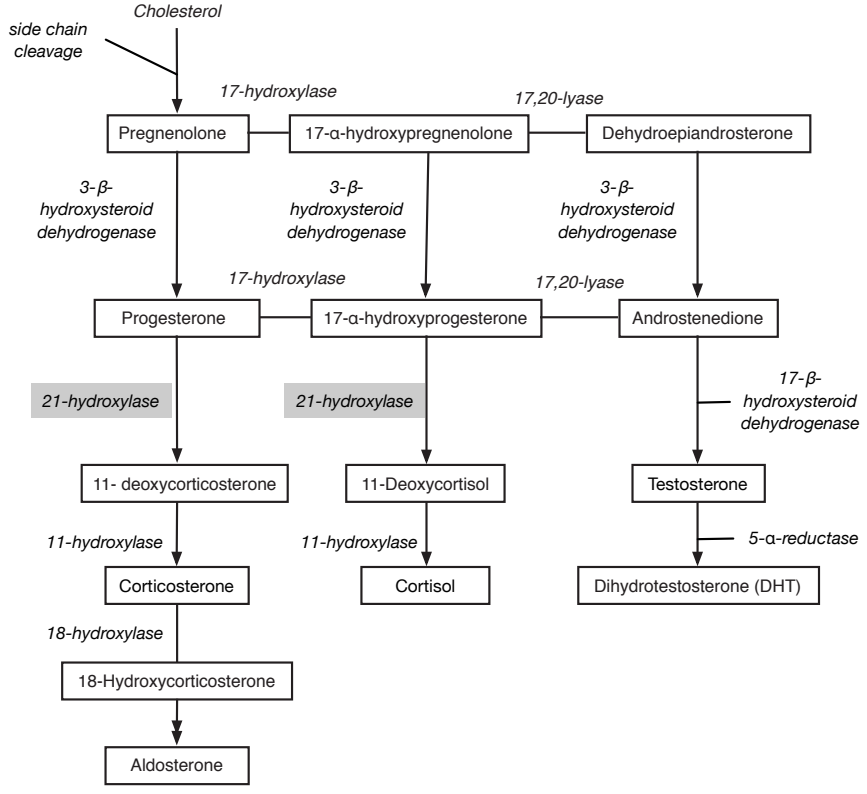


Figure. Illustration of 21-hydoxylase pathway.

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.

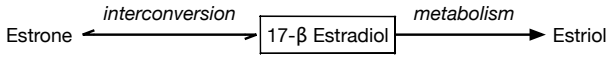


Figure. Interconversion and metabolism of estrogens.

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.

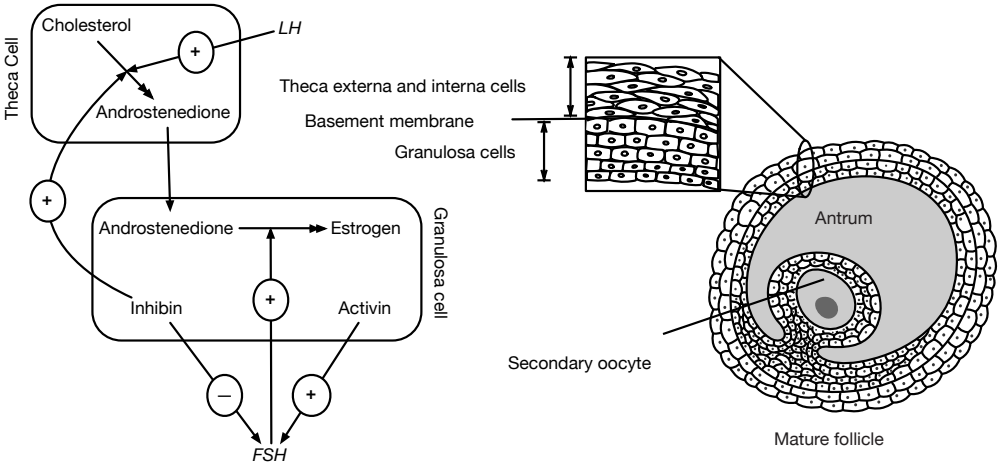


Figure. Illustration of hormonal control by gonadotropins from epithelial cells of ovaries.

- 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.

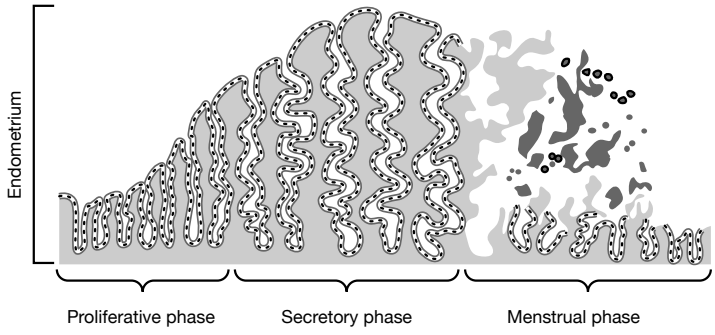


Figure. Endometrial cycle—changes in endometrial glands and vessels.

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).

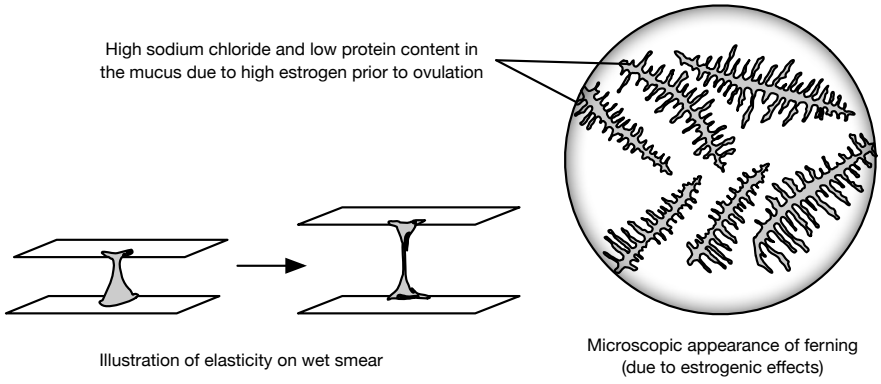


Figure. Illustration of observable effects of estrogen to cervical secretions.

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).

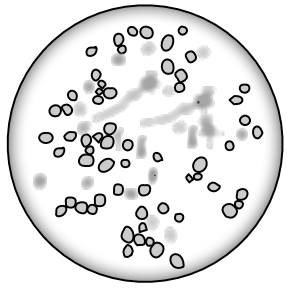


Figure. Illustration of thick and cellular mucus due to effects of progesterone.

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).

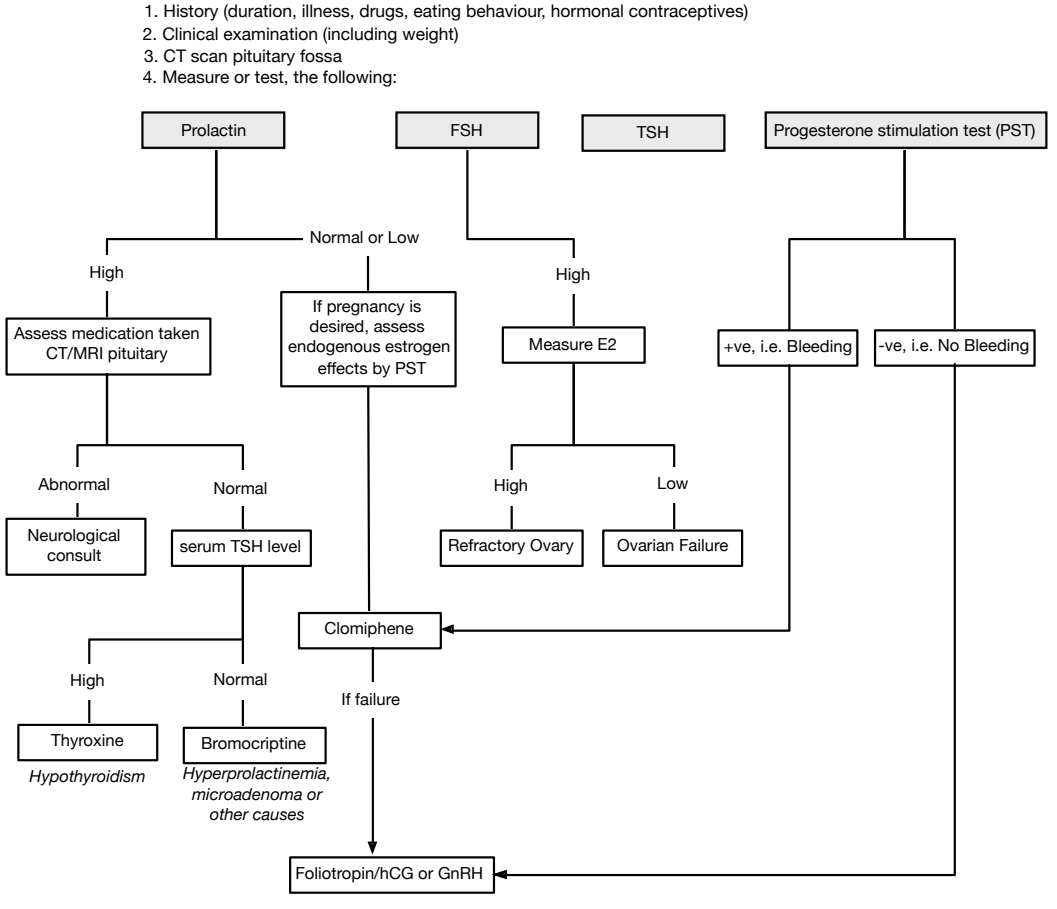


Figure. Algorithmic approach to workup of secondary amenorrhea. *E2: Estradiol.*

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.

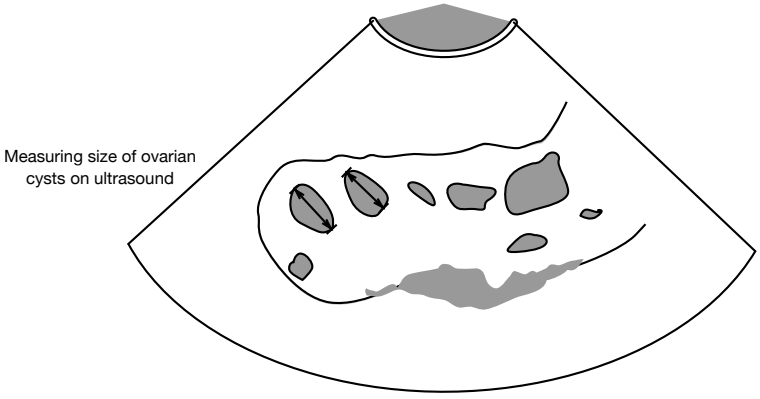


Figure. Illustration of polycystic ovaries on a transvaginal ultrasound scan (TVUSS).

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.

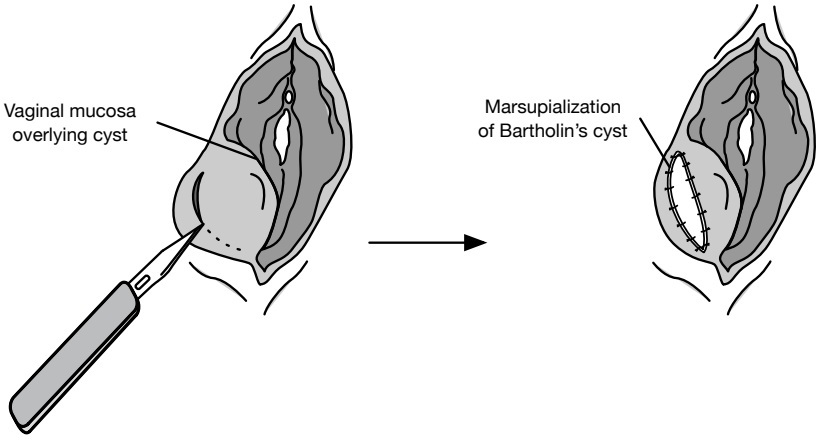


Figure. Illustration of a right-sided Bartholin's **abscess** and its marsupialization procedure.

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).

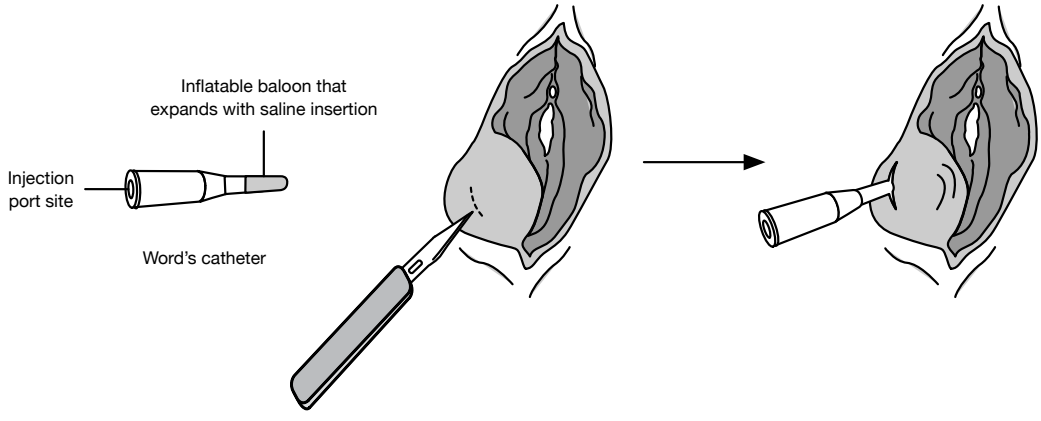


Figure. Illustration of a Word's catheter and method of insertion to a right-sided Batholin's **cyst**.

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).

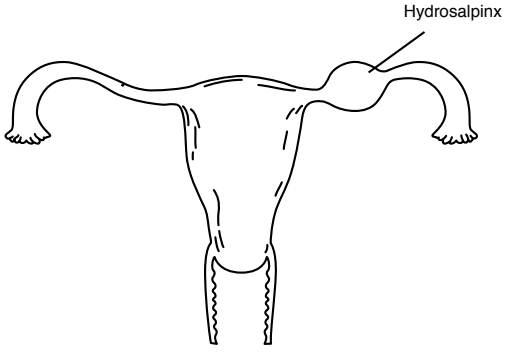


Figure. Illustration of a hydrosalpinx in left fallopian tube.

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.

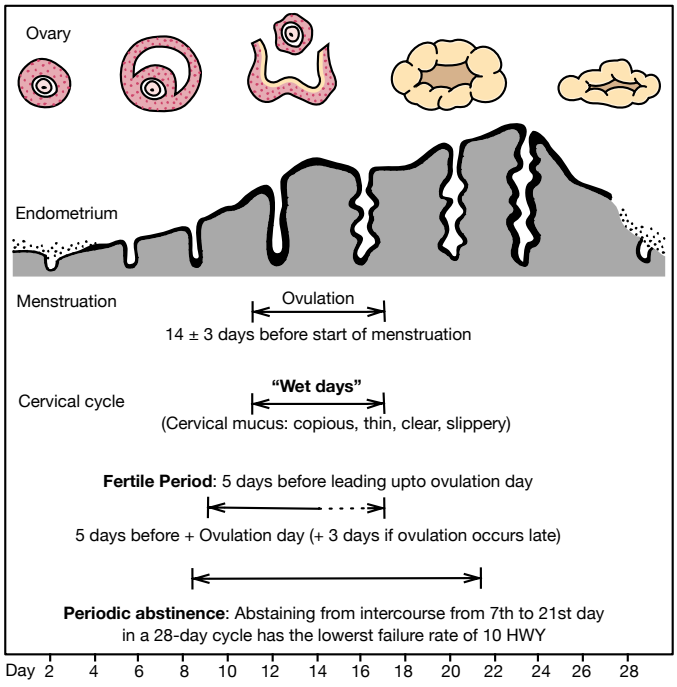


Figure. Fertile period with respect to ovulation and recommended abstinence period for family planning.

(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.

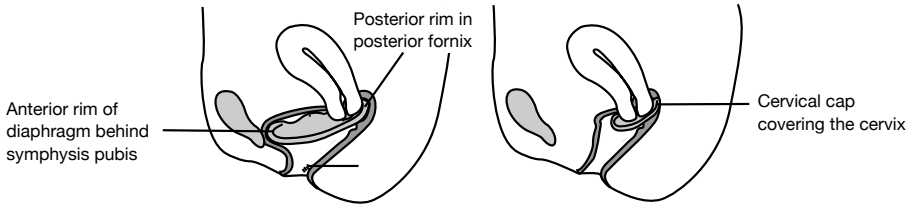


Figure. Illustration of the contraceptive diaphragm (left) and cervical cap (Right).

(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

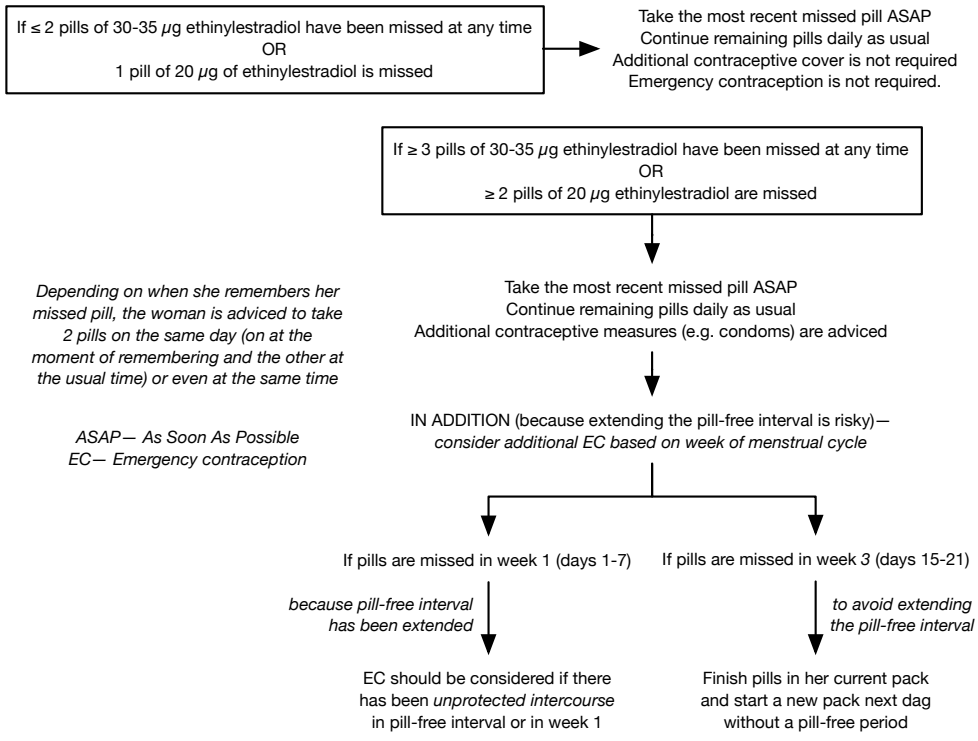


Figure. Flowchart outlining measures to take in case of forgetting pills— to maintain contraception.

(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.

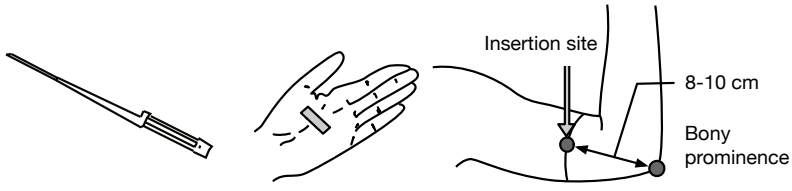


Figure: Implanon insertion instrument, its insertion site, and size of the Implanon silastic capsule.

(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.

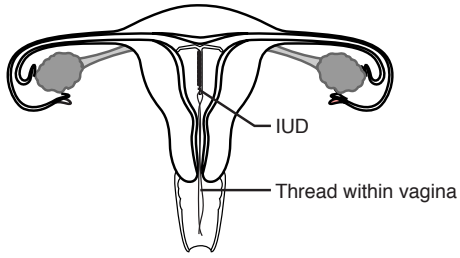


Figure. IUD in the uterine cavity

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.

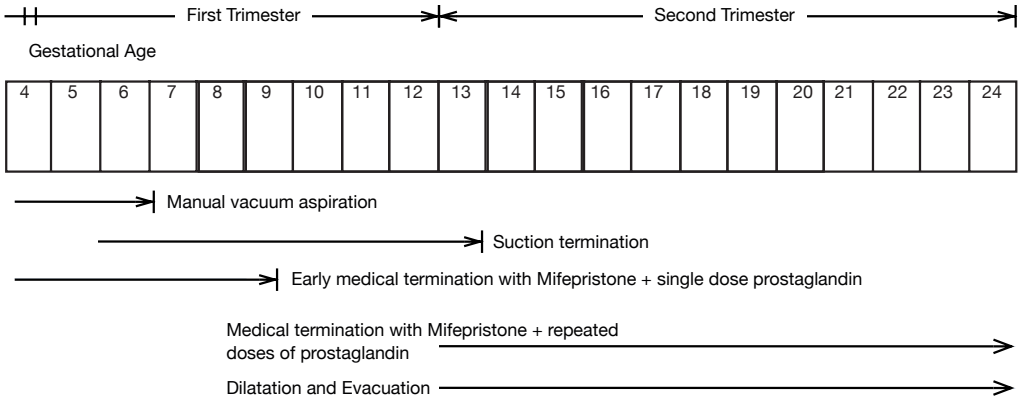


Figure. Choice of abortive techniques with respect to gestational age.

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).

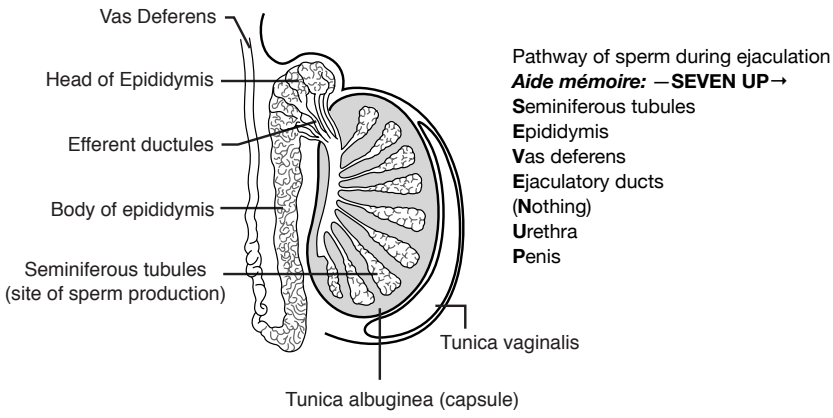


Figure. Anatomy of a testis

(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.

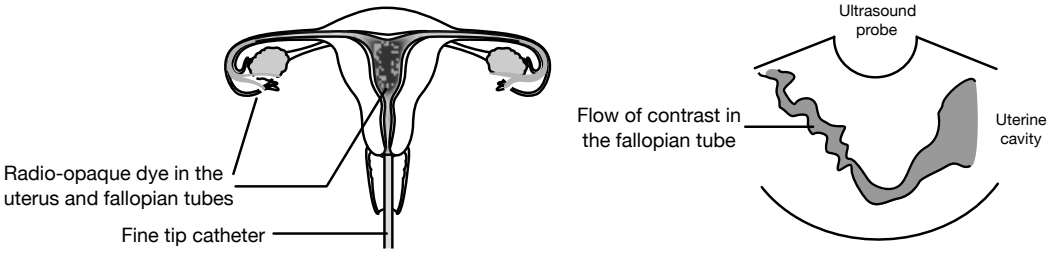


Figure. Schematic representation of HSG (left) and HycoSy (right).

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.

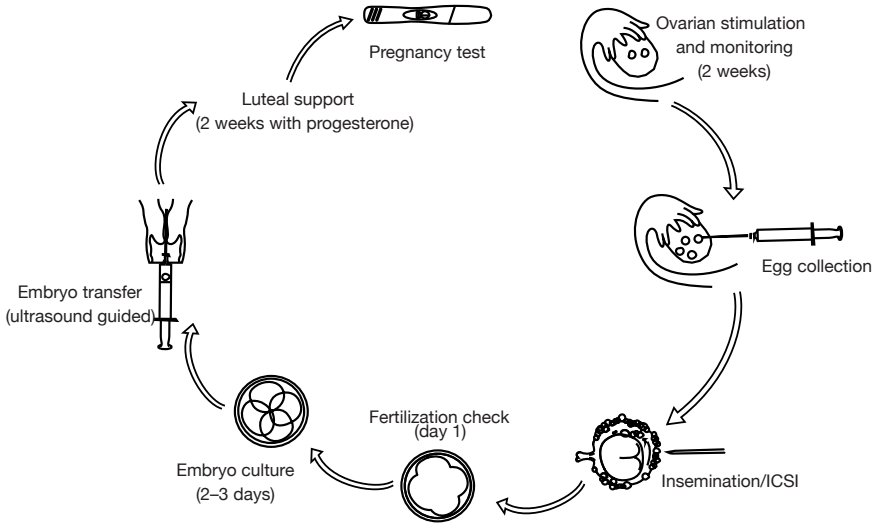


Figure. Illustration of an IVF treatment cycle.

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.

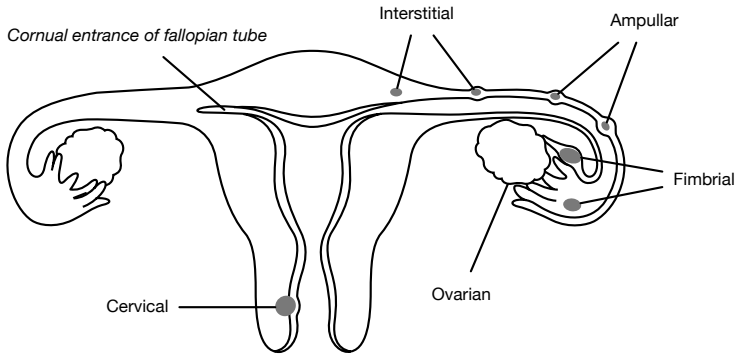


Figure. Possible sites of implantation of an ectopic pregnancy.

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).

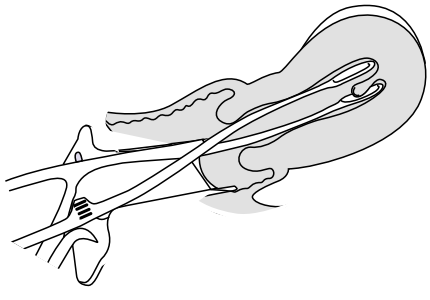


Figure. Illustration of surgical removal of endometrial polyps using polyp forceps.

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);

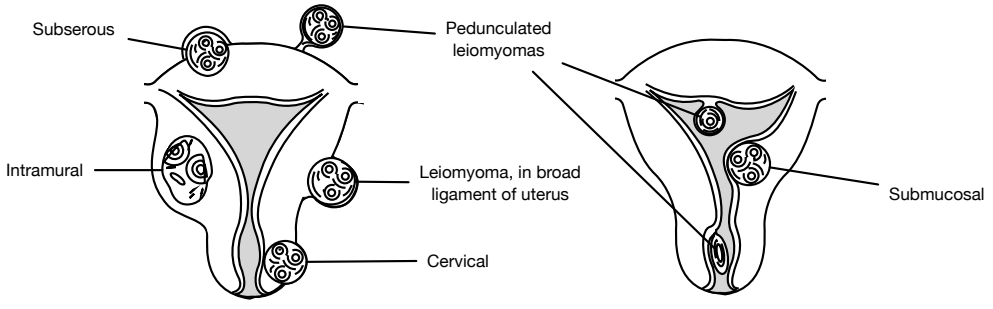


Figure. Location and types of uterine fibroids.

- 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).

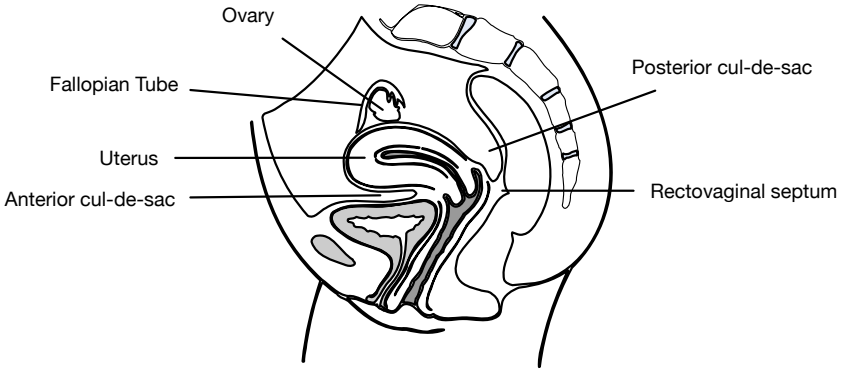


Figure. Common sites of endometriosis deposits.

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).

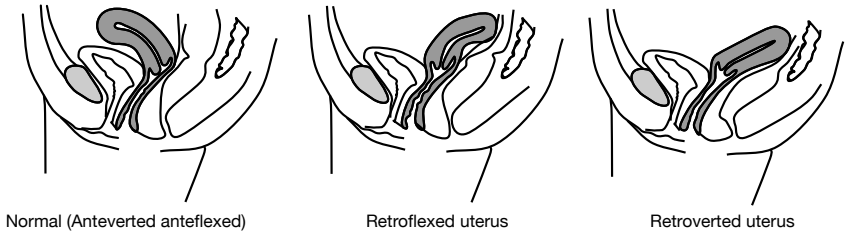


Figure. Normal uterine position, retroflexion and retroversion seen in endometriosis.

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).

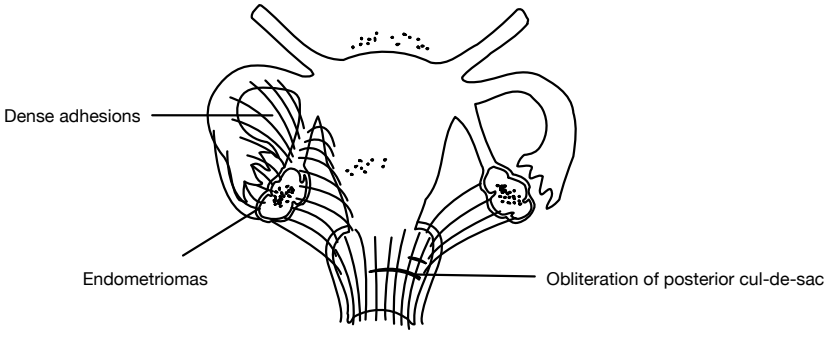


Figure. Schematic of endometriomas and periadnexal adhesions as seen in endometriosis.

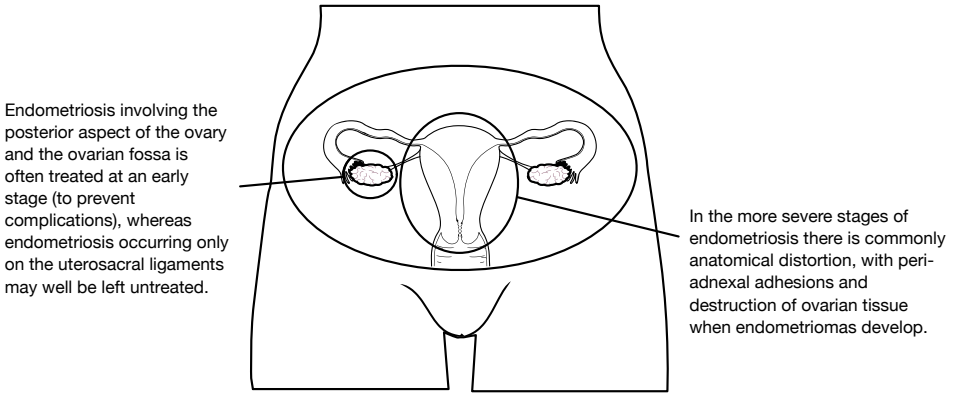


Figure. Endometriosis and infertility.

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.

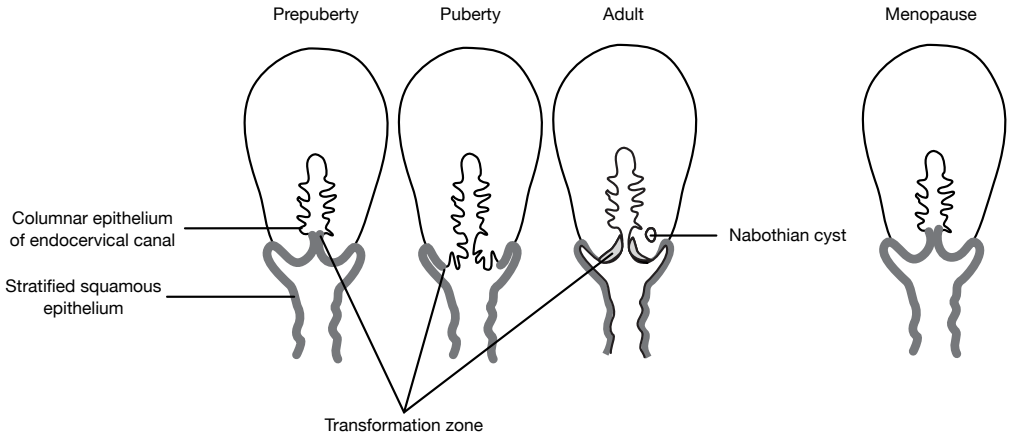


Figure. Transformation zone of the squamocolumnar junction.

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).

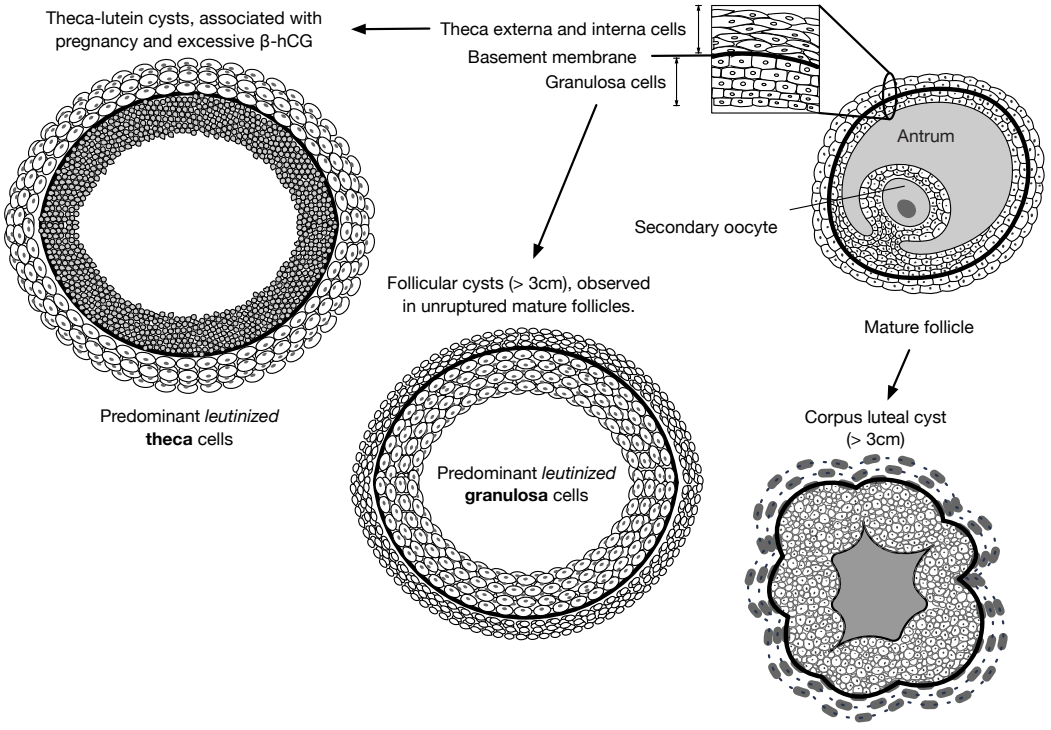


Figure. Illustration of ovarian cyts.

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;

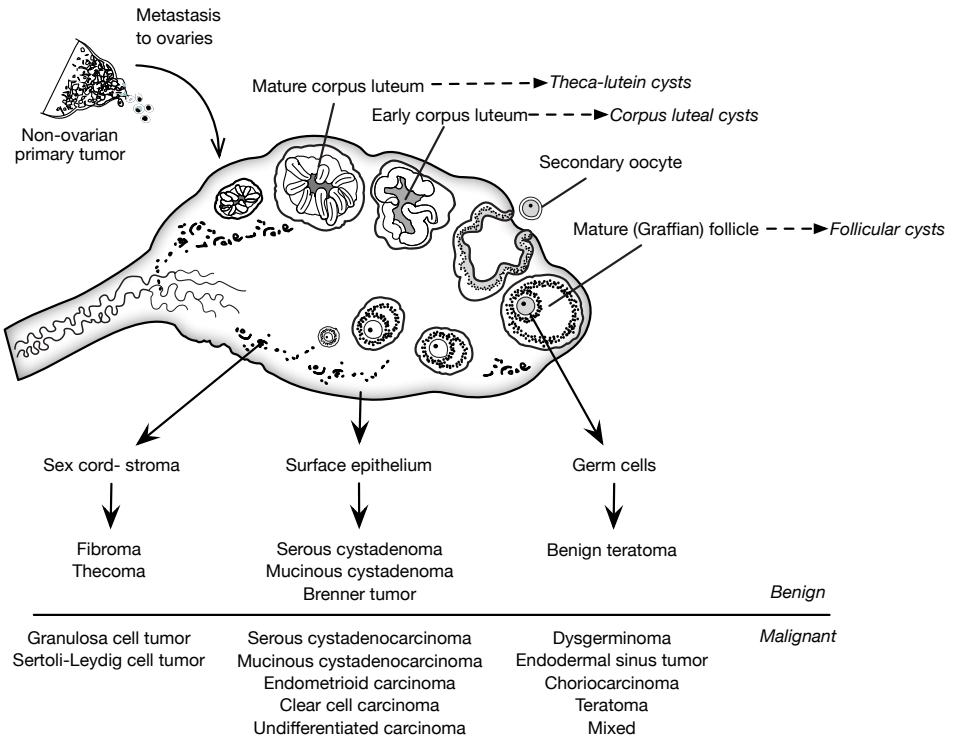


Figure. Ovarian cysts, tumors and their origins.

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.

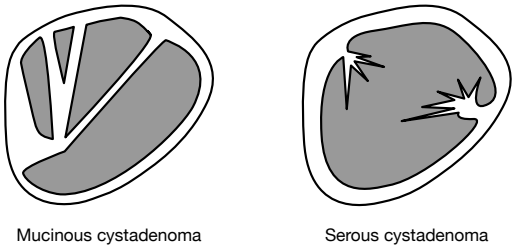


Figure. Illustration of gross appearance on cross sections of common epithelial cells tumors.

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).

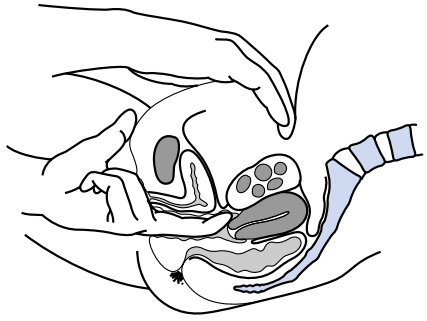


Figure. Illustration of bimanual examination for a peri-adnexal mass.

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.

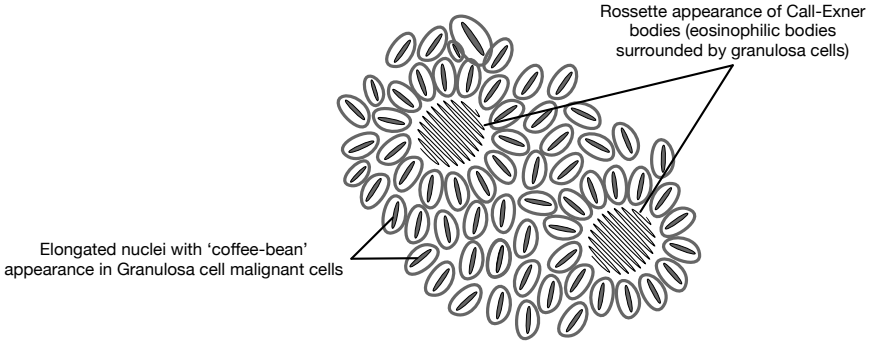


Figure. Illustration of Call-Exner bodies, pathognomonic for granulosa cell tumors on histopathology.

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***.

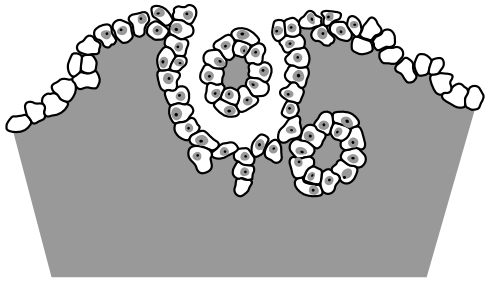


Figure. Illustration of type 2 endometrioid adenocarcinomas.

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.

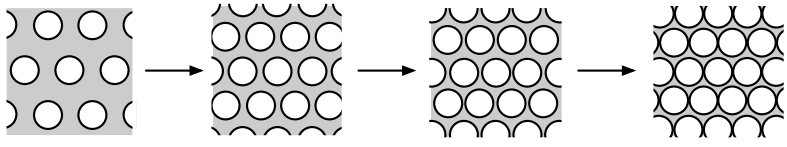
Endometrial hyperplasia is often associated with inactivation of the PTEN tumor suppressor gene (20% of cases), leading to increased cellular proliferation and diminished apoptosis.

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.

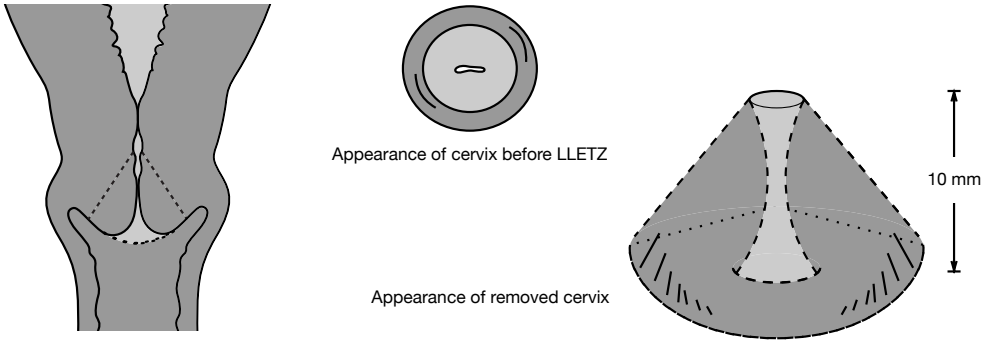


Figure. Illustration of LLETZ using a diathermy wire loop.

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.

-x-

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.

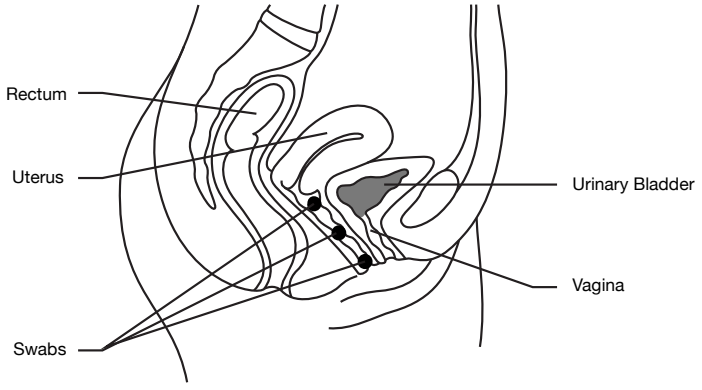


Figure. Methylene blue test.

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;

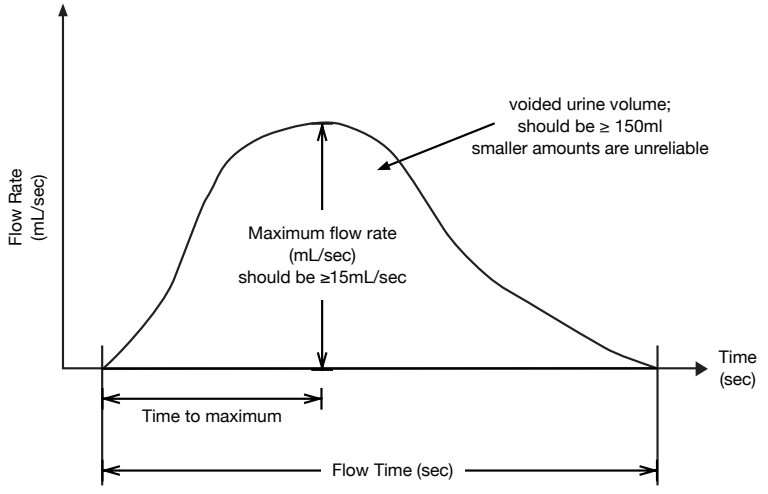


Figure. A normal uroflowmetry– bell shaped curve.

- 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).

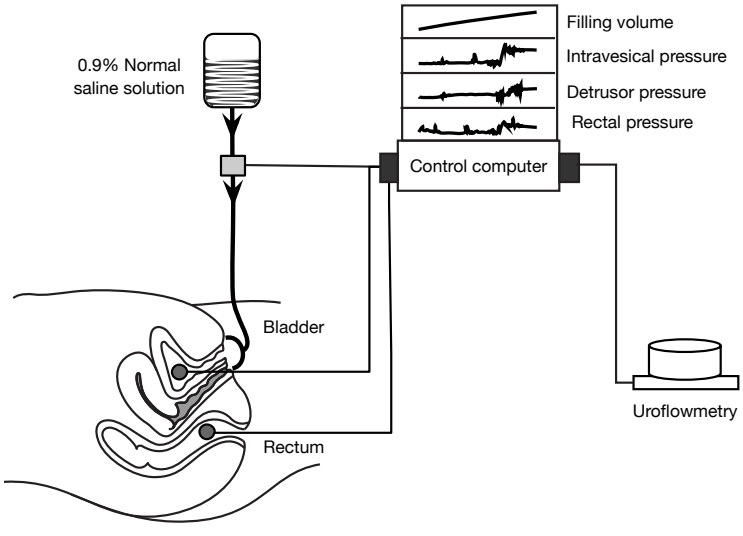


Figure. Illustration of cystometry.

- 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.

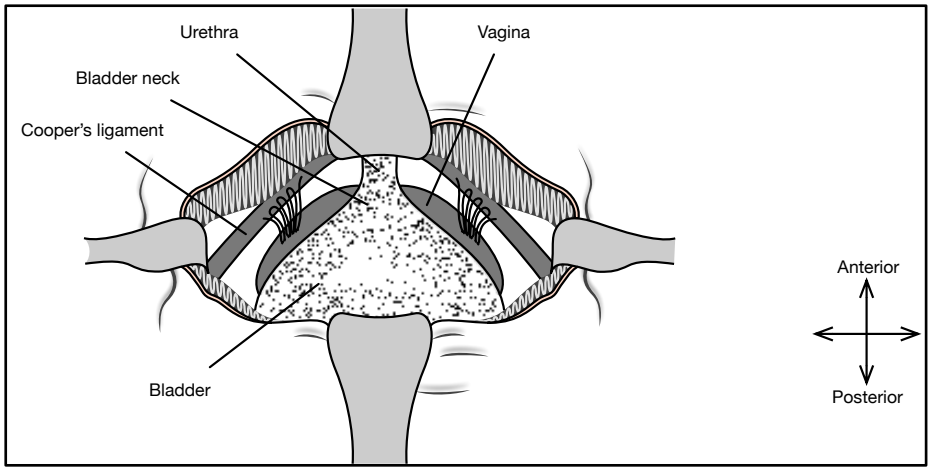


Figure. Colposuspension— Suprapubic view during surgery.

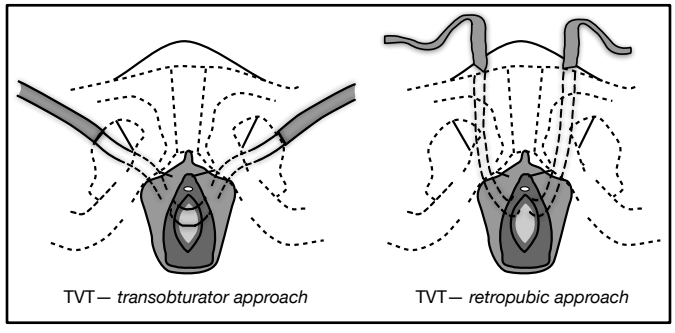


Figure. Illustration of tension-free vaginal tape— inserted by transobturator and retropubic approaches..

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.

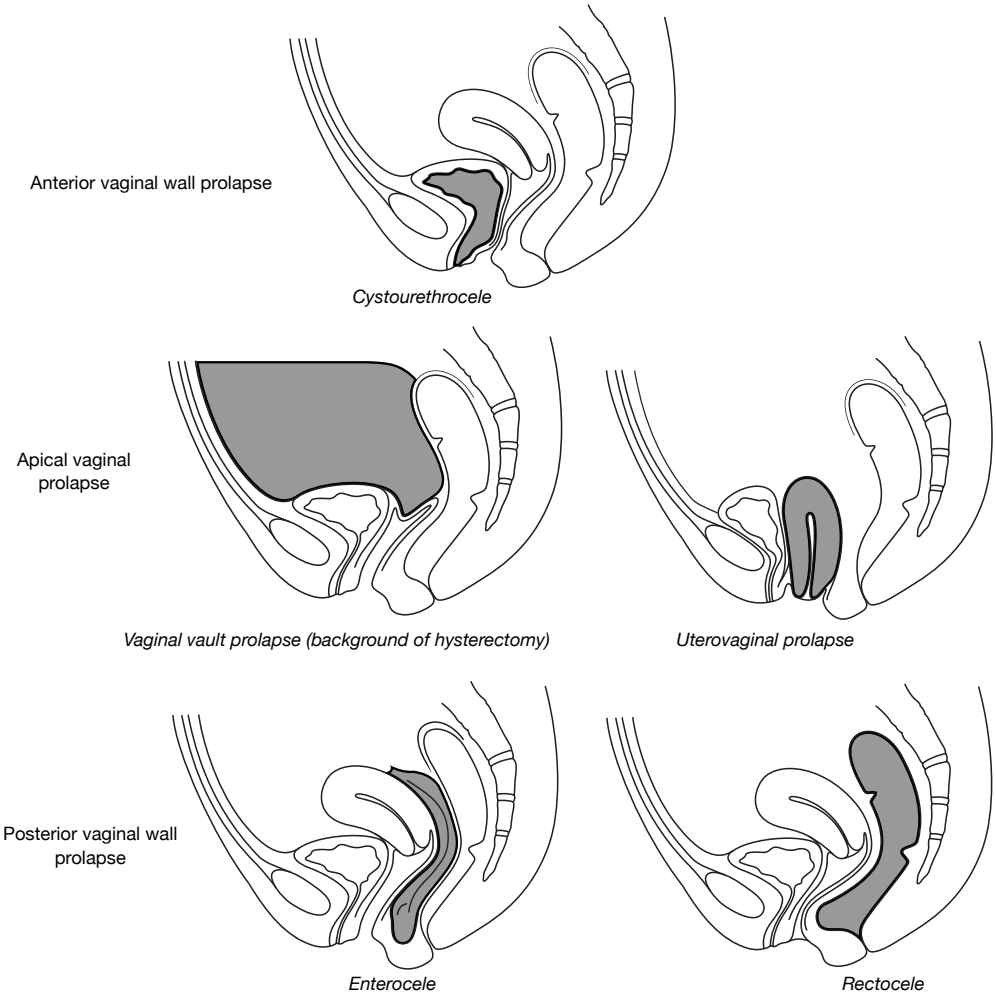


Figure. Illustration of anterior, apical vaginal and posterior vaginal wall prolapses.

(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.

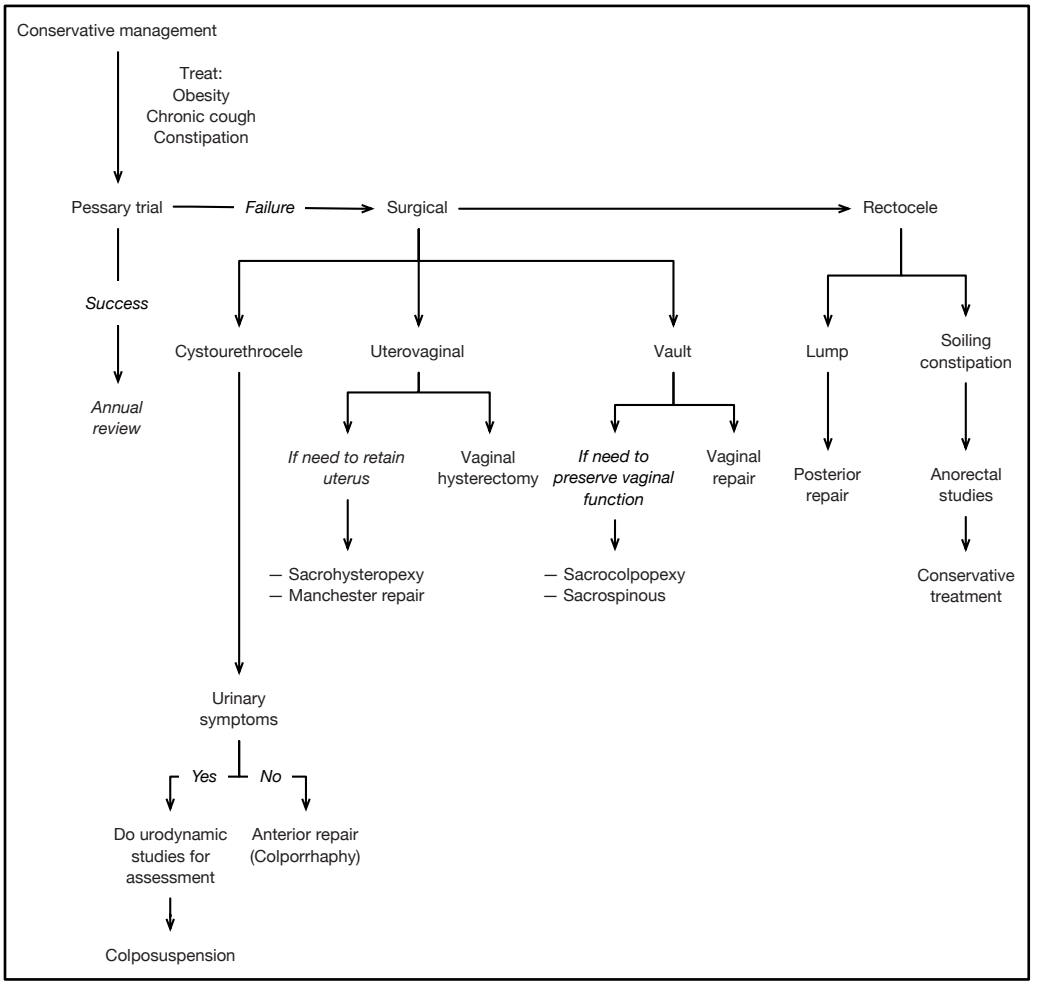


Figure. Algorithmic approach to treatment of POP.

i) Treatment with pessaries

The three commonly used pessaries are shown below (see Figure).

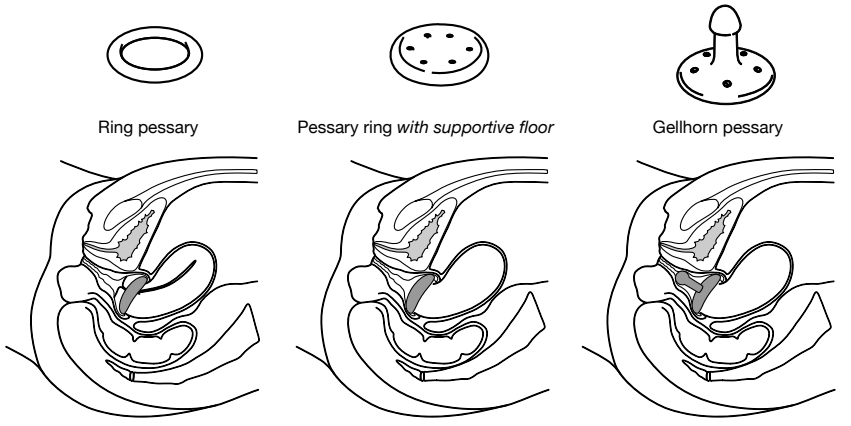


Figure. Illustration of the famous types of pessaries.

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.

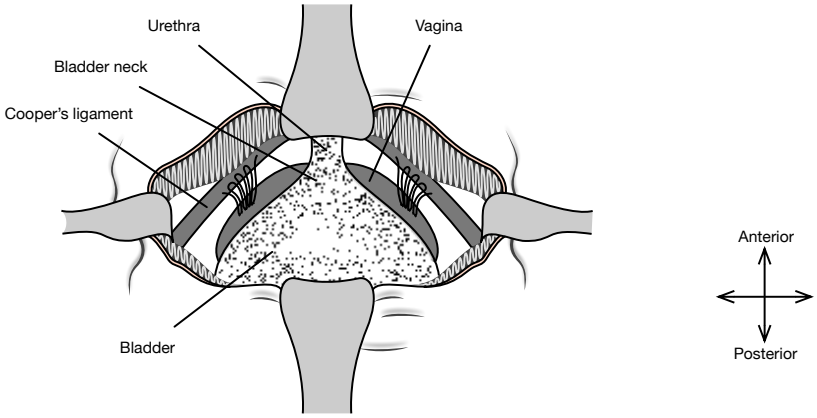


Figure. Colposuspension— suprapubic view during surgery.

- 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.

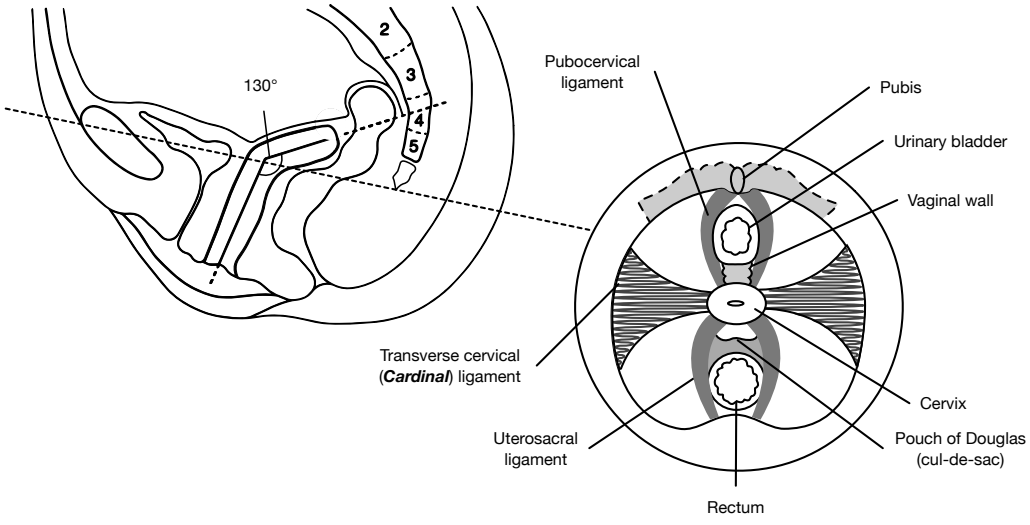


Figure. *Sagittal* and *axial views* of the pouch of douglas, uterosacral ligaments and surrounding structures.

- 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);

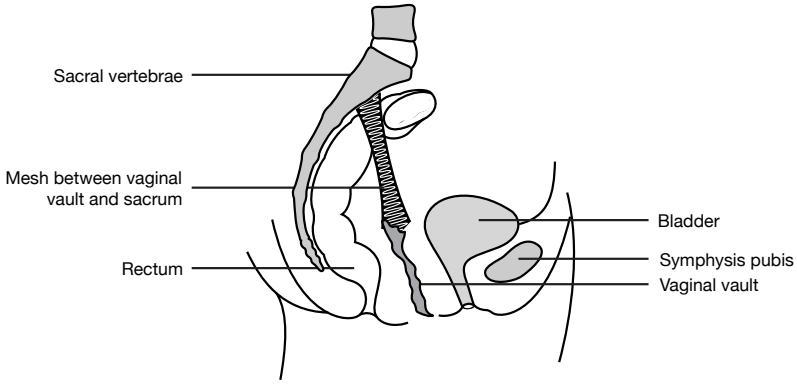


Figure. Sacrocolpopexy.

- **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.

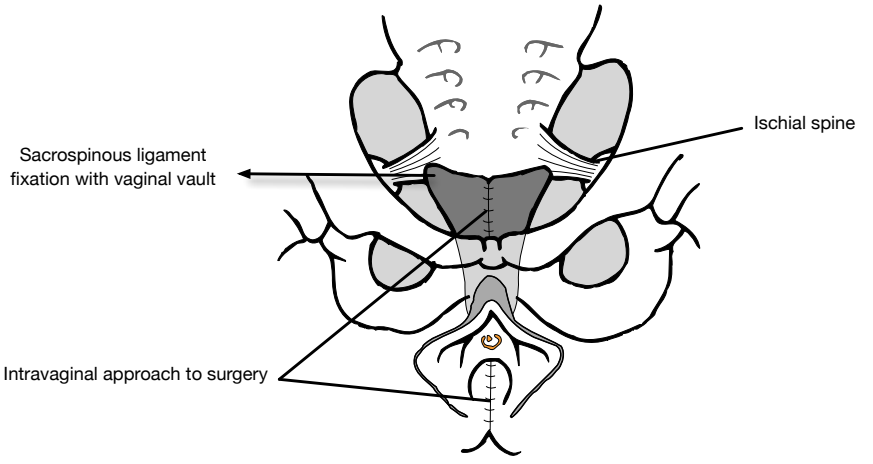


Figure. Sacrospinous ligament fixation. The urinary bladder is *not* shown in the illustration.

(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.

-x-

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

-x-

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.

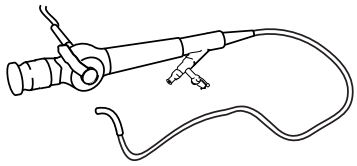


Figure. Illustration of a *flexible* fibreoptic hysteroscope.

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.

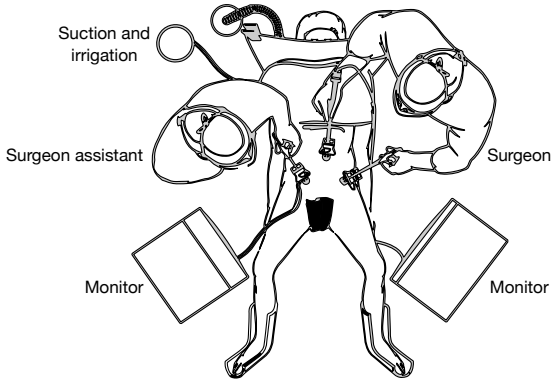


Figure. Laparoscopy— operative setup.

(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).

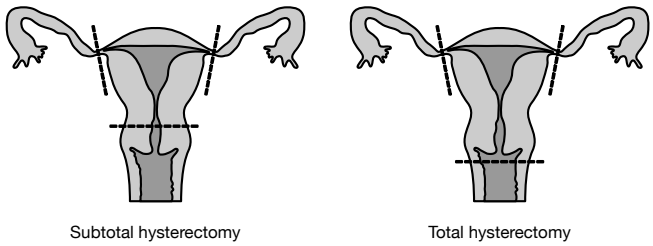


Figure. Illustration of subtotal (left) and total hysterectomy (right).

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.

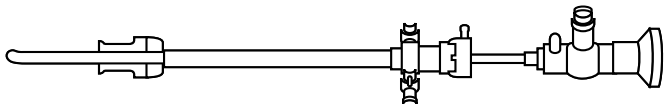


Figure Illustration of a *rigid* cystoscope.

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).

CHAPTER 16 GENERAL OBSTETRICS PEARLS

(I) Obstetric history

Obstetric history can be expressed in shorthand denotion as;

Gravida; total number of pregnancies regardless of how they ended;

Parity; total number of live births at any gestation, or stillbirths after 24 weeks.

Examples—

- Gravida 1, parity 0— a woman who is pregnant for the first time;
- Parity 2— a woman who has had 2 live births/stillbirths after 24 weeks gestation OR gave birth to ***twins***;
- Parity 1^{+6} — a woman who has had 1 live birth/stillbirth after 24 weeks and 6 miscarriages;
- Gravida 8, parity 1^{+6} — a woman who is pregnant, had 7 pregnancies previously leading to 1 live birth/still birth after 24 weeks and 6 miscarriages.

Major pre-existing diseases that impact pregnancy—

- Diabetes mellitus: macrosomia, FGR, congenital abnormality, pre-eclampsia, stillbirth, neonatal hypoglycaemia;
- Hypertension: pre-eclampsia;
- Renal disease: worsening renal disease, pre-eclampsia, FGR, preterm delivery;
- Epilepsy: increased fit frequency, congenital abnormality;
- Venous thromboembolic disease: increased risk during pregnancy; if associated thrombophilia, increased risk of thromboembolism and possible increased risk of pre-eclampsia, FGR;
- Human immunodeficiency virus (HIV) infection: risk of mother-to-child transfer if untreated;
- Connective tissue diseases, e.g. systemic lupus erythematosus: pre-eclampsia, FGR;
- Myasthenia gravis/myotonic dystrophy: fetal neurological effects and increased maternal muscular fatigue in labour.

Obstetric events that are likely to impact future pregnancies include, but not limited to;

- Recurrent miscarriage (↑ risk of miscarriage, fetal growth restriction (FGR));
- Preterm delivery (↑ risk of preterm delivery);
- Early-onset pre-eclampsia (↑ risk of pre-eclampsia/FGR);
- Abruptio placenta (↑ risk of recurrence);
- Congenital abnormality (recurrence risk depends on type of abnormality);
- Macrosomic baby (may be related to gestational diabetes);
- Unexplained stillbirth (↑ risk of *gestational* diabetes).

(II) The obstetric visit

i) Dating the pregnancy

The date of the last menstrual period (LMP) is most commonly used to date the pregnancy with assumptions as;

- The menstrual cycle is of 28 days;
- Ovulation occurs generally on the 14^{th} day of the cycle;
- The cycle is a normal cycle (i.e. not after recent discontinuation of OCPs or after a previous pregnancy);

Thus, the Expected Date of Delivery (EDD) is calculated using the Naegele's rule, i.e;

EDD = Date of LMP + 9 calender months + 7 days.

If the cycle is greater than 28 days (unlike the previous assumption), then the difference between 28 days and actual cycle length days can be *added* to get a corrected estimation.

A more accurate EDD can be estimated using an ultrasound scan;

- If performed before 20 weeks gestation, ultrasound can be used to date the pregnancy;
- If performed after 20 weeks, dating a pregnancy can vary because of variable growth rates of fetuses.

ii) Maternal weight and height

The measurement of weight at the initial examination is important to identify women who are significantly underweight or overweight.

- BMI of < 20 are at ↑ risk of FGR and perinatal mortality— especially those with poor weight gain during pregnancy;
- Obesity (BMI > 30)—
    - In the mother— ↑ risks of gestational diabetes and hypertension;
    - In the fetus— ↑ birthweight and perinatal mortality rate.
- Shoe size is unhelpful when height is known, unlike previously thought.

iii) Blood pressure evaluation

Blood pressure measurement should be performed at every visit.

- Hypertension diagnosed if the BP is ≥ 140/90 mmHg on two separate occasions at least 4 hours apart.
- If hypertension is observed in early pregnancy, underlying causes should be ruled out; i.e. renal, endocrine and collagen-vascular disease.
- *Essential hypertension* is the diagnosis of exclusion after ruling out secondary causes.

iv) Obstetric physical examination

a) Cardiovascular system

- Women with significant cardiac symptoms or a known history of heart murmur or heart disease should be evaluated.
- Conditions of concern during pregnancy include, but not limited to— mitral or aortic stenosis, mitral valve prolapse, cardiomyopathies and untreated right-to-left shunts.
- Flow murmurs (systolic innocent murmurs) can be heard in approximately 80 per cent of women *at the end of* the first trimester, and may be evaluated to rule out more serious pathology.

b) Breast examination

Women should be encouraged to report new or suspicious breast lumps that develop and, appropriate investigation should not be delayed because of pregnancy.

c) Abdominal examination

Abdominal examination in a pregnant individual is focused upon;

- Symphysis–fundal height measurement (SFH)
    - First, measure the symphysis–fundal height using a measuring tape with the centimeters scale not visible.
    - Assessment can be made roughly during examination or using customized SFH charts (*see Figure and Graph*).
    - Discrepancy in SFH and gestational age can point to conditions like *polyhydramnios, multiple pregnancy or growth restriction* (see Table).

Table. Causes of discrepancies between SFH and gestational age.

SFH > gestational age	**SFH < gestational age**
Incorrect dates	Incorrect dates
Macrosomia	Intrauterine growth restriction (IUGR)
Multiple pregnancy	Oligohydramnios
Polyhydramnios	Presenting part *down* in the pelvis

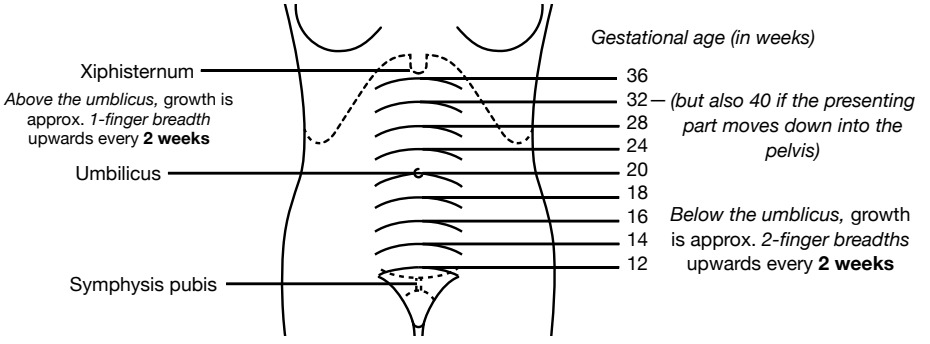
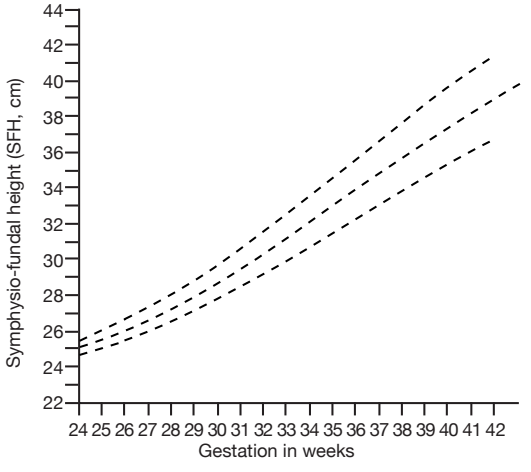


Figure. Symphysiofundal height (SFH) and gestational age— rough estimation.



Graph. Symphysiofundal height (SFH) and gestational age—estimation with 95% CI (=confidence interval).

- The 'four **Leopold manoeuvres**'— assess the fetus as a whole inside the uterus. It consists of (see Fig.);
    - Fundal grip—to assess the fundal height and poles;
    - Lateral, or abdominal grip—to determine which side is the fetal belly and limbs;
    - Pelvic grip— to determine the presenting part of fetus and external ballotment;
    - Pawlik's grip— to determine the presenting part of fetus and its degree of descent.
- Fetal poles—
    - A fetal pole (head or buttocks) can be palpable on abdominal examination;
    - If more than 2 fetal poles are palpable, twin pregnancy or uterine fibroids are likely.
- Fetal lie—the relationship of the long axis of the fetus with respect to long axis of the uterus;
    - By 38th week of gestation, fetus may have a longitudinal, oblique or transverse lie (see Fig);
    - It is said to be longitudinal if either fetal pole lies over the pelvis;
    - An oblique lie is where the leading pole does **not** lie over the pelvis— *but to one side*;
    - Transverse lie is said to occur when the fetus lies across the abdomen.

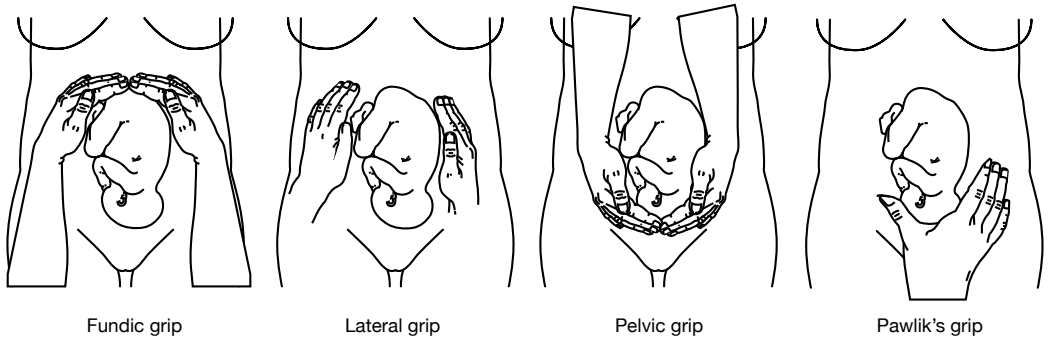


Figure. The four '**leopold manoeuvres**'.

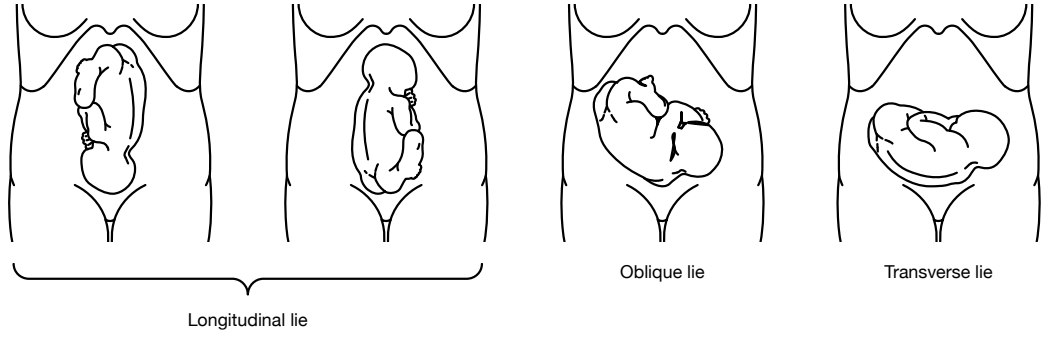


Figure. Illustration of fetal lies— longitudinal, oblique and transverse.

- If the gestation is ≥ 34 weeks, assess the presentation *in a longitudinal lie*. As the head is *more firm*, examination can guide whether the presention is cephalic (head-down) or breech (buttocks/feet-down).
- Assess for engagement. This is done by examining the abdomen;
    - Engaged means that *the widest diameter of the fetal head* has passed through pelvic inlet.
    - Using a two-handed approach, assess if the head is not moveable (engaged).
    - Alternatively, engagement is expressed as 'number of finger breadths of fetal head palpable above the pelvic brim' as— it can be from $1/5^{ths}$ to $5/5^{ths}$ palpable (see figure).

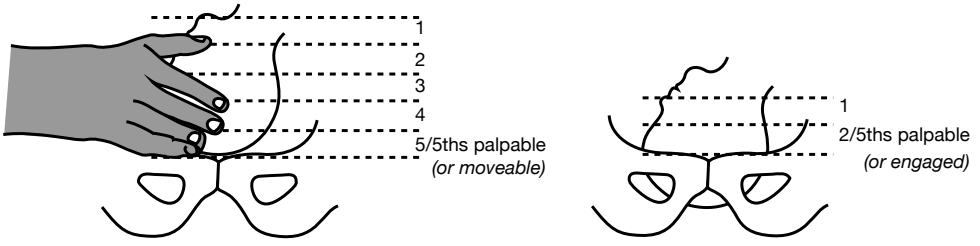


Figure. Assessment of engagement at the pelvic inlet on examination.

- Assess the attitude of fetus— relationship of the various fetal parts to its other parts. Usually, the fetus lies with all its joints flexed, but in some breech presentations, the legs are extended along its body.
- Assessment of the fetal position (~ occipito-posterior, lateral or anterior) is the relationship of the fetus to the bony pelvic walls. It is not needed until start of labor.
- Auscultation using a pinard stethoscope may help detect the fetal heart sounds if put at the correct location (over the fetal shoulder, see Figure). In difficult cases, use of a hand-held doppler device is recommended.

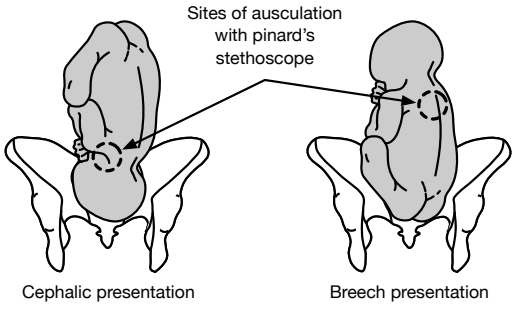


Figure. Illustration of sites for pinard's auscultation for fetal heart sounds in cephalic and breech presentations.

d) Pelvic examination

A pelvic examination, digital or speculum, may be unpleasant for the pregnant individual. But it is necessary if;

- Excessive or offensive discharge;
- Vaginal bleeding (in the known absence of a placenta praevia);
- To perform a cervical smear;
- To confirm potential rupture of membranes.

A digital examination may be performed when an assessment of the cervix is required. This can provide information about the consistency and effacement of the cervix that is not obtainable from a speculum examination.

- The Bishop's score can be calculated (see Table). It helps assess for readiness for induction of labour;
- However, conditions in which a *digital* examination is contraindicated are;
    - Known placenta praevia or vaginal bleeding when the placental site is unknown and the presenting part unengaged;
    - Prelabour rupture of the membranes (↑ risk of ascending infection).

Table. The bishop scoring.

	Score			
	0	1	2	3
Dilatation of the cervix (cm)	0	1 or 2	3 or 4	5 or more
Consistency of cervix	Firm	Medium	Soft	
Length of cervical canal	>2	2-1	1-0.5	<0.5
Position	Posterior	Central	Anterior	—
Station of presenting part (cm above ischial spine)	3	2	1 or 0	*Below*

e) Optional aspects of examination

- In the presence of hypertension and in women with headache, fundoscopy should be performed.
- In severe pre-eclampsia and some intracranial conditions (space-occupying lesions, benign intracranial hypertension), papilloedema may be observed.
- Oedema of the extremities affects 80% of term pregnancies. Its presence should be noted, but it is not a good indicator for pre-eclampsia as it is so common.
- If pre-eclampsia is suspected, reflexes and clonus should be assessed usually checked at the ankle. The presence of ≥ 3 beats of clonus is pathological.

v) Lab investigations

- Urinalysis— screening of midstream urine for asymptomatic bacteriuria has proved to be of benefit in pregnancy.
    - The risk of ascending UTI and pyelonephritis is ↑ in pregnancy;

- Acute pyelonephritis raises the risk of pregnancy loss/ premature labour, and is associated with considerable maternal morbidity;
- *Trace proteinuria* is unlikely to be problematic in terms of pre-eclampsia, and may point to a UTI. However, **persistent trace proteinuria** warrants further investigation.

- Cervical cancer screening ***should not be deferred during pregnancy***;
  - If a cervical smear is due, it can be taken during the *first* trimester with minimal risk;
  - Knife cone biopsy is associated with an ↑ risk for both cervical incompetence (weakness) and stenosis (leading to preterm delivery and dystocia in labour, respectively);
  - Large loop excision of the transformation zone (LLETZ) is found to have very small increase in the risk of preterm birth. But individuals who have needed ≥ 2 excisions are likely to have *a much shorter cervix*, which does ↑ risk for 2nd and early 3rd trimester delivery.

(III) Millenium Development Goals (MDGs)

Three-quarters of maternal deaths are due to a complication directly attributable to pregnancy, such as hemorrhage or hypertension. The most life- threatening complication at delivery is *haemorrhage*.

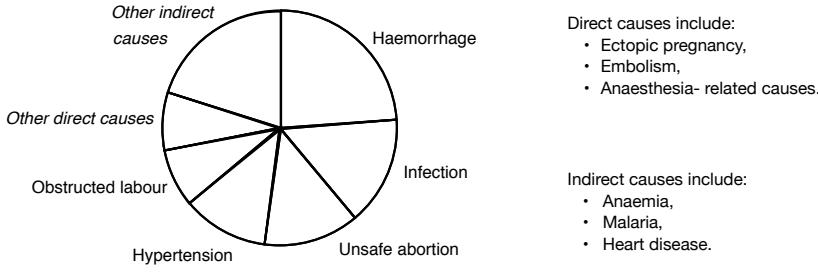


Figure. Pie chart showing causes of maternal mortality;

At the Millennium Summit in September, 2000, the largest gathering of world leaders in history adopted the UN Millennium Declaration, committing their nations to a new global partnership to reduce extreme poverty and setting out a series of time-bound targets, with a deadline of 2015, that have become known as the Millennium Development Goals.

The Millennium Development Goals (MDGs) are the world's time-bound and quantified targets for addressing extreme poverty in its many dimensions-income poverty, hunger, disease, lack of adequate shelter, and exclusion-while promoting gender equality, education, and environmental sustainability. They are also basic human rights-the rights of each person on the planet to health, education, shelter, and security.

i) Goals

Goal 1: Eradicate Extreme Hunger and Poverty

Goal 2: Achieve Universal Primary Education

Goal 3: Promote Gender Equality and Empower Women

Goal 4: Reduce Child Mortality

Goal 5: Improve Maternal Health

Goal 6: Combat HIV/AIDS, Malaria and other diseases

Goal 7: Ensure Environmental Sustainability

Goal 8: Develop a Global Partnership for Development

ii) Targets

The internationally agreed framework of 8 goals and 18 targets was complemented by 48 technical indicators to measure progress towards the Millennium Development Goals. These indicators have since been adopted by a consensus of experts from the United Nations, IMF, OECD and the World Bank.

Each indicator below is linked to millennium data series as well as to background series related to the target in

question.

Goal 1: Eradicate Extreme Hunger and Poverty

Target 1. Halve, between 1990 and 2015, the proportion of people whose income is less than $1 a day

Target 2. Halve, between 1990 and 2015, the proportion of people who suffer from hunger

Goal 2: Achieve Universal Primary Education

Target 3. Ensure that, by 2015, children everywhere, boys and girls alike, will be able to complete a full course of primary schooling

Goal 3: Promote Gender Equality and Empower Women

Target 4. Eliminate gender disparity in primary and secondary education, preferably by 2005, and in all levels of education no later than 2015

Goal 4: Reduce Child Mortality

Target 5. Reduce by two-thirds, between 1990 and 2015, the under-five mortality rate

Goal 5: Improve Maternal Health

Target 6. Reduce by three-quarters, between 1990 and 2015, the maternal mortality ratio

Goal 6: Combat HIV/AIDS, Malaria and other diseases

Target 7. Have halted by 2015 and begun to reverse the spread of HIV/AIDS

Target 8. Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases

Goal 7: Ensure Environmental Sustainability

Target 9. Integrate the principles of sustainable development into country policies and programs and reverse the loss of environmental resources

Target 10. Halve, by 2015, the proportion of people without sustainable access to safe drinking water and basic sanitation

Target 11. Have achieved by 2020 a significant improvement in the lives of at least 100 million slum dwellers

Goal 8: Develop a Global Partnership for Development

Target 12. Develop further an open, rule-based, nondiscriminatory trading and financial system

Target 13. Address the special needs of the least developed countries

Target 14. Address special needs of landlocked developing countries and small island developing states

Target 15. Deal comprehensively with the debt problems of developing countries to make debt sustainable in the long term

Target 16. In cooperation with developing countries, develop and implement strategies for decent and productive work for youth

Target 17. In cooperation with pharmaceutical companies, provide access to affordable essential drugs in developing countries

Target 18. In cooperation with the private sector, make available the benefits of new technologies, especially information and communications technologies.

CHAPTER 17 PHYSIOLOGIC CHANGES IN PREGNANCY

Pregnancy triggers a cascade of events that transform mother's cardiovascular, respiratory and renal systems.

The maternal adaptation to pregnancy can be categorized based on;

- ↑ availability of precursors for hormone production and fetal placental metabolism;
- Improved transport capacity;
- Maternal-fetal exchange;
- Removal of additional waste products.

(I) Skin changes

Certain characteristic skin changes are observed in pregnancy. These include;

- ↑ pigmentation— especially on face (***melasma***), areolae, axillae and abdominal midline (***linea nigra***);
- Chloasma— refers to blotchy pigmentation of the nose and face;
- Spider angiomata and palmer erythema— secondary to ↑ skin vascularity;
- Spider naevi can also be observed on the face, arms and upper torso;
- Striae gravidarum—broad pink linear striae that frequently appear over the lower abdomen and thighs;
- Pruritus without rash affects up to 20% of normal pregnancies, but liver function tests should always be performed to exclude obstetric cholestasis of pregnancy;
- Striae gravidarum— "stretch marks" that develop in genetically predisposed women on the abdomen and buttocks;
- Chadwick sign—Bluish or purplish discoloration of vagina and cervix as a result of increased vascularity.

(II) Volume homeostasis

- Maternal blood volume expands during pregnancy to allow adequate perfusion of organs, including the placenta, and to anticipate blood loss associated with delivery.
    - The rapid expansion of blood volume begins at 6–8 weeks and *plateaus* at 32–34 weeks.
    - Overall, total body water increases from 6.5 to 8.5 liters by the end of pregnancy.
- Most marked expansion occurs in extracellular fluid volume, especially circulating plasma volume.
    - This expanded extracellular fluid volume accounts for between 8 and 10 kg of the average maternal weight gain during pregnancy.
    - Larger increase of plasma volume, relatively, results in;
        - Haemodilution and a physiologic anaemia;
        - ↓ in plasma osmolality by about 10 mOsmol/kg.
- Plasma **osmotic** and **oncotic** pressures are observed to be ↓ during pregnancy. Plasma oncotic pressure partly determines the degree to which fluid passes into and out of capillaries, and its decrease here is associated with ↑ glomerular filtration rate (GFR) during pregnancy while also contributing to the *peripheral oedema* seen in pregnancies.

Table. Summarizing volume homeostasis during pregnancy.

Factors contributing to fluid retention	**Consequences of fluid retention**
Sodium retention	↓ haematocrit and hemoglobin concentration
Resetting of the osmostat to a lower serum osmolality	↓ Serum albumin *concentration*
↓ Thirst threshold	↑ Stroke volume
↓ Plasma oncotic pressure	↑ Renal blood flow

(III) Haematological homeostasis

- Maternal haemoglobin levels and haematocrit ↓ due to dilutional effect.
- Transfer of iron stores to the fetus— pregnant individuals require ↑ amounts of iron and gut absorption is also increased.
- Renal clearance of folic acid increases substantially during normal pregnancy and plasma folate concentrations fall. However**, red cell folate** concentrations do not decrease to the same extent.
- Pregnancy is a hypercoagulable state, which returns to normal around 4 weeks after delivery;
    - Almost all procoagulant factors, including factors VII, VIII, IX, X and XII and fibrinogen, are ↑ during pregnancy.
    - Antithrombin III levels remain unchanged, whereas protein S activity decreases, and there is an increase in activated protein C resistance.
- Maternal plasma D-dimer concentration is observed to ↑ progressively from conception until delivery, which limits the use of D-dimer testing *to rule out suspected venous thromboembolism* in symptomatic pregnant women.
- The increase in procoagulants, potential for vascular damage and increased venous stasis particularly in the lower extremities, explains— ↑ incidence of venous thromboembolic complications.
- During delivery, myometrial contractions first compress the blood vessels supplying the placental bed, followed by fibrin deposition over the placental site, with ↑ amounts of of fibrinogen being used up.
- Lack of maternal immune reactivity to the fetus is most likely thought to be due to;
    - ↓ numbers of cytotoxic T (CD-8) cells during pregnancy;
    - Downregulated T-cell mediated immune response.
- White blood cells do not show a dilutional decrease during normal pregnancy, unlike red cells;
    - This is mainly because of ↑ numbers of polymorphonuclear leukocytes observed as early as 3 weeks of gesation;
    - Counts of B cells appear to be unaltered throughout pregnancy, while absolute numbers of natural killer (NK) cells increase in early pregnancy and decrease in late gestation.

Table. Summarizing haematological homeostasis during pregnancy.

Decrease in	**Increase in**
Hemoglobin concentration	ESR
Hematocrit	Fibrinogen *concentration*
Plasma folate concentration	Activated protein C *resistance*
Protein S activity	Factors VII, VIII, IX, and XII
Plasma protein concentration	D-dimer level
Creatinine, urea, uric acid	Alkaline phosphatase

(IV) Respiratory tract and ventilation/perfusion homeostasis

During pregnancy congestion and rhinitis is often observed secondary to ↑ in respiratory tract vascularity and nasal mucosal edema;

Pregnancy is associated with ↑ pulmonary blood flow without ↑ in pulmonary vascular resistance/pressures as;

- Cardiac supply to the lungs increases, and;
- Relative decrease in pulmonary vascular resistance/pressure with vasodilation and perfusion of relative more pulmonary capillaries;

As pregnancy progresses, the diaphragm is elevated up to 4 cm by the enlarging uterus, and the lower ribcage circumference expands by up to 5 cm. This brings about;

- ↑ minute ventilation (= tidal volume x respiratory rate) by 30-50% distinctly **without** changes in maximum inspiratory or expiratory pressures and respiratory muscle function—
    - This is predominantly due to ↑ tidal volume without changes in respiratory rate secondary to progesterone-stimulated increase in alveolar ventilation;
    - However, increases in respiratory rate may be also be observed secondary to ↑ metabolic rate and progesterone-sensitization of the respiratory center.
- ↓ functional residual capacity (FRC) by 10–25%. This occurs secondary to;
    - Decrease in both expiratory reserve volume and residual volume (see Figure);
    - Positional variation as FRC is further reduced in the supine position.

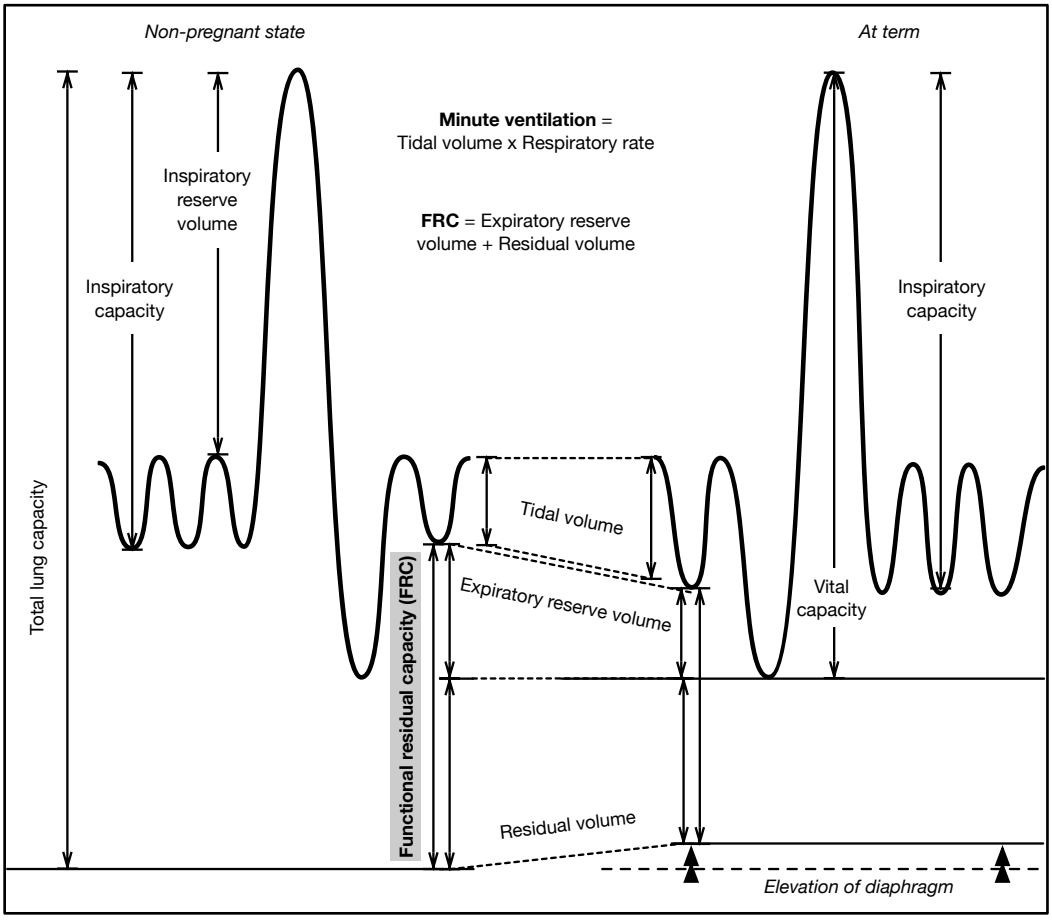


Figure. Illustration of changes in respiratory mechanics in pregnancy.

These physiological changes do not affect the interpretation of tests of ventilation such as forced expiratory volume in 1 second (FEV 1) and peak expiratory flow rate (PEFR). *Thus, these pulmonary function tests remain useful during pregnancy*.

Due to increased tidal volume and minute volume relatively ↑ pO_2 and ↓ pCO_2 levels are also observed.

(V) Oxygenation and acid-base balance

Pregnancy is associated with shift of oxygen-hemoglobin dissociation curve to the right. This is thought to be due to ↑ levels of 2,3-DPG observed during pregnancy. The end result of this change leads to;

- ↑ the availability of oxygen to peripheral tissues;
- ↑ transfer of oxygen to fetus;

Fetal haemoglobin F also has higher affinity for oxygen relative to maternal adult hemoglobin.

Oxygen consumption increases along with increase in metabolism during the course of pregnancy. This combined with ↓ functional residual capacity (FRC) associated with altered respiratory mechanics (as discussed above) predisposes pregnant women to hypoxemia during respiratory depression or apnoea.

Certain characteristic changes are also seen in arterial-blood gases;

Relatively ↓ pO_2 and pCO_2 levels without significant decrease in O_2 saturation;

↓ pCO_2 can potentially lead to alkalosis due to ↓ carbonic acid H_2CO_3. The kidneys counter this effect by ↑ excretion of bicarbonate (HCO_3^-)— the main anion in blood, such that pH remains stable between 7.40-7.45.

(VI) Cardiac homeostasis

Cardiovascular signs and symptoms of pregnancy mimic those of heart disease;

- Breathlessness— occurs secondary changes in chest wall dimensions due enlarging uterus than cardiovascular disea;
- Palpitations are common and usually benign secondary to sinus tachycardia. Premature atrial and ventricular ectopic beats are common in pregnancy and reflect ↑ cardiac output;
- Oedema in the extremities is a common finding, and results from an increase in total body sodium and water, as well as venous compression by the gravid uterus.

Major cardiovascular changes associated with pregnancy include;

- ↑ cardiac output (secondary to both ↑ heart rate and ↑ stroke volume) by 30-50%. But this becomes positionally dependant associated with compression of inferior vena cava by the enlarging uterus;
- Relatively ↓ mean arterial pressure by 10% — and thus increased blood pressure may be suspicious for HTN and pre-eclampsia;
    - Decreases in diastolic BP are more marked than the decrease in systolic BP in early pregnancy— ***a relative ↑ in pulse pressure may be observed here***;
    - This pulse pressure normalizes later as the diastolic BP rises slightly relative to systolic BP.
- ↓ peripheral resistance by upto 35% — thought to be associated with ↑ perfusion of uterus.

Clinically, most noticeable cardiovascular changes on examination include, but not limited to;

- Positional variation of blood pressure— it is optimal when the pregnant woman lies in left lateral position while most significantly reduced when in supine or right lateral positions;
- Jugular veins fill and pulsate dynamically— secondary to ↑ plasma volume but mean right atrial pressure and the height of the jugular venous pressure *should* remain unchanged;
- An ejection systolic murmur can be heard in 96 per cent of apparently normal pregnant women;
- A third heart sound is audible in upto 84% of pregnant women— this should be distinguished from a diastolic murmur;
- The tricuspid and mitral components in first heart sound (S1) is loud and sometimes split;

Changes in cardiovascular homeostasis are also observed in peripartum. Labour is associated with progressive increase of cardiac output as uterine contractions squeeze blood and **autotransfuse** into maternal circulation.

Within the first 2 weeks after delivery the cardiac output falls rapidly, at 6 weeks postpartum it is almost halfway between pregnant and non-pregnant values

(VII) Renal homeostasis

Renal and excretory changes associated with pregnancy include;

- ↑ Kidney size (1 cm), ***right-sided*** dilatation of renal pelvis and ureters on the (due to uterine dextrorotation) and ↑ predisposition to ascending urinary tract infections;
- ↑ Glomerular filtration rate (GFR) by upto 50% in 1st trimester and thereafter ↓ in GFR by upto 20% relatively— this reflects increased clearance of plasma creatinine, urea and urate by excretion.
- ↑ Blood and plasma flow to kidneys initially in the 2nd trimester and later relative ↓ by upto 25% near-term— due to complex alteration in cardiac output and renal vasodilatation;

- Glycosuria is very common during pregnancy—
    - The reabsorptive mechanism in the proximal renal tubules may become saturated so that the 'renal threshold' is exceeded, explaining the increased amount of glucose in the urine;
    - Glucose reabsorption also occurs with absorption of sodium via exchange pumps in tubules and thus other factors contributing to volume homeostasis and sodium retention are also held responsible for the physiological glycosuria of pregnancy.

Despite *physiologic glycosuria of pregnancy* being a well-known entity in pregnancy, significant symptoms of hyperglycemia often prompt further testing to rule out gestational diabetes of pregnancy.

(VIII) Gastrointestinal changes in pregnancy

Gastrointestinal motility is common affected during pregnancy. This manifests as;

- ↓ Gastric motility resulting in delayed gastric emptying;
- ↓ Small bowel motility decreases, but nutrient absorption remains unchanged. *except for iron absorption which is* ↑;
- Large bowel motility decreases, resulting in constipation caused associated with multiple factors;
    - Smooth muscle relaxation from progesterone;
    - Pressure effects from the enlarging uterus;
    - Increased water absorption;
    - Increased sodium absorption.

Decreased tone of lower esophageal sphincter (LES), ↑ gastrin (from placenta) and thus gastric acid is responsible for reflux esophagitis/*heartburn* symptoms observed during pregnancy.

(IX) Genital tract changes during pregnancy

i) Uterus

It undergoes a 10-fold increase in weight to 1000 g at term— related to both hyperplasia and hypertrophy of myometrial cells, secondary to high levels of maternal estradiol and progesterone.

By the third trimester, the uterus is described in lower and upper segments. The lower segment is thinner, contains less muscle and fewer blood vessels. These characteristics make this segment a good site for incision in C-sections (i.e. *lower-segment C-section, **LSCS**).*

The uterine arteries undergo massive hypertrophy, mainly in first half of pregnancy and uterine blood flow increases by upto 500-700 ml/min at term.

ii) Cervix

The cervix becomes swollen and softer during pregnancy under the influence of estradiol and progesterone.

Under influence of estradiol, columnar epithelium of endocervical canal proliferates and can be visible on ectocervix— referred to as 'cervical **ectropion**'.

The cervix also appears bluish during pregnancy, as a result of ↑ vascularity.

The cervical collagen ↓ towards term, enabling cervical dilatation.

iii) Vagina

Under the influence of oestrogens, the vaginal epithelium also becomes more vascular during pregnancy and and increased vaginal discharge may be observed. This is in parts due to;

- ↑ desquamation of squamous epithelium;
- ↑ glycogen synthesis;
- Conversion of glycogen to lactate— thus acidic pH of vaginal discharge.

This acidic vaginal discharge is observed to have a protective role against ascending infections.

(X) Breast changes during pregnancy

Estrogen, progesterone and human placental lactogen (hPL) play pivotal roles in development of breast tissue during pregnancy;

- Estrogen— increases number of glandular ducts;
- Progesterone and human lacental lactogen (hPL)— increase number of alveoli.

On the other hand, prolactin during pregnancy prepares the alveoli for milk production. However, lactation does not occur— this is thought to be associated with antagonization of alveolar receptors by oestrogen.

Suckling of the areola of breast by newborn stilumates both prolactin and oxytocin release;

- Prolactin, from anterior pituitary, stimulates milk production;
- Oxytocin, from posterior pituitary stimulates milk ejection— the so-called milk 'let-down' reflex.

(*see also Chapter 33: Breasts and breastfeeding*).

(XI) Endocrine changes during pregnancy

i) Pituitary gland

An increase in size of pituitary gland is observed. This predominantly affects the anterior lobe and is thought to be due to progressive hormonal stimulation during pregnancy.

Prolactin level is increased secondary to estrogen stimulation of lactotrophes.

The increase in size also predisposes pituitary gland to relative ischemia during peri-partum. **Post-partum Sheehan's syndrome**— refers to ischemic pituitary necrosis as a result of prolonged hypotension after obstetric haemorrhage. Affected indivduals present with varying degrees of homonal deficiency depending on severity of necrosis.

ii) Thyroid gland

Thyroid gland also increases in size due to increased vascularity and increased demand, as renal clearance of iodine increases resulting in relative iodine deficiency.

Certain characterisitic changes in measureable thyroid profile are also observed;

- Thyroid binding globulin (TBG) increases.
- Protein-bound levels of T_3 and T_4 increase relatively, but levels of free T3 and T4 remains unchanged.
- TSH may decrease slightly (associated with thyrotropic properties of hCG) but tends to remain normal.

Due to changes in levels of protein-bound levels of T_3 and T_4, *investigations of choice* for suspected thyroid dysfunction **during pregnancy** are **free T_3, T_4** and TSH.

iii) Adrenal glands

Unlike pituitary and thyroid glands, the size of adrenal glands remains almost unchanged.

Placental trophoblast cells also produce corticotrophin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) in addition to their secretion by pituitary gland;

- This explains the progressive increase in cortisol levels with pregnancy which is predominantly bound to cortisol-binding globulin (CBG);
- CBG almost doubles in concentration during pregnancy;
- A slight increase in unbound cortisol is also observed

For investigation of cortisol imbalances, a dexamethasone suppression test, if carried out on a pregnant female can show *an attenuated less-than-optimal response*. This is thought to be related to placental trophoblastic secretion of ACTH.

Increased production of adosterone is also seen.

CHAPTER 18 FETAL DEVELOPMENT

(I) Fetal growth

The final birthweight of a newborn results from interaction between fetal genome and maternal uterine environment. In addition;

- Insulin-like growth factors (IGFs) coordinate a precise and orderly increase in growth throughout late gestation;
- Insulin and thyroxine (T4) are required through late gestation to ensure appropriate growth in normal and adverse nutritional circumstances.

Fetal hyperinsulinaemia, which occurs in association with maternal diabetes mellitus when maternal glycaemic control is suboptimal, results in fetal macrosomia with, in particular, excessive fat deposition.

The failure of a fetus to reach its full growth potential is known as **fetal growth restriction (FGR)**. FGR can occur secondary to fetal, maternal or placental influences;

- Fetal influences;
    - Genetic; chromosomal defects, trisomies;
    - Infection of fetus by rubella, cytomegalovirus, toxoplasma, syphilis.
- Maternal influences;
    - Ethnic differences, and age;
    - Recreational drug use during pregnancy;
    - Chronic diseases like hypertension, cardiac, pulmonary diseases.
- Placental influences— occurring as a result of suboptimal function.

FGR is associated with a significant increased risk of perinatal morbidity and mortality. FGR ↑ risk of;

- Intrauterine hypoxia/asphyxia;
- Hypoxic-ischaemic encephalopathy (HIE), including seizures;
- Neonatal hypothermia, hypoglycaemia, infection;
- Necrotizing enterocolitis;
- Multiorgan damage or failure in the neonatal period;
- Stillbirth.

FGR can also have long lasting effects on the newborn. These include, but not limited to;

- Cerebral palsy;
- Hypertension;
- Cardiovascular disease (ischaemic heart disease and stroke);
- Diabetes in adult life.

FGR is discussed in more detail later (*see Chapter 24: Placentation and related disorders*).

(II) Fetal development

i) Cardiovascular system and fetal circulation

The fetal circulation is quite different from that of the adult. Its distinctive features are:

- Oxygenation occurs in the placenta, not the lungs;
- Right and left ventricles work in parallel rather than in series;
- Heart, brain and upper body receive blood from the left ventricle, while the placenta and lower body receive blood from both right and left ventricles.

Three shunts in fetal vascular circulation ensure good oxygen supply to the fetal brain (see Figure);

- The ductus venosus— shunts blood away from the liver;
- The foramen ovale— shunts blood from right to left atrium;
- The ductus arteriosus— shunts blood from pulmonary artery to the aorta.

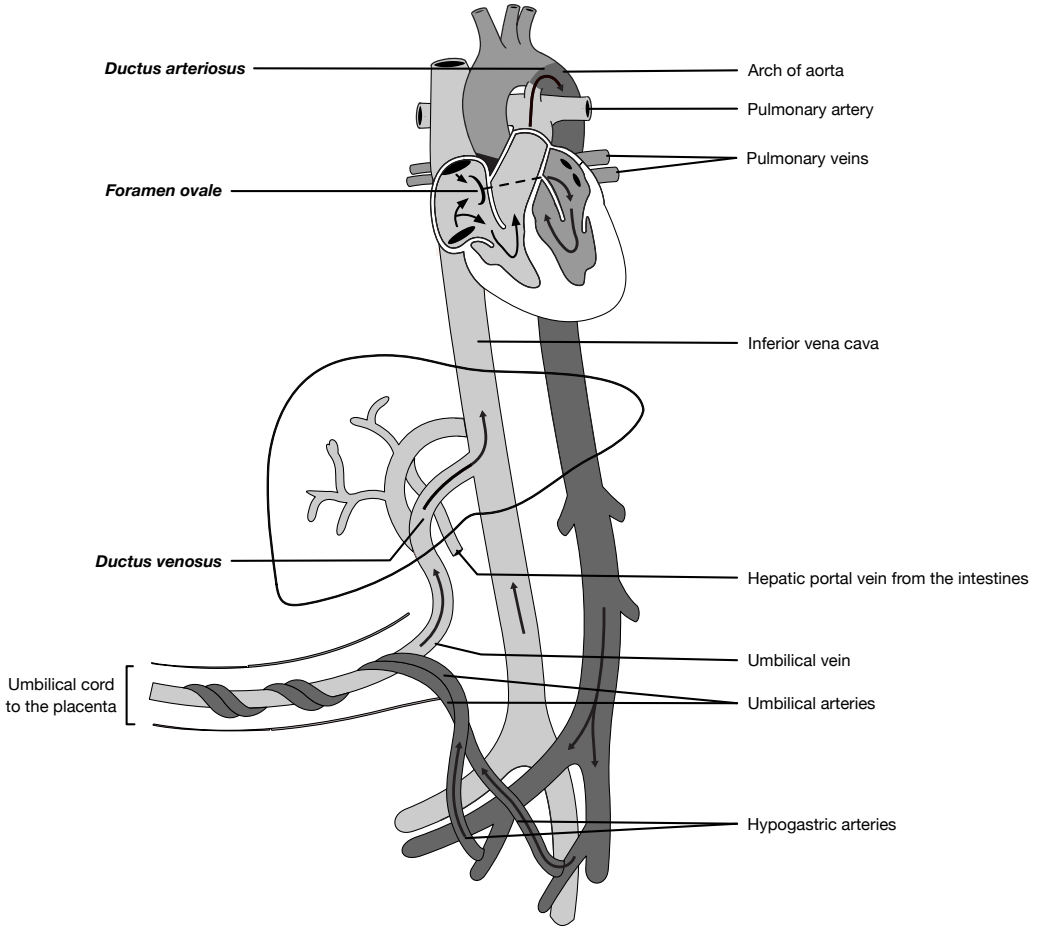


Figure. The fetal cardiovascular circulation and its shunts.

The ductus venosus is a narrow vessel and consequently, high velocities are generated in it;

- This streaming of the ductus venosus blood, together with a membranous valve in the right atrium (the *crista dividens*), prevents *significant mixing* of the well-oxygenated blood from the ductus venosus with the desaturated blood of the inferior vena cava;
- The high-velocity blood from the ductus venosus stream passes across the right atrial septum through foramen ovale and through left ventricle to keep good oxygen supply to the head/developing brain.

As the lungs are not functional, desaturated blood from the right ventricle passes down the aorta to enter the umbilical arterial circulation— *to return to the placenta for reoxygenation using* ***ductus arteriosus***;

- Prior to birth, the ductus remains patent due to the production of prostaglandin E2 and prostacyclin, which act as local vasodilators;
- Premature closure of ductus arteriosus is seen with administration of cyclooxygenase (COX) inhibitors;
- Naturally, due to pulmonary ventilation, the ductus arteriosus closes functionally within a few days of birth due to ↓ in pulmonary vascular resistance.
- Occasionally, this transition from fetal to adult circulation may be delayed, usually because the pulmonary vascular resistance fails to fall despiteadequate breathing— termed '**persistent fetal circulation**. This presents in newborns as cyanosis.

ii) Respiratory system

The lung first appears as an outgrowth from the primitive foregut.

The fetal lung is filled with fluid. At birth, the production of this fluid ceases and the fluid present is absorbed. Adrenaline appears to play a major role in this process.

Type I and surfactant-producing type II epithelial cells mature and produce surfactant;

- Surfactant is a mix of phospholipids [phosphatidylcholine (lecithin)] and protein;
- Surfactant prevents collapse of small alveoli in the lung during expiration by lowering surface tension. Its production is maximal after 28-30 weeks;
- The production of lecithin is enhanced by cortisol, growth restriction and prolonged rupture of the membranes, and is delayed in diabetes;
- Respiratory distress syndrome is specific to babies born premature and is associated with surfactant deficiency. Its complications include *asphyxia, intraventricular haemorrhage, necrotizing enterocolitis.*

iii) Gastrointestinal system

The primitive forgut and hidgut are present by the end of 4th week.

As the abdominal cavity is too small to accommodate the enlarging liver and intestine—

- The midgut herniates into the base of the umblical cord during the 6th week;
- While herniated, the gut undergoes rotation prior to re-entering the abdominal cavity by 12th week;
- Failure of the gut to re-enter the abdominal cavity results in development of **omphalocele**.

The swallowing reflex develops and matures gradually. An anencephalic fetus that fails to develop a swallowing reflex or a fetus with atretic oesophagus— can develop polyhydramnios.

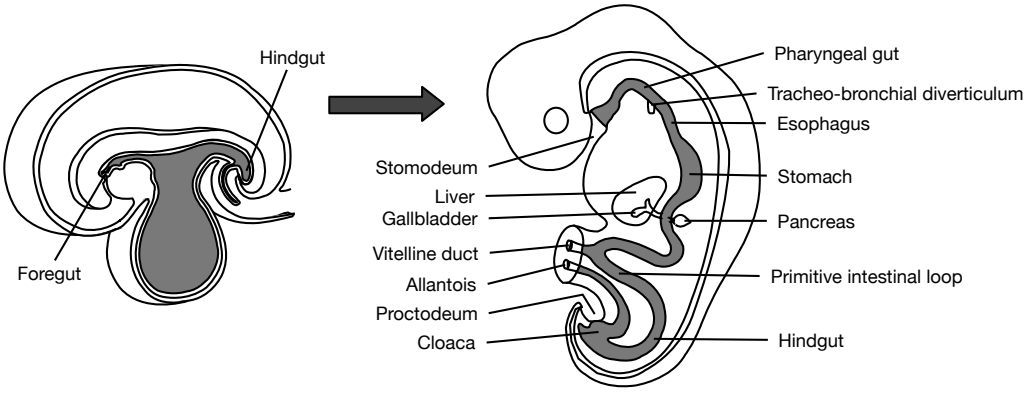


Figure. Development of the digestive system

The swallowed amniotic fluid, and the cellular material it contains, enters the gut, where it is acted upon by the enzymes and bacteria to produce meconium.

The meconium remains in the gut unless an episode of *severe hypoxia* leads to contractions of the gut, at which time the meconium is expelled to mix with the amniotic fluid. Consequently, meconium aspiration syndrome in the neonate can occur.

iv) Hepatobiliary system and pancreas

- The pancreas, liver and epithelial lining of the biliary tree derive from the endoderm of the foregut.
- By the sixth week, the liver performs haematopoiesis.
- In utero, the normal metabolic functions of the liver are performed by the placenta. The fetal liver also has ↓ ability to conjugate bilirubin because of relative deficiencies in liver enzymes such as glucuronyl transferase.
- The loss of the placental route of excretion of unconjugated bilirubin, and ↓ conjugation, particularly in the premature infant, may result in *transient unconjugated hyperbilirubinaemia* or *physiological jaun-*

dice of the newborn.

- Glycogen is stored within the liver in maximal quantities in the 3rd trimester. Growth-restricted and premature infants have deficient glycogen stores; this ↑ risk of neonatal hypoglycaemia.

v) Kidneys and urinary tract

Development of the metanephric kidneys— the final permanent form is preceded by 2 primitive forms; pronephros and mesonephros.

During the fifth week of gestation the ureteric bud develops as an out-pouching from the Wolffian duct (*see Chapter 1: Genital embryology and anatomy*).

Fetal urine forms much of the amniotic fluid;

- Renal agenesis will result in severe reduction or absence of amniotic fluid (oligohydramnios);
- Babies born with bilateral renal agenesis (Potter's syndrome) do not pass urine and have features that occur secondary to oligohydramnios;
- These include widely spaced eyes, small jaw, low set ears and pulmonary hypoplasia.

The most common sites of congenital urinary tract obstructive uropathies are at the **pyeloureteric junction**, the vesicoureteric junction or as a result of *posterior urethral valves*.

Severe obstruction *in utero* can lead to hydronephrosis and renal interstitial fibrosis.

vi) Skin

Fetal skin protects and facilitates homeostasis.

The skin and its appendages (nails, hair) develop from the ectodermal and mesodermal germ layers;

- The epidermis develops from the surface ectoderm.
- At about 6 weeks this ectodermal layer differentiates into an outer periderm and an inner basal layer. The periderm eventually sloughs as **the vernix**, a creamy protective coat that covers the skin of fetus.
- The dermis and the hypodermis, which attaches the dermis of the skin to underlying tissues, develop from mesenchymal cells in the mesoderm.
- By 24 weeks, hair follicles (derived from inner basal layer of ectoderm) produce fetal hair called lanugo, first on the head and then on other parts of the body. This lanugo is usually shed before birth.

Preterm babies have no vernix and thin skin; this allows a proportionately large amount of insensible water loss.

vii) Blood and immune system

Most haemoglobin in the fetus is fetal haemoglobin (HbF, alpha-2 and gamma-2 chains);

- 90% per cent of fetal haemoglobin is HbF between 10- and 28-weeks gestation;
- From 28 to 34 weeks, a switch to HbA occurs, and at term the ratio of HbF to HbA is 80:20;
- By six months of age, only 1 per cent of haemoglobin is HbF.

The fetus requires an effective immune system to resist intrauterine and perinatal infections. Lymphocytes appear from 8 weeks and, by the middle of the second trimester, all phagocytic cells, T and B cells and complement are available to mount a response.

viii) Endocrine system

Major components of the hypothalamic–pituitary axis are in place by 12 weeks gestation.

Testosterone produced by the interstitial cells of the testis is also synthesized in the first trimester of pregnancy and increases to 17–21 weeks, which mirrors the differentiation of the male urogenital tract.

Growth-restricted fetuses exist in a state of relative hypothyroidism which may be a compensatory measure to decrease metabolic rate and oxygen consumption.

ix) Behaviour

The first activity is the beating of the fetal heart followed by fetal movements at 7–8 weeks.

In the second trimester, for example, cycles of absence or presence of movements change, increasing in frequency of occurence.

Four fetal behavioural states have been described;

- 1F is quiescence, similar to quiet or non-REM sleep;
- 2F is characterized by frequent and periodic gross body movements with eye movements, similar to REM sleep;
- 3F no gross body movements but eye movements, similar to quiet wakefullness;
- 4F vigorous continual activity again with eye movements, similar to active wakefulness.

These fetal behavioural states also have potential implications in the interpretation of cardio-tocography/non-stress tests and biophysical profiles (*see Chapter 20: Antenatal assessment of fetus*).

(III) Amniotic fluid

The amniotic fluid is initially secreted by the amnion, but by the 10th week it is mainly a transudate of the fetal serum via the skin and umbilical cord.

Amniotic fluid volume increases progressively (*10 weeks— 30 mL, 20 weeks— 300 mL, 30 weeks— 600 mL, 38 weeks— approx. 1000 mL*), but from term there is a rapid fall in volume (*40 weeks— 800 mL and 42 weeks— 350 mL*).

The function of the amniotic fluid is to;

- Protect the fetus from mechanical injury;
- Permit movement of the fetus while preventing limb contracture;
- Prevent adhesions between fetus and amnion;
- Permit fetal lung development in which there is two- way movement of fluid into the fetal bronchioles.

Alterations in amniotic fluid volume can occur;

- Renal agenesis, cystic kidneys or fetal growth restriction— oligohydramnios;
- Anencephaly and oesophageal/ duodenal atresia— polyhydramnios.

CHAPTER 19 ANTENATAL CARE

The aims of antenatal care are;

- To prevent, detect and manage those factors that adversely affect the health of mother and baby;
- To provide advice, reassurance, education and support for the woman and her family;
- To deal with the 'minor ailments' of pregnancy;
- To provide general health screening.

(I) Basic plan for antenatal care

It may be possible to hear the fetal heart with the Doppler ultrasound from approximately 12 weeks onwards.

i) 'Booking' visit

The initial visit by a pregnant individual to an obstetric health care professional is called the 'booking visit'.

The booking visit provisions obstetric history-taking, physical examination, and a series of routine investigations for appropriate antenatal care.

a) Dating the pregnancy

A pregnancy can be dated either by using the date of the first day of last menstrual period (LMP) or, more accurately, by ultrasound scan.

The Expected Date of Delivery (EDD) can be calculated using the Naegele's rule, i.e;

EDD = Date of LMP + 9 calender months + 7 days.

If the cycle is greater than 28 days (unlike the previous assumption), then the difference between 28 days and actual cycle length days can be added to get a corrected estimation.

A more accurate EDD can be estimated using an ultrasound 'dating' scan and this should be offered to all;

- If performed before 20 weeks gestation (ideally between 10-14 weeks), ultrasound can be used to date the pregnancy;
    - Crown-rump length (CRL) can be used uptill 13 weeks + 6 days;
    - Head circumference can be used from 14 to 20 weeks.
- If performed after 20 weeks, dating a pregnancy can vary because of variable growth rates of fetuses.

Benefits of accurate dating include;

- Accurate dating in women with irregular menstrual cycles or poor recollection of LMP;
- Reduced incidence of induction of labour for 'prolonged pregnancy';
- Increased yield of antenatal screening tests for fetal abnormalities;
- Early detection of multiple pregnancies;
- Detection of otherwise asymptomatic failed intrauterine pregnancies.

b) Obstetric history

- Past medical, gynaecological, and obstetric history is relevant as there may be events of significance;
- Family history of chromosomal abnormalities, genetic diseases should be explored

c) Obstetric examination

This consists of cardiovascular, respiratory, abdominal, full pelvic and breast examinations.

For most healthy women, without complicating medical problems, the booking examination will include the following;

- Accurate measurement of blood pressure;
- Abdominal examination to record the size of the uterus;

- Recognition of any abdominal scars indicative of previous surgery;
- Measurement of height and weight for calculation of the BMI;
- Urine dip testing for protein, glucose, leukocytes, nitrates and blood.

d) Investigations at **the booking visit**

- **Complete blood count (CBC)**;
    - This is done at the booking visit and repeated again for surveillance at 28 weeks.
    - Routine iron supplements are not recommended unless Hemoglobin falls below 11 g/dL (at booking) or 10.5 g/dL (at 28 weeks).
- **Blood grouping and red cell antibodies**
    - Women found Rh D negative are offered prophylactic anti-D administration to prevent rhesus D iso-immunization and haemolytic disease of the fetus in future pregnancies.
    - Prophylactic anti-D is either given as a single dose **at 28 weeks** gestation, or in divided doses *at 28 and 34 weeks*.
    - Other isoimmunizing events— e.g. threatened miscarriage after 12 weeks gestation, antepartum haemorrhage and delivery of the baby, will require additional anti-D prophylaxis in rhesus D-negative women.
- **Midstream urinalysis** to detect asymptomatic bacteriuria, which is common in pregnancy. Treating urinary infections reduces risk of pyelonephritis.
- **Rubella antibody serologic testing** for *maternal immunity*. Women found to be not-immune to rubella should be strongly advised to avoid infectious contacts.
    - Due to risk of viral reactivation from vaccine— it should not be given during pregnancy.
    - Following immunization, pregnancy should be avoided for upto **3- months** *(1-3 months)*.
    - A history of previous immunization is not a guarantee of permanent immunity.
- **Hepatitis B surface antigen (HBsAg) testing**— to prevent horizontal transmission to maternity staff nurses and take necessary measures to minimize vertical transmission to newborns.
- **Anti-human immunodeficiency virus (anti-HIV) testing on ELISA;**
    - Recommended for all pregnant women *at booking;*
    - Use of antiretroviral agents, elective Caesarean section and avoidance of breastfeeding may reduce the vertical transmission rate from 30% to < 2 %.
- **Syphilis testing** in all women— because effective treatment is available and prevents fetal morbidity.
- Women *may be* offered **screening for haemoglobinopathies**.
    - The mean corpuscular volume (MCV) is part of the CBC testing at booking. If it is found low can be suggestive of a hemoglobinopathy or other hematologic pathologies.
    - Prenatal genetic tests following chorionic villus sampling (CVS) or amniocentesis can usually definitively diagnose or exclude the condition in the fetus.

Investigations that are **not** supported by evidence-based medicine to be performed *routinely at booking*;

- Bacterial vaginosis;
- Cytomegalovirus (CMV);
- Toxoplasmosis;
- Hepatitis C;
- Group B streptococcus colonization;
- Chlamydia;
- Cervical smears (this can be performed later during pregnancy or in those that are due for surveillance).

ii) Follow-up antenatal visits

Following table shows schedule of antenatal visits.

Table. Schedule of antenatal visits

Visit	**Purpose**
Initial contact	Folic acid supplementation; Information provision; Lifestyle issues.
Booking visits (by 10th week)	Calculating BMI, BP, urinalysis; Identification of women needing additional care; *Booking visit investigations*; Down's syndrome screening.
Dating scan (between 10-14 weeks)	Determine accurate gestational age, multiple pregnancies; Calculating EDD.
16th week	Quadruple test *if not yet screened for Down's syndrome*; BP testing, urine for dipstick testing.
18 – 20 weeks	Ultrasound for structural anomalies.
25th week	Symphysiofundal height (SFH) measurement; BP testing, urine for dipstick testing.
28th week	**Second screening for anemia, red cell antibodies**; *Anti-D prophylaxis for RhD-negative women;* BP testing, urine for dipstick testing.
31st weeks	BP testing, urine for dipstick testing.
34th week	*2nd dose of prophylactic anti-D for RhD-negative*; BP testing, urine for dipstick testing.
36th week	Palpation for fetal presentation; BP testing, urine for dipstick testing.
38th week	Palpation for fetal presentation; BP testing, urine for dipstick testing.
40th week	Palpation for fetal presentation; BP testing, urine for dipstick testing.
41st week	Offer membrane sweep and formal induction of labor; Palpation for fetal presentation; BP testing, urine for dipstick testing.

Screening for fetal abnormalities should be carried out between 11 and 22 weeks gestation as;

- Screening for down's syndrome— nuchal translucency scanning (11-13 weeks), or serum screening (15-19 weeks);
- Screening for neural tube defects e.g. spina bifida, anencephaly— maternal serum alpha-fetoprotein (15-19 weeks);
- Screening for structural congenital abnormalities— by ultrasound scan at 18 – 20 weeks + 6.

All women should be assessed at booking for risk factors for gestational diabetes, i.e.

- BMI above 30 kg/m^2;
- Previous baby weighing 4.5 kg, or above;
- Previous gestational diabetes;

- First-degree relative with diabetes;
- Family origin from high prevalence area (South Asian, black Caribbean and Middle Eastern).

If risk factors are positive, the woman should be offered testing as;

- 2-hour 75 g oral glucose tolerance test (OGTT) at 24–28 weeks gestation.
- A previous history of gestational diabetes should prompt glucose monitoring, or an OGTT, **at 16–18 weeks**. If these results are normal, the test should be **repeated at 24–28 weeks**.

All women should be screened at every antenatal visit for pre-eclampsia by;

- Measurement of blood pressure and urinalysis for protein.
- Edema of the hands and face is more important as a warning feature of pre-eclampsia.

Rhesus D-negative women should be offered routine antenatal prophylaxis, either as a single large dose at 28 weeks gestation, or in smaller divided doses at 28 and 34 weeks gestation.

-x-

CHAPTER 20 ANTENATAL ASSESSMENT OF FETUS

(I) The obstetric ultrasound

Ultrasound scanning is a safe, non-invasive, accurate and cost-effective investigation in the fetus.

The ultrasound technique uses very high frequency sound waves of between 3.5 and 7.0 mega hertz emitted from an ultrasonic transducer.

The transducer can be placed on the maternal abdomen (~ transabdominal ultrasound) or inserted into the vagina (~ transvaginal ultrasound).

It is recommended that all pregnant individuals be offered scans at 10-14 weeks and 18-21 weeks gestation;

- The earlier scan is done to determine gestational age, multiple pregnancies and to determine nuchal translucency as part of screening for Down's syndrome;
- The 18–21 week scan primarily screens for structural anomalies;
- Scans performed after this stage in pregnancy are only performed if there is a clinical indication such as concern about fetal growth or well-being.

i) Indications and goals of fetal ultrasound in the three trimesters

a) Ultrasound in first trimester

- Diagnosis of pregnancy—
    - Gestational sac can be visualized from as early as 4–5 weeks of gestation;
    - The yolk sac at about 5 weeks;
    - A visible heartbeat can be visualized by about 6 weeks.
- To confirm fetal viability;
- To provide an accurate estimation of gestational age;
- To diagnose multiple gestation, particularly to determine chorionicity;
- To identify markers which would indicate an increased risk of fetal chromosome abnormality such as Down's syndrome;
- To identify fetuses with gross structural abnormalities.

b) Ultrasound in second trimester

- To provide an accurate estimation of gestational age if an early scan has not been performed;
- To carry out a detailed fetal anatomical survey to detect any fetal structural abnormalities or markers for chromosome abnormality;
- To locate the placenta and identify the 5 per cent of women who have a low-lying placenta for a repeat scan at 34 weeks to exclude placenta praevia;
- To estimate the amniotic fluid volume;
- Additionally, in some centres:
    - To perform doppler ultrasound assessment of maternal uterine arteries to screen for adverse pregnancy outcome, for example pre-eclampsia;
    - To measure cervical length to assess the risk of preterm delivery.

c) Ultrasound in third trimester

- To assess fetal growth;
- To assess fetal well-being.

ii) Fetal ultrasound for estimation of gestational age

Gestational age can be estimated by measuring fetal parts and comparing it with percentile reference charts. The earlier the measurement is made, the more accurate the prediction;

- If performed before 20 weeks gestation (ideally between 10-14 weeks), ultrasound can be used to date the pregnancy;
    - Crown-rump length (CRL) can be used uptill 13 weeks + 6 days (***accuracy of prediction is ± 5 days***);
    - Head circumference (HC) can be used from 14 to 20 weeks .
    - The biparietal diameter (BPD, ***accuracy of prediction ± 7 days***) and femur length (FL) can also be used to determine gestational age.
- If performed after 20 weeks, dating a pregnancy can vary because of variable growth rates of fetuses.

iii) Ultrasound *diagnoses* in pregnancy

Transvaginal ultrasound is of a higher sensitivity in ultrasound diagnosis;

- In a missed miscarriage, the fetus can be identified, but with an absent fetal heart;
- In a blighted ovum, the absence of fetal development results in the presence of a gestational sac which is empty;
- An ectopic pregnancy is suspected if there is a positive pregnancy test, but ultrasound does not identify a gestational sac within the uterus. There may be an adnexal mass with or without a fetal pole, or presence of fluid in the pouch of Douglas;
- In addition to AC; HC, BPD and FL, when combined in an equation, provide a more accurate estimate of fetal weight (EFW) than any of the parameters taken singly;
    - Numerous formulas have been proposed to calculate estimated fetal weight (EFW) using measurements;
    - Abdominal circumference (AC) is used in almost all formulas for EFW as it strongly influences fetal weight estimates.
- Abdominal circumference (AC) and Head circumference (HC) allows assessment of the size and growth of the fetus. This assists in the assessment of fetal growth restriction;
    - Asymmetry between head measures (BPD, HC) and AC can be identified in fetal growth restriction (FGR);
    - A **brain-sparing effect** will result in a relatively large HC compared with the AC (see Figure).
    - An opposite would occur in a diabetic pregnancy, where the abdomen is disproportionately large due to the effects of insulin on the fetal liver and fat stores;
    - A symmetric cessation of growth is an omnious sign of placental failure.
- First trimester ultrasound can detect features consistent with chromosomal abnormalities, e.g. absence of fetal nasal bone and ↑ fetal nuchal translucency seen with Down's syndrome;
- Ultrasound for structural abnormalities (at 18-20 weeks) can detect spina bifida, hydrocephalus, achondroplasia, abdominal wall defects (e.g. exomphalos and gastroschisis), cleft lip/palate and congenital cardiac abnormalities.

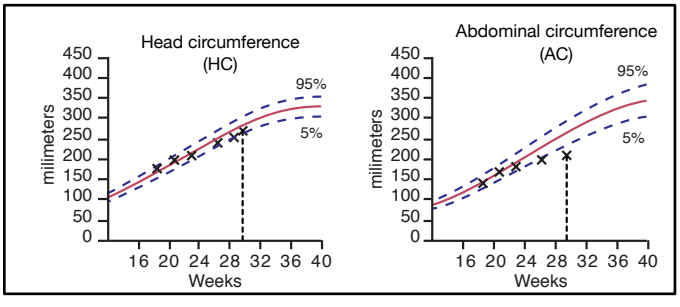


Figure. Asymmetrical FGR— AC < 5th centile but brain sparing effect (HC near 50th centile).

iv) Multiple pregnancy

Ultrasound can identify multiple multiple pregnancy as well as determine **chorionicity** of the in twin/multiple pregnancy (*see also Chapter 23: Multiple pregnancy*).

Chorionicity is important to determine because twin/multiple pregnancy that shares a single placenta (~ monochorionic) are at an ↑ risk of complications and mortality.

The optimal gestation at which to perform such ultrasonic chorionicity determination is 9–10 weeks;

- A tongue of placental tissue is seen within the base of dichorionic membranes and has been termed the 'twin peak' or 'lambda' sign;
- Dichorionic twins have a thick inter-twin separating membrane septum flanked on either side by a very thin amnion (see Figure). Monochorionic twins have a very thin inter-twin septum;
- Dichorionicity may also be evident later in the gestation in the presence of different-sex fetuses.

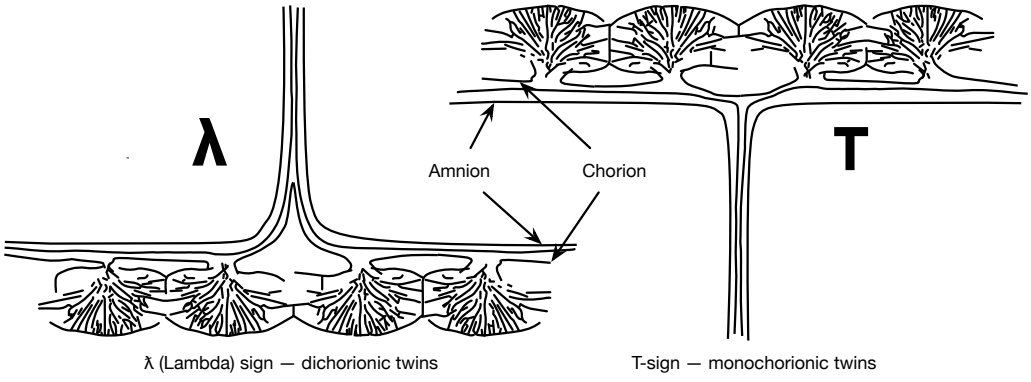


Figure. Illustration of ƛ (lambda) sign and T-sign— can be observed on ultrasound testing.

v) Placental localization

- At the 20 weeks scan, placental attachment site should be identified;
- At this stage, the lower uterine segment is not fully expanded and most low-lying placentas will appear to migrate upwards as the lower segment stretches in the late second and third trimesters.
- Only 5% women with low-lying placenta at 20 weeks will eventually be shown to have a placenta praevia.

vi) Amniotic fluid volume assessment

The fetus controls the amniotic fluid volume by swallowing and excreting urine into the amniotic sac. Ultrasound can be used to identify amniotic fluid volume— oligo- or polyhydramnios;

- Anencephaly or esophageal atresia result in an increase in amniotic fluid because of impaired swallowing ability;
- Renal agenesis and posterior urethral valves result in reduced or absent amniotic fluid due to impaired urine production and passage, respectively.

Fetal growth restriction (FGR) can be associated with ↓ amniotic fluid because of ↓ renal perfusion and urine output. Thus, the amniotic fluid volume can be associated with fetal well-being.

Ultrasound measurement of two parameters is indicative of amniotic fluid volume— ***maximum vertical pool*** and ***amniotic fluid index (AFI).*** AFI is equal to the sum of deepest cord-free pool of amniotic fluid in all 4 uterine quadrants;

- Maximum vertical pool measurement of < 2cm suggests oligohydramnios, and > 8cm suggests polyhydramnios.
- The AFI in the third trimester should be between 10 and 25 cm; values ≥ 5cm indicate oligohydramnios, while values > 25cm indicate polyhydramnios.

(II) Assessment of fetal well-being

i) Fetal movement (kick counts)

This is oldest screening for ↓ fetal movements that may be perceived as unusual by the pregnant woman. It is often taught to pregnant women at antenatal visits for self monitoring.

The pregnant individual is asked to record 10 kicks. The time interval between the first kick and the 10th kick. Usually occurs in a 3-hour period.

If the fetus *fails to kick 10 times in a day*, then the woman should be instructed to contact her care-giver and cardiotocographic assessment should be performed.

ii) The cardiotocogram/non-stress test (NST)

Cardiotocograph (CTG) is a *continuous* tracing of the fetal heart rate (FHR) using the doppler effect with reference to uterine activity.

In a left lateral/semi-recumbent position (to avoid compression of the maternal vena cava), an external ultrasound transducer for monitoring the fetal heart and a tocodynometer (stretch gauge) for recording uterine activity are secured overlying the uterus to obtain a recording.

CTG depends on the assumption that a *healthy fetus will normally be more active than an at-risk fetus*, and that its heart will respond to a uterine contraction by accelerating;

- Recordings are made for at least 30 minutes of 1) fetal heart rate and 2) tracing of uterine activity;
    - The baseline heart rate is first determined over a period of 5–10 minutes with limits from 110 to 160 beats per minute. FHR < 110 or > 160 may be of significance;
    - There is short-term variability (i.e. variation in interval between successive heart beats) and longer-term variability (occurring 2 to 6 times every minute) in *baseline fetal heart-rate*.
- There are fetal heart rate accelerations— positive sign of fetal health;
    - By definition, this is ↑ in baseline fetal heart rate of ≥ 15 bpm lasting ~ 15 seconds;
    - Presence of ≥ 2 accelerations/30 minute CTG indicates of a **reactive** *non-hypoxic fetus*.
- Decelerations are periodic, transient decreases in fetal heart rate. These can be normal or may suggest pathology (*see Figure below*).

Detection of pathology on CTG employs the principle that fetal hypoxia modifies fetal cardiac behaviour that is regulated through the autonomic nervous system by vasomotor, chemoceptor and baroreceptor mechanisms;

- Baseline variability is considered abnormal if it is <10 beats/minute. This is subjected to retesting as the fetus may be in a deep sleep cycle that lasts 20-30 minutes.
- Recurrent late or variable decelerations, if observed, should be interpreted in clinical context.

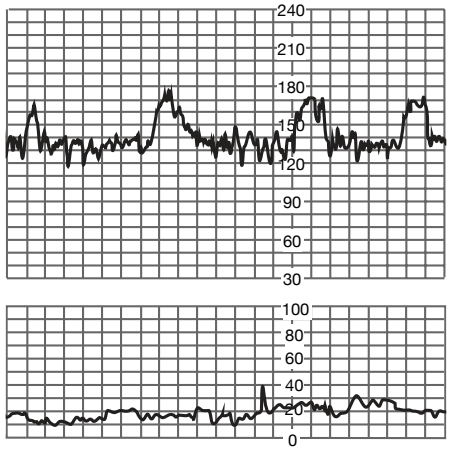


Figure. A reactive CTG showing baseline between 110–150 bpm, with baseline variability exceeding 10 bpm, and with more than one acceleration being seen in a 20–30 minute tracing.

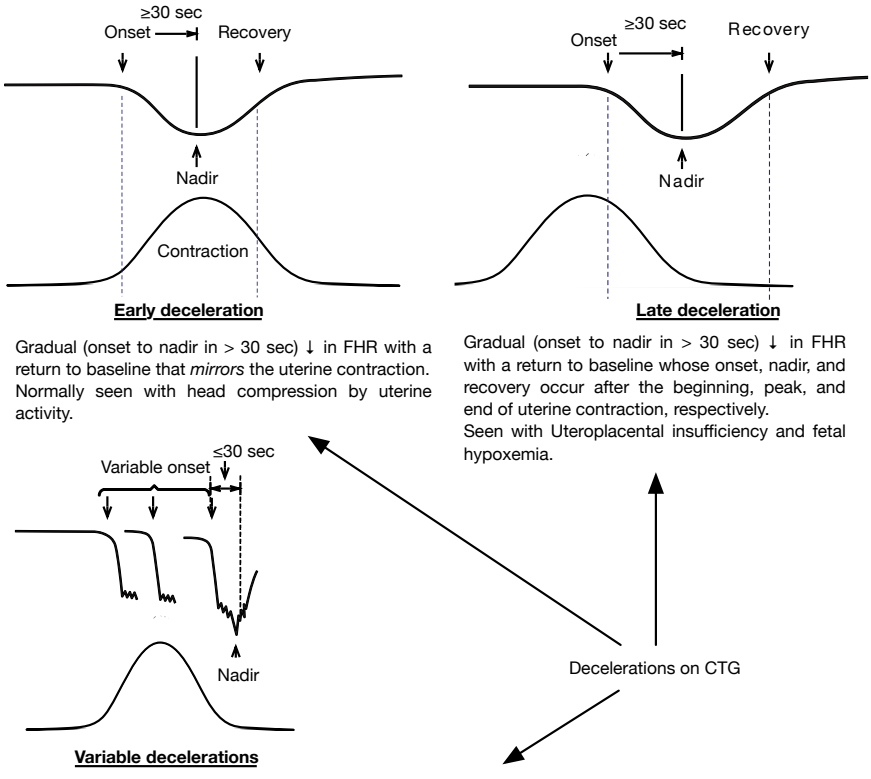


Figure. Illustrations of patterns of FHR decelerations.

Table. RCOG classification of CTG.

FHR Features	Baseline (bpm)	Variability (bpm)	Decelerations	Accelerations
Reassuring	110-160	≥5	None	Present
Non-reassuring	Either 100-109 or 161-180	<5 for ≥40 but <90 min	-- Early --Variable --Single, prolonged for upto 3 min	Absent (*CTG is of uncertain importance if absent accelerations but otherwise normal*)
Abnormal	Either <100 or >180, or sinusoidal pattern for ≥10 min	<5 for >90 min	--Atypical --Late --Single prolonged for >3 min	
The RCOG classification of CTG is as follows: • Normal— a CTG with all 4 features are in reassuring category. • Suspicious— a CTG with 1 feature non-reassuring but remainder 3 features reassuring. • Pathological— a CTG with either ≥2 features non-reassuring or ≥1 features abnormal.				

Some other characteristic patterns observed in cardiotocography (see Figure);

- Sinusoidal pattern (one with normal baseline, decreased variability, and a cyclic sinusoidal pattern with a frequency of 2–5 cycles/min and amplitude of 5–15 beats/min) is associated most strongly ***with fetal anemia***. It may also be seen in the setting of chorioamnionitis, *impending* fetal demise, and maternal drug administration (especially opiate analgesics).
- A saltatory pattern (in which there are large oscillations in baseline) is of unclear clinical significance. It may indicate intermittent cord occlusion.

- A lambda pattern (an acceleration followed by a deceleration) is attributed to fetal movement. It is not thought to be of pathological significance.

Though the interpretation of a CTG is subjective, it is especially useful for antenatal and intrapartum monitoring.

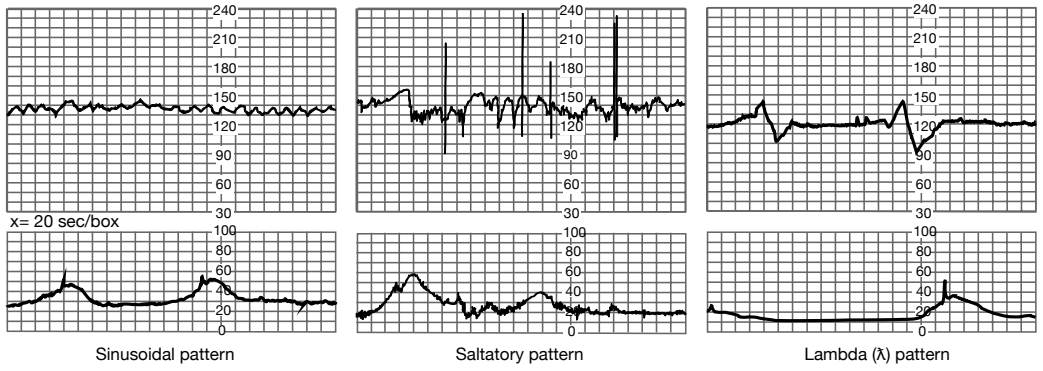


Figure. Sinusoidal, saltatory and lambda patterns on CTG.

iii) Biophysical profile (BPP)

To refine the ability of fetal CTG to identify antenatal hypoxia, a nonstress CTG is combined with assessment of four additional parameters for biophysical profile scoring.

A recording is carried out for 30-40 minutes and scoring is done as seen Table;

Table. Biophysical profile scoring system.

Parameters	**Normal (score = 0)**	**Abnormal (score = 2)**
Non-stress CTG	Reactive	< 2 accelerations in **40 minutes**
Fetal breathing movements	≥30 seconds in 30 minutes	<30 seconds in 30 minutes
Fetal body movements	≥3 movements in 30 minutes	≤2 *gross body movements* in 30 minutes
Fetal tone	1 episode of limb flexion	No evidence of fetal movement or flexion
Amniotic fluid volume	*Largest* pocket of fluid > 1cm	<1 cm pocket of fluid

The interpretation of biophysical profiling is based on the notion that fetal breathing movements and limb movements are reduced in hypoxic conditions;

A score of 0, 2 or 4 is considered abnormal and a score of 8 or 10 is considered normal. A score of 6 is equivocal and requires retesting after some time to exclude fetal sleep as a cause of low score.

Limitations with biophysical profile testing include;

- Time consuming;
- False positive low-scoring due to fetal sleep;
- If a low score on BPP prompts delivery, as the fetus is likely to already be severely hypoxic. This does not improve long-term survival as there may be physical and mental impairment.

Recent evidence, however, questions the value of BPP as a test of fetal well-being in high-risk pregnancies.

iv) Doppler velocimetry investigations

Doppler ultrasound testing can evaluate umblical and fetal vessels for circulation. This indirectly gives information about small foetuses that may be growth restricted.

a) Fetal umblical artery—

Waveforms obtained from the umbilical artery provide information on placental resistance to blood flow and hence indirectly placental 'health' and function.

A normal umblical arterial waveform (see Figure) on doppler shows that there is forward flow of blood

throughout the cardiac cycle including diastole. This diastolic flow ↑ throughout the gestation as the placental resistance ↓.

Resistance index (RI) is a calculable parameter for resistance in umblical artery doppler (see Equation and Figure). RI rising beyond 95th centile implies faulty placental perfusion.

$$\text{RI} = \frac{\text{maximum umblical artery systolic velocity} - \text{minimum umblical artery enddiastolic velocity}}{\text{maximum umblical artery systolic velocity}}$$

Pulsatility index (PI) is a similar calulable parameter for resistance expressed as;

$$\text{PI} = \frac{\text{maximum umblical artery systolic velocity} - \text{minimum umblical artery enddiastolic velocity}}{\text{time averaged velocity (over one cardiac cycle)}}$$

Diastolic flow, RI and PI are thus useful for identifying placental malfunction (↑ resistance) and fetal distress. There may be absent diastolic flow abnormally or even reversed (see Figure).

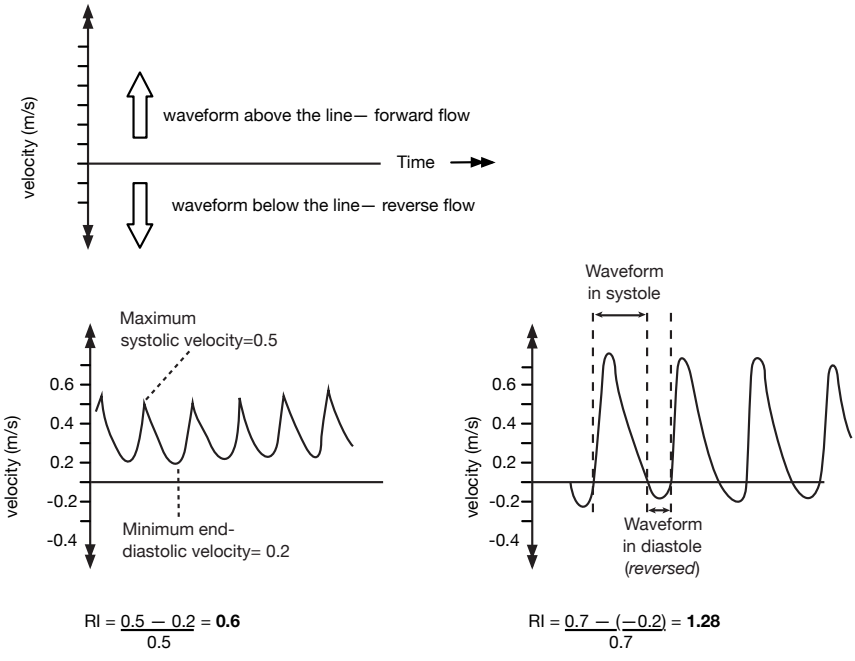


Figure. Umblical artery waveforms (schematic) on Doppler velocimetry.

Doppler ultrasound is particularly beneficial in small for gestational age (SGA) foetuses. Its use (compared with BPP) in *high risk pregnancies* appears to improve obstetric outcomes.

b) Fetal vessels

The fetus under continuing stress has protective mechanisms to protect blood flow to brain, heart, adrenals and spleen; with vasoconstriction in all other vessels. This is called '**centralization of flow**'.

The most commonly measured fetal vessels for flow are the middle cerebral artery, ductus venosus and aorta.

- Doppler assessment of middle cerebral artery can;
    - Show ↑ diastolic flow as hypoxia increases;
    - ↑ peak systolic velocity— indicates presence of fetal anemia. This makes it useful in assessment of the severity of rhesus disease and twin-to-twin transfusion syndrome.
- Doppler assessment of aorta;
    - Absent diastolic flow in the fetal aorta— implies fetal academia;
    - A rising resistance in the fetal aorta reflects compensatory vasoconstriction
- Increasing pulsatility in the central veins supplying the heart (ductus venosus and IVC)— most sensitive for fetal academia (anaerobic metabolism).

- If late diastolic flow is absent in ductus venosus, delivery should be discussed as ***fetal death is imminent.***

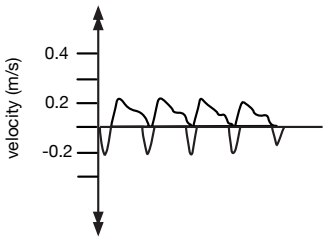


Figure. Schematic of Doppler velocimetry— reverse flow in *ductus venosus*, as seen with fetal compromise.

c) Maternal uterine arteries

Doppler studies of the uterine artery during the second trimester have been used to predict pregnancies at risk of adverse outcomes.

This is reflected in the doppler waveforms obtained from the maternal uterine circulation which may show markers of increased resistance to flow, including a **diastolic 'notch'** in waveforms in early diastole (see Figure).

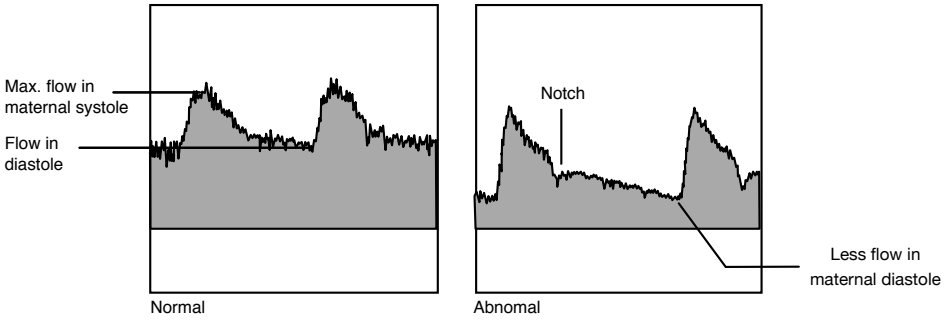


Figure. Illustration of doppler velocimetry of uterine artery— normal and ***'high-risk'*** diastolic notch.

Upto 60-70% of women at 20-24 weeks gestation with bilateral uterine notches on Doppler scanning will subsequently develop one or more complications like pre-eclampsia, fetal growth restriction and placental abruption.

Such pregnancies, thus, require close monitoring of fetal growth rate and increased surveillance for possible development of maternal hypertension and proteinuria.

CHAPTER 21 PRENATAL DIAGNOSIS

Prenatal testing by screening and diagnostic tests aids early detection of disease.

Diagnostic test	Condition
Ultrasound diagnosis	Neural tube defect Gastroschisis Cystic adenomatoid malformation of lung Twin-to-twin transfusion syndrome
Invasive test— CVS or amniocentesis	Down's syndrome Cystic fibrosis Thalassemia
Invasive test— cordocentesis	***Alloimmune thrombocytopenia***
Ultrasound then invasive test	Congenital diaphragmatic hernia Exomphalos Ventriculomegaly Duodenal atresia

(I) Invasive tests

Cells of fetal origin can be obtained via relatively invasive techniques, and this sample can be used for cytogenetic, biochemical, enzymatic or DNA analysis to give prenatal diagnosis.

With chorionic sampling, placental mosaicism can be observed. This is the occurrence of two different cell genotypes in a single sample.

i) Chorionic villus sampling (CVS)

A thin needle is passed transabdominally or transcervically under ultrasound guidance into the placenta. Chorionic villi containing trophoblast cells are aspirated that are feto-placental in origin.

ii) Amniocentesis

A thin needle is passed transabdominaly under ultrasound guidance into the amniotic cavity and a small amount (15-20 mL) of amniotic fluid is sampled (which contains fetal fibroblasts).

iii) Cordocentesis

A thin needle is passed transabdominally under ultrasound guidance into the umblical cord to sample fetal blood contains nucleated WBCs.

Table. Invasive prenatal diagnostic tests.

	CVS	Amniocentesis	Cordocentesis
Gestation (weeks)	10— 40	15— 40	20— 40
Route	Transabdominal/transcervical	Transabdominal	Transabdominal
Cells sampled	Trophoblast cells	Fetal fibroblasts	Fetal WBCs
Risk of miscarriage (%)	2%	1%	1%
Direct karyotype result (early reporting)	24-48 hours for aneuploides	FISH for chromosomes 13, 18, 21 and XY— takes 24-48 hours.	Not needed
Culture karyotype results	1—2 weeks	2— 3 weeks	24— 48 hours
Mosaicism rate on karyotype	1%	None	None

(II) Lab analysis

Samples obtained from invasive diagnostic tests need to have enough number of cells in mitosis for cytogenetic analysis. The more rapidly the tissue divides, the earlier the results are available.

Time required for tests to complete from invasively obtained samples;

- 1— 2 weeks for CVS;
- 2— 3 weeks for amniocentesis;
- 24— 48 weeks for cordocentesis;

Fluorescence in-situ hybridization (FISH) technique detects DNA sequences directly in mitotic phases and can give results before cell culture. It is commonly used for major aneuploides (13, 18, 21 and XY).

DNA analysis techniques can detect *sickle-cell disease, cystic fibrosis, congenital toxoplasmosis, cytomegalovirus infection, and fragile X syndrome*. Testing for these can be performed on samples from *these invasive tests*.

Enzymatic analysis can be performed for congenital adrenal *hypoplasia* and mucopolysaccharidoses as well.

(III) Diagnosis of congenital anomalies

The RCOG recommends two-stage screening programme for screening congenital structural anomalies;

- Initial scan at booking (11— 14 weeks);
- Anomaly scan around 20 weeks gestation.

i) Neural tube defects (NTDs)

NTDs are the most common major abnormalities. These occur due to defects in neural tube formation during embryogenesis and the aetiology is multifactorial.

Ultrasound scanning can detect neural tube defects; anencephaly, encephalocele, and spina bifida;

- 1st trimester ultrasound has potential to detect anencephaly (frog-eye appearance) and encephaloceles.
- 2nd trimester maternal serum alpha fetoprotein (MSAFP) levels are ↑ in ***open*** NTDs— screening.
- Presence of acetylcholinesterase neurotransmitter in amniotic fluid is taken as diagnostic of open NTDs.
- Anomaly scan can show '**lemon**' shaped skull and '**banana**' signs (absent cerebellum) in fetal brain as cranial signs of spina bifida.

Folic acid deficiency and antiepileptic drugs are often associated with incidence of NTDs. Folic acid supplementation is recommended to be started at least 3 months preconception.

In women with previous NTDs, *a higher dose of 4mg folic acid oral tablets* daily is recommended.

ii) Heart defects

Congenital heart defects (CHDs) have a heterogeneous etiology and includes genetic factors, environmental factors and viral infection. CHDs are also associated with mothers having type-1 diabetes.

For detection, the anomaly scan is sensitive only if performed by specialists in interpretation. Fetal echocardiography is another option.

iii) Gastrointestinal anomalies

Duodenal and oesophageal atresia along with resulting polyhydramnios can be visualized.

Duodenal atresia is long known to show an appearance of a '**double-bubble**' on ultrasound.

Abdominal wall defects can occur through which peritoneal sac herniates. These can be seen on ultrasound;

- Omphalocele— a midline abdominal wall defect through which peritoneal sac with contents herniates;
- Gastroschisis—loops of bowel in the amniotic cavity. The bowel is *not* covered by a sac and floats freely.

Omphaloceles are associated with other cardiac and chromosomal abnormalities. These should be ruled out.

iv) Renal anomalies

The commonest abnormality seen in renal tract is mild pelvicalyceal dilatation. However, its significance is questionable.

Major anomalies such as renal agenesis is detected by 20 weeks because of associated oligohydramnios.

v) Other anomalies

Cleft lip can be identified on ultrasound but the diagnosis of isolated cleft palate is difficult.

Talipes equinovarus (club foot) is a condition in which the forefoot is supinated and ankle plantarflexed;

- More commonly seen in males (approx. male:female ratio is 2:1);
- Positional talipes (non-fixed) is temporary and often associated with oligohydramnios;
- These can be detected antenatally using ultrasound;
- Talipes equinovarus is also associated with spina bifida.

Congenital cystic adenomatoid malformation is a rare form of lung disease where the normal alveolar tissue is replaced by a proliferation of cysts resembling bronchioles.

- Ultrasound shows a cystic mass present within the lung parenchyma at anomaly scan.
- The prognosis is good, but occasional very severe cases may cause hydrops.

(IV) Diagnosis of chromosomal abnormalities

Most chromosomal abnormalities are incompatible with life and result in a miscarriage. However, some aneuploides and sex chromosomal abnormalities are important for prenatal testing.

Since trisomies 13 and 18 have high intrauterine lethality, prenatal testing is most emphasized for Down's syndrome.

i) Down's syndrome

It is recommended that all pregnant women should be offered screening for down's syndrome as part of routine antenatal care.

Several forms of screening tests are available;

- UK National Screening Committee recommends use of the combined testing between 11-14 weeks gestation;
    - For each woman, the individual risk (based on maternal age) is calculated and adjusted for by results from nuchal lucency, hCG, and PAPP-A;
    - Foetuses with Down's syndrome tend to have thicker nuchal lucency;
    - A trend of ↑ hCG and ↓ PAPP-A levels is seen.
- Ultrasound can also show associated features e.g. altered nasal bone, duodenal atresia, tricuspid regurgitation etc.
- Second trimester testing of maternal serum AFP levels (15-22 weeks) is another option and levels are observed to be ↓ in cases of Down's syndrome.

Based on her individual results, the women can then choose whether to have an invasive test as it must be performed to reach a definitive diagnosis.

ii) Sex chromosomal abnormalities

These include Turner's syndrome (45, XO) and Klinefelter's syndrome (47, XXY) among others.

The prevalence of sex chromosomal abnormalities does not change with maternal age (unlike trisomies).

Routine screening for these conditions is not carried out generally, but in light of other abnormalities karyotyping may reveal this abnormality.

iii) Fragile X syndrome

Fragile X syndrome is the most common inherited cause of mental retardation. It occurs due to hypermethylation of fragile X gene (FMR1).

PCR testings and southern blot analysis on samples obtained from invasive tests can give prenatal diagnosis but is not routine without relevant positive family history.

(V) Genetic disorders

These are not tested routinely unless there is a positive family history. The common genetic diseases are cystic fibrosis and hemoglobinopathies.

(VI) Congenital viral and parasitic infections

Infections during gestation can have deleterious effects on the fetus. These infections are;

- Rubella;
- Cytomegalovirus (CMV);
- Toxoplasma;
- Parvovirus.

Though most infected foetuses (>95%) remain unaffected. This risk is inversely proportional to gestational age with most serious effects seen in foetuses infected at 12-18 weeks gestation.

Parvovirus infection during gestation can be transmitted vertically to the fetus. Aplastic anemia can occur as a result with hydrops in the fetus.

It is routine to test women for rubella antibodies. If the individuals do not have antibodies they are adviced to take necessary precautions to avoid being exposed to the virus. After pregnancy, rubella vaccination can be administered.

Table. Source and some characteristics of congenital infections.

	Rubella	**Cytomegalovirus**	**Toxoplasmosis**	**Parvovirus**
Source	Infected individuals	Infected individuals	Cat litter	Infected children
Features of congenital infection	Cataracts Heart defects Growth restriction Hepatomegaly Thrombocytopenia Mental retardation	Microcephaly Ventriculomegaly Cerebral calcification Heart defects Growth restriction Hepatomegaly Thrombocytopenia Mental retardation	Microcephaly Ventriculomegaly Cerebral calcification Heart defects Growth restriction Hepatomegaly Thrombocytopenia Mental retardation	Aplastic anemia Hydrops fetalis

For these infections, it is not routine to carry out serologic testing as part of antenatal care if asymptomatic, except rubella immunity testing in the pregnant female.

CHAPTER 22 ANTENATAL OBSTETRIC COMPLICATIONS

(I) Minor obstetric complications

- Backache;
- Symphysis pubis dysfunction;
    - A very painful condition most common in 3rd trimester;
    - The symphysis pubis joint becomes 'loose', causing the two halves of the pelvis to rub on one another when walking or moving;
    - Under a physiotherapist's direction, a low stability belt may be worn.
- Compression neuropathies— due to soft tissue swelling. Most commonly carpal tunnel syndrome;
- Constipation;
- Hyperemesis gravidarum is a severe, intractable form of nausea and vomiting;
    - *It is important to note, that in severe cases LFTs may be deranged.* Biopsy of the liver in these cases may show non-specific fatty infiltration or very mild cholestasis;
    - Treatment include fluid replacement and thiamine supplementation;
    - Avoid glucose containing IV fluids as they can precipitate *Wernicke's encephalopathy*;
    - Phenothiazine anti-emetics are safe and commonly prescribed, e.g. prochlorperazine (Stemetil®).
- Gastroesophageal reflux— histamine-2 receptor antagonists e.g. ranitidine are preferred over PPIs.
- Varicose veins;
    - These are thought to be due to the relaxant effect of progesterone on vascular smooth muscle and the *dependent venous stasis* caused by the weight of pregnant uterus on the inferior vena cava;
    - Varicose veins of the legs may be symptomatically improved with support stockings, avoidance of standing for prolonged periods.
- Haemorrhoids;
    - Pregnant individuals are predisposed due to effects of circulating progesterone on the vasculature, pressure on the superior rectal veins by the gravid uterus and increased circulating volume;
    - Management is conservative with local anesthetic/anti-irritant creams and high-fiber diet.
- Other common minor disorders;
    - Edema, mostly of the lower limbs due to increased circulating volume;
    - Itching;
    - Urinary incontinence;
    - Nose bleeds;
    - Thrush (vaginal candidiasis);
    - Headache;
    - Fainting;
    - Breast soreness;
    - Tiredness;
    - Leg cramps;
    - Striae gravidarum— stretch marks over the abdomen;
    - Chloasma— brown patches of pigmentation seen especially on the face (*see Chapter 17: Physiologic changes in pregnancy*).

(II) Complications in pelvic organs

i) Ovarian cysts

Ovarian cysts are common in pregnant women. These can be physiological or pathological;

- Physiological cysts that are seen in pregnancy are corpus luteal cysts and occasionally dermoid cysts.
- The most common types of pathological ovarian cysts are serous cysts and benign teratomas.

Large ovarian cysts (>8 cm) can undergo torsion, haemorrhage or rupture presenting with acute pain. These, in severe cases, can result in miscarriage or preterm labor.

Emergency laparotomy is considered if there is torsion of the cyst. Elective surgery, if needed, for large cysts is usually delayed till late 2nd or early 3rd trimester.

ii) Uterine fibroids

Fibroids can enlarge in pregnancy and result in complications;

- Red degeneration— most common complication of fibroids in pregnancy;
    - Sometimes with increase in size during pregnancy, a fibroid can outgrow its blood supply. The ischemia manifests as acute pain and may be accompanied with vomiting.
    - In more severe cases, pain can precipitate uterine contractions and result in miscarriage/preterm labor.
    - Ultrasound can not confirm red degeneration.
- Torsion of a pedunculated fibroid can occur in a manner similar to ovarian cysts. Ultrasound scan can aid in diagnosis.

iii) Persistent uterine retroversion in pregnancy

Pregnant individuals with a normal anteverted uterus and most cases of a retroverted uterus (see Figure) expand and reposition upwards to the abdominal cavity to accommodate growth in size.

But occasionally, this does not occur and uterus pushes against the pelvic organs. By 12-14 weeks of gestation, the base of the bladder and urethra can be stretched resulting in retention of urine ± overflow incontinence.

Urinary tract catheterization is essential in this condition till the position of the uterus has changed.

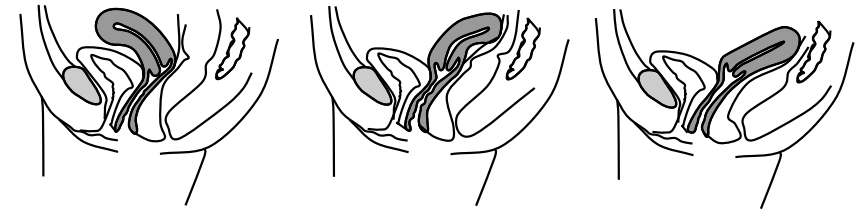


Figure. Illustration of normal uterine position, retroflexion and retroversion seen in endometriosis.

iv) Congenital uterine anomalies

Structural anomalies of the uterus can occur during embryonic development. These are often detected incidentally at the time of a pelvic ultrasound.

Of concern is a bicornuate uterus (see Figure) which can be associated with;

- Miscarriage;
- Preterm labor;
- Preterm prelabor rupture of membranes (PPROM);
- Abnormalities of lie and presentation;
- Higher C-section rate.

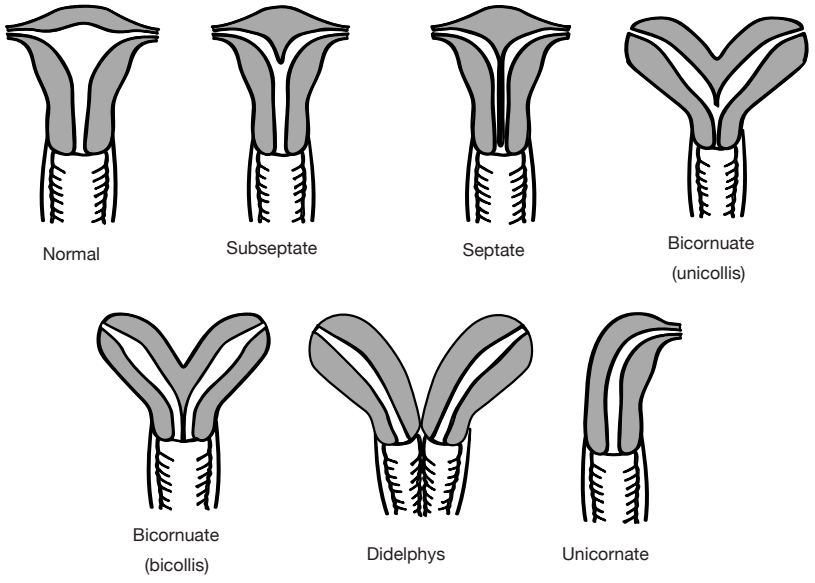


Figure. Illustration of some congenital uterine anomalies.

v) Cervical malignancy

Cervical malignancy is rare to be detected during pregnancy especially in those who are up-to-date on cervical screening via smears;

- Presentation can be vaginal bleeding, often post-coital (vs. placenta previa which is more likely);
- Examination can reveal a friable or ulcerated lesion on the cervix with bleeding ± purulent discharge;
- Management of cervical malignancy during pregnancy requires multidisciplinary care.

(III) Urinary tract infections

UTIs are common during pregnancy. Urinalysis for asymptomatic bacteriuria is carried out for screening at the booking visit.

Untreated asymptomatic bacteriuria can progress to pyelonephritis and it is recommended to repeat testing with another midstream sample or send urine for culture/sensitivity testing;

- The most common organism for UTI is *E. coli*.
- Presence of $>10^5$ organisms on urine culture is confirmatory of a UTI.
- First line antibiotic for UTI in pregnancy is amoxicillin or an oral cephalosporin.
- Treatment of pyelonephritis is with IV antibiotics and baby must be monitored with CTG.

(IV) Venous thromboembolism (VTE)

Venous thromboembolism (VTE) is the most common cause of direct maternal deaths in developed countries.

Pregnancy is a hypercoagulable state. There is an ↑ in clotting factors VIII, IX, X and fibrinogen levels, and ↓ in protein S and anti-thrombin III concentration.

These physiologic changes are meant to counter the upcoming blood loss during labor. But these also predispose the pregnancy female to thromboembolism causing ↑ risk of non-fatal pulmonary embolism and deep vein thrombosis (DVT) in the peripartum.

Other thrombophilic disorders that predispose to thrombosis include;

- Hereditary deficiencies of anticoagulants— either protein C, protein S or anti-thrombin III;
- Gain-of-function genetic mutations in procoagulants— e.g. Factor V Leiden mutation and the prothrombin mutation G20210A.

- Acquired thrombophilia, notoriously associated with autoimmune antiphospholipid syndrome (APS) that results in recurrent miscarriage.

Table. Risk factors for thromboembolic disease.

Pre-existing risk factors	
Maternal age (> 35 years)	
Thrombophilic disorders	*Heritable* Anti-thrombin deficiency Protein C deficiency Protein S deficiency Factor V Leiden mutation Prothrombin gene mutation *Acquired* Anti-phospholipid antibodies Persistent lupus anticoagulant and/or persistent moderate/high titer anticardiolipin antibodies and/or β2-glycoprotein 1 antibodies.
Certain medical conditions	Nephrotic syndrome Sickle-cell disease
Obesity (weight > 80 kg)	
Previous thromboembolism	
Severe varicose veins	
Smoking	

Risk factors with pregnancy
Multiple gestation
Pre-eclampsia
Grand multipara (**gravidity ≥ 8**)
C-section, especially if as an emergency procedure
Damage to pelvic veins
Malignancy
Sepsis
Prolonged bed rest

i) Clinical features and diagnosis

For deep vein thrombosis;

- Compression ultrasound for deep vein thrombosis should be the first investigation in a woman with swollen, unilateral tender calf.
- Venography is an invasive test. Its use in obstetrics is limited due to use of intravenous contrast.

For pulmonary embolism;

- With a pregnant woman presenting with breathlessness accompanied with pleuritic chest pain and tachycardia (pulse >90), pulmonary embolism is of high suspicion.
- ECG, and ABGs remain the first line investigations and are good for ruling out other sources of the acute syndrome;
    - ECG may show the famous S1Q3T3 pattern for pulmonary embolism but is uncommon;
    - CXR may also be considered if the benefits outweight potential risks.
- D-dimer can be elevated due to the physiological changes in the coagulation system, thus limiting its clinical usefulness here.
- With high suspicion and a positive ultrasound for lower limb DVT, it is recommended to treat on presumptive diagnosis of PE.
- A ventilation-perfusion (V/Q) scan or CT pulmonary angiogram (CTPA) can also be performed—with both, *the radiation to the fetus is below the threshold considered safe*.

ii) Treatment

Graduated elastic stockings should be used for the initial treatment of DVT and should be worn for 2 years following a DVT to prevent post-phlebitic syndrome— ***but only during day-time of mobility and not at night***.

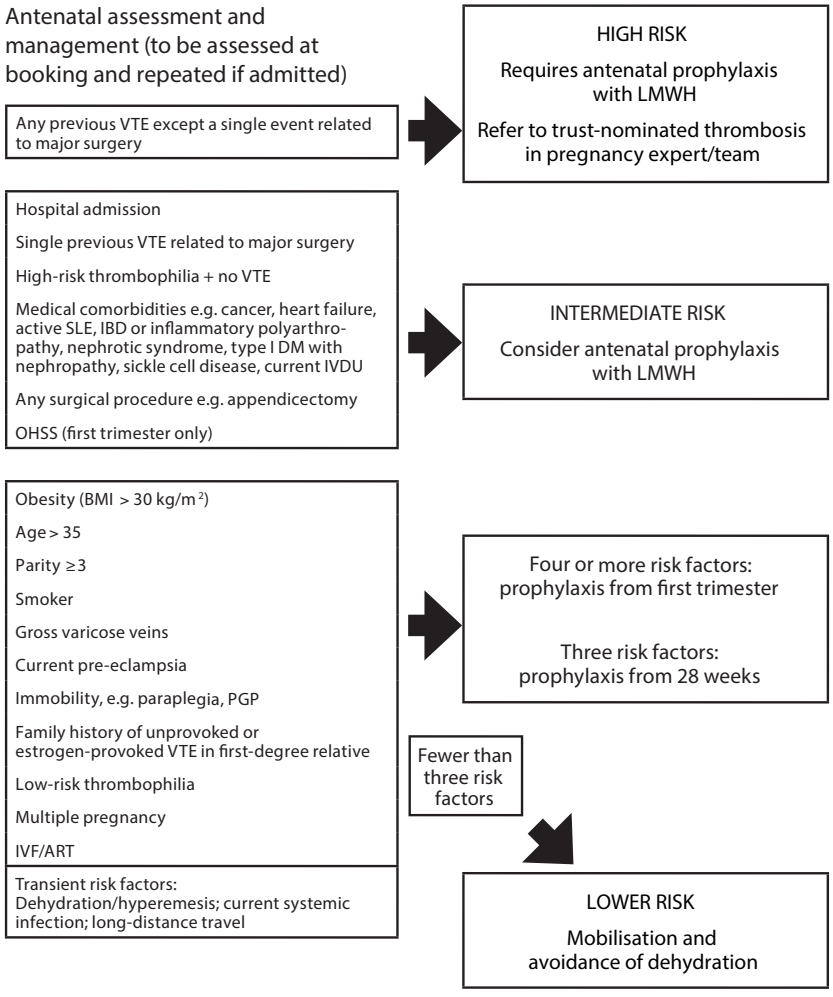
Subcutaneous low molecular weight heparins (LMWHs)—are treatment of choice;

- LMWHs are continued thereby till the end of pregnancy;
- Post-partum they can be either switched to oral warfarin or continue with subcutaneous LMWHs;
- Both warfarin and LMWHs are safe in women who are breastfeeding.

Warfarin is contraindicated in pregnancy (teratogenic and causes facial and limb defects). The only exception is women with mechanical heart valves.

iii) Prevention of VTE

The RCOG Green Top Guidelines No. 37 recommend an algorithmic approach to need for thromboprophylaxis;



APL = antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, β_2-glycoprotein 1 antibodies); ART = assisted reproductive technology; BMI based on booking weight; DM = diabetes mellitus; FHx = family history; gross varicose veins = symptomatic, above knee or associated with phlebitis/oedema/skin changes; high-risk thrombophilia = antithrombin deficiency, protein C or S deficiency, compound or homozygous for low-risk thrombophilias; IBD = inflammatory bowel disease; immobility = ≥3 days; IVDU = intravenous drug user; IVF = in vitro fertilisation; LMWH = low-molecular-weight heparin; long-distance travel = > 4 hours; low-risk thrombophilia = heterozygous for factor V Leiden or prothrombin G20210A mutations; OHSS = ovarian hyperstimulation syndrome; PGP = pelvic girdle pain with reduced mobility; PPH = postpartum haemorrhage; thrombophilia = inherited or acquired; VTE = venous thromboembolism.

Figure. Illustration of antenatal thromboprophylaxis (RCOG Green Top Guidelines No. 37, *for post-natal see Chapter 32: Puerperium*).

(V) Substance abuse in pregnancy

Substance abuse in pregnancy can have effects on both the pregnanct woman and developing fetus (see Table);

Use of alcohol during gestation—

- An intake of less than 100 g per week (approximately two drinks per day, e.g. two medium glasses of wine or one pint of beer) is not associated with any adverse effects;
- Heavy alcohol consumption in pregnancy (more than 120 g, or 12 standard drinks a day) is associated with fetal growth restriction, developmental delay and neurological complications in the baby;
- Massive doses, i.e. > 2 g/kg of body weight (~17 drinks/day), have been associated with fetal alcohol syndrome (*see facial features in Figure below*).

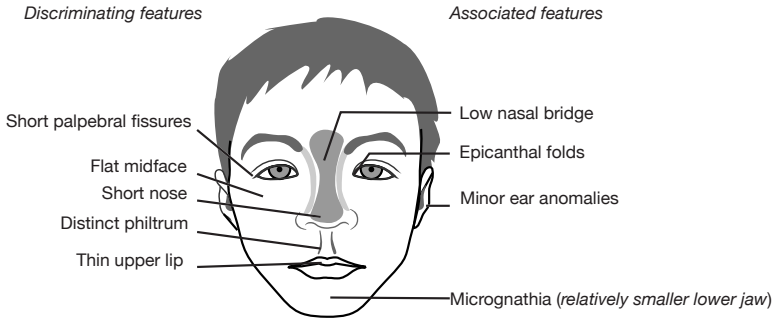


Figure. Facial features of fetal alcohol syndrome.

Smoking acutely reduces placental perfusion;

- There is an ↑ risk of placental abruption, SGA, FGR and low weight at birth;
- It is recommended to quit smoking pregestation. For those struggling individuals, quiting by 15th week of gestation reduces the risk as much as quitting before pregnancy.

For these high-risk populations, it is recommended to test for HIV and hepatitis B serology. So that preventative measures can be taken for both vertical and horizontal transfer.

Table. Certain relevant fetal, neonatal and maternal effects of substance abuse.

	Effects on fetus	**Neonatal effects**	**Maternal effects**
Tobacco	Fetal growth restriction (FGR) Placental abruption	Low birth weight	Malnutrition; Anemia; Iron deficiency; Vitamin B12 deficiency; Vitamin C deficiency; Folic acid deficiency.
Alcohol	FGR	Fetal Alcohol Syndrome (FAS)	
Opiates	Preterm labor Small for gestational age (SGA) Anemia	Neonatal withdrawal syndrome ↑ risk of sudden infant death syndrome (SIDS) ↑ perinatal mortality	
Cocaine	SGA Placental abruption Preterm labor	↑ risk of cerebral infarction	
Cannabis	Preterm labor		

(VI) Amniotic fluid

Amniotic fluid in the amniotic sac comes exclusively from the fetal urine output from 2 provides a cushion effect to the fetus protecting it from trauma. It also has role in development of fetal lungs.

Amniotic fluid imbalances are diagnosed on ultrasonography;

- Oligohydramnios— amniotic fluid index (AFI) < 5th centile for gestational age. examination may reveal a small SFH for gestational age (see Table). Its common complications;
    - Pulmonary hypoplasia;
    - Limb deformities— contractures, talipes.
- Polyhydramnios— amniotic fluid index (AFI) > 95th centile for gestational age. If detected, its cause should be determined (see Table). Polyhydramnios is associated with an ↑ risk of;
    - Abnormal lie;
    - Preterm labor (secondary to uterine overdistention);
    - Intrauterine death of twins can occur if there is twin-to-twin transfusion syndrome.

Table. Causes of amniotic fluid imbalances.

Causes of oligohydramnios	**Diagnosis by**	**Causes of polyhydramnios**	**Diagnosis by**
Renal agenesis	*Ultrasound*	Maternal diabetes	*Glucose tolerance test*
Polycystic kidneys	*Ultrasound*	Placental chorioangioma, AV fistula	*Color Doppler*
Urinary tract obstruction	*Ultrasound*	Multiple gestation with twin-to-twin transfusion syndrome	*Ultrasound/Doppler*
FGR/Placental insufficiency	*Clinical— ↓ SFH, changes on CTG;* *Ultrasound/Doppler velocimetry.*	Esophageal atresia/tracheoesophageal fistula	*Ultrasound*
Maternal drugs (e.g. NSAIDS)	*Stopping NSAIDS may allow amniotic fluid to reaccumulate.*	Duodenal atresia	*Ultrasound*
Amniotic fluid leakage/PPROM	*Speculum examination*	Impaired swallowing/anencephaly	*Ultrasound*

Management of amniotic fluid imbalances is centered around the cause;

- Cessation of drugs, e.g. NSAIDs, tobacco may improve the amniotic fluid volume;
- Polyhydramnios due to maternal hyperglycemia should correct when sugar levels are optimized;
- Twin-to-twin transfusion syndrome in monochorionic twins can be fatal for both foetuses. Amniodrainage and removal of placental vascular connections by laser aid in management of this condition;
- To assess risk of preterm labor due to uterine overdistention, ultrasound for cervical length is used;
- The cervix can be scanned regularly and only sutured if there is significant shortening (see Figure);
- If prior to 24 weeks, following amniotic fluid drainage, the cervical length is less than 25 mm, consideration might be given to cervical suture insertion (cervical cerclage).

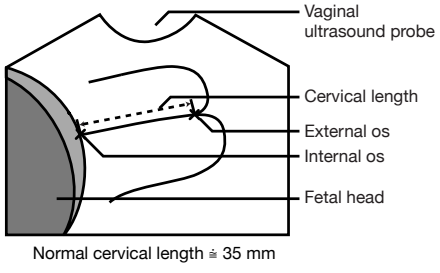


Figure. Illustration of cervical length measurement on ultrasound.

(VII) Fetal malpresentations

Any presentation that is not cephalic is a malpresentation. These include;

- In a longitudinal lie;
    - Breech presentation;
    - Face presentation;
    - Brow presentation.
- Shoulder presentation in a transverse lie.

Malpresentations are closely followed and most correct themselves by term ~37 weeks.

i) Breech presentation

Breech is the most common malpresentation. There are three types of breech presentation— extended 'frank' breech (most common), flexed 'complete' breech, and footling breech (least common, see Figure).

Table. Predisposing factors for breech presentation.

Maternal factors
Fibroids (*most common);* Congenital uterine anomalies, e.g. bicornuate uterus; Uterine surgery.
Feto-placental factors
Multiple gestation (*most common);* Prematurity; Placenta previa; Structural anomalies, e.g. *anencephaly or hydrocephalus*; Fetal neuromuscular disease; Oligo-/polyhydramnios.

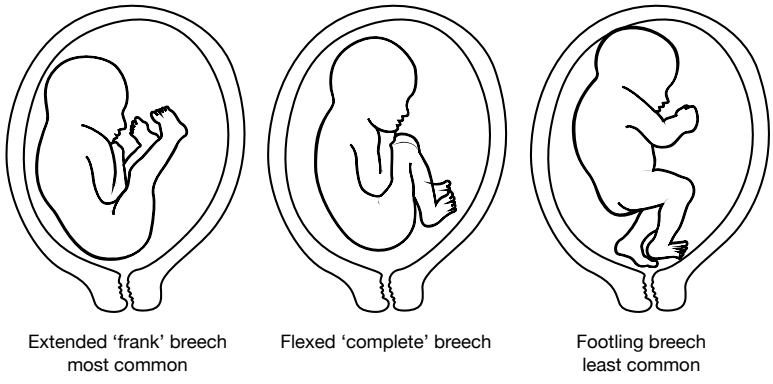


Figure. Types of breech presentations.

If a breech presentation is clinically suspected ***antenatally*** at or after 36 weeks, this should be confirmed by ultrasound scan. The management can be approached in an algorithmic manner (see Figure below).

ii) External cephalic version (ECV)

ECV is a relatively safe technique to convert breech presentation to cephalic. ECV is performed at 37 weeks or after at a specialized unit.

- CTG is done before and after the procedure;
- Anti-D administration is important if the woman is Rh D negative;

- Tocolytic agents (e.g. nifedipine) ↑ success rate of technique;
- With ultrasound guidance, the presenting breech is elevated manually over the pelvis and rotated to bring the fetal head down to the maternal pelvis (see Figure).

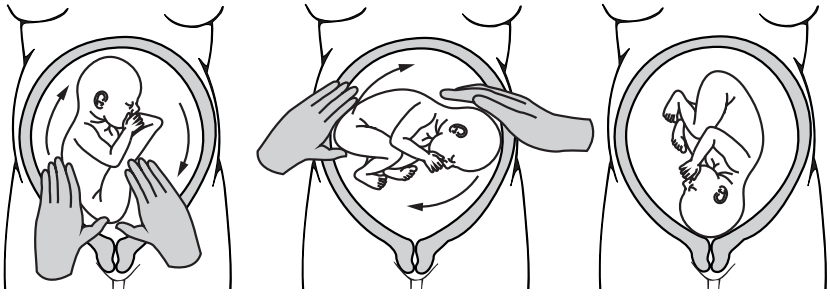


Figure. External cephalic version (ECV) technique illustration.

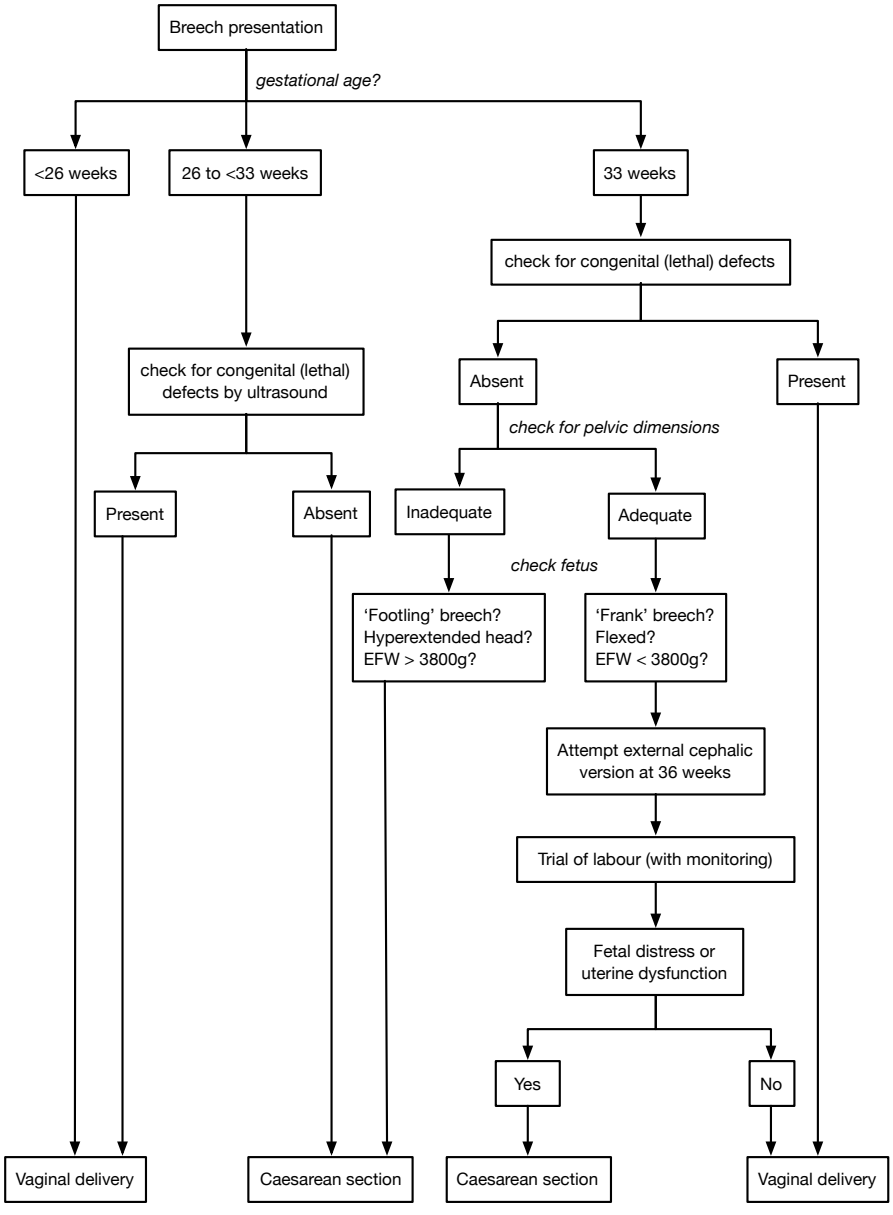


Figure. Antenatal management of breech presentations.

Table. Risk associated with, and contraindications to ECV.

Contraindications to ECV	Risks associated with ECV
Inadequate pelvic dimensions; Fetal abnormality (e.g. hydrocephalus); Placenta previa; Oligo-/polyhydramnios; History of antepartum haemorrhage; Previous C-section/myomectomy scar; Multiple gestation; Pre-eclampsia/hypertension.	Placental abruption; Premature rupture of membranes; Cord accident; Transplacental haemorrhage; Fetal bradycardia.

iii) Other fetal malpresentations

A **lie** is said to **unstable** if it is alternating between transverse, oblique and longitudinal. Any woman presenting at term with a transverse or oblique lie is at ↑ risk peripartum complications;

- ↑ risk of cord prolapse after spontaneous rupture of the membranes;
- ↑ risk of prolapse of hand, shoulder or foot once in labour.

These lies are often observed in multiparous individuals. Gentle version of the baby's head restores the presentation to cephalic in most cases especially if the uterus is lax.

(VIII) Post-term pregnancies

A pregnancy that has extended to or beyond 42 weeks' gestation is called a prolonged or post-term pregnancy. The cause is not known but it is associated with maternal and fetal complications.

Immediate induction of labour or delivery post-dates should be carried out if;

- ↓ amniotic fluid observed on scan;
- Fetal growth is reduced;
- There are reduced fetal movements;
- Changes observed on CTG;
- The mother is hypertensive or suffers a significant medical condition.

Perinatal mortality is ↑ (~ about 2 times) beyond 42 weeks. There is a higher likelihood of need for C-section even with induction of labor beyond 42 weeks.

(IX) Antepartum haemorrhage

Antepartum haemorrhage is defined as any vaginal bleeding occurring after 20th weeks till delivery of the baby.

Its causes include, but not limited to;

- Placental abruption— premature separation of placenta from the uterus;
- Placenta previa— placenta attached to the lower uterine segment;
- Vasa previa— fetal vessels traversing fetal membranes over the internal cervical os (see Figure);
- Vaginal trauma;
- Vaginal infection;
- Cervicitis;
- Cervical ectropion;
- Cervical carcinoma.

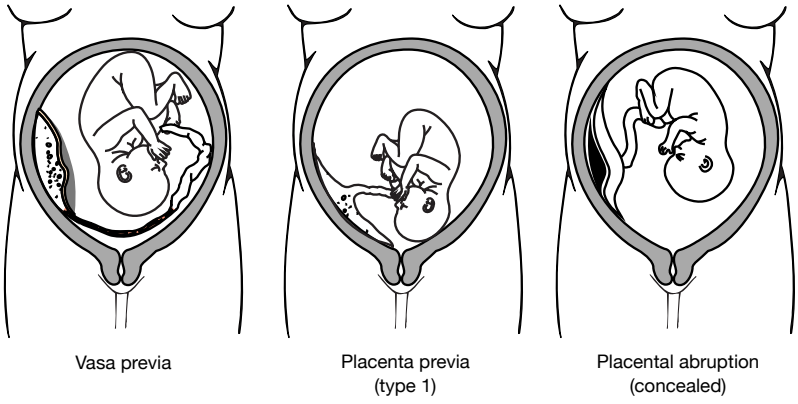


Figure. Illustration of vasa previa, placenta previa, and placental abruption.

Placental causes of antepartum haemorrhage are most important. These should be ruled out with relevant investigations as they pose a threat to the fetus as well as mother.

The first line investigations in such cases are CBC, clotting profile, ultrasound scan and CTG.

Management is centered around the aetiology;

- If the cause was a suspected placental abruption, the woman must be admitted for 48 hours as the risk of rebleeding is high within this time frame.
- Steroids should be administered if the gestation is < 34 weeks.
- If the mother is Rhesus negative, send for a Kleihauer test (see below) and administer anti-D.

(X) Rhesus isoimmunisation

The rhesus blood group system comprises of C, D, and E antigens. The presence or absence of D antigen characterizes an individual as Rh D positive or negative.

The rhesus blood grouping is important because it is most commonly associated with *haemolytic disease of the fetus and newborn (HDFN)*. **Both** *anti-C* and *anti-D antibodies* can cause HDFN but the latter is more common.

It is recommended to prevent maternal sensitization to RhD antigen by;

- Testing for maternal blood grouping at booking visit;
- Offering prophylactic IM anti-D administration at 28 ± 34 weeks routinely to Rh D negative individuals;
- Performing **Kleihauer test** to determine maternal exposure to fetal cells (because fetal cells resist denaturation by alcohol or acid) at ***all*** potentially sensitizing obstetric events (see Figure);
- Rhesus disease does not affect the first pregnancy as IgG antibodies can cross placenta but ***IgM can not*** (*see Figure below*).

Once sensitized, regular monitoring of antibody levels in subsequent pregnancies. Fetal hemolysis can occur if the IgG antibodies are in sufficient quantities in maternal circulation (see Table).

Table. Maternal anti-D levels and fetal risk prediction.

Anti-D level	**Outcome**	**Management**
< 4 IU/mL	HDFN unlikely	Monitor monthly
4-15 IU/mL	Moderate risk of HDFN	Monitor every 2 weeks
> 15 IU/mL	High risk of hydrops fetalis	Perform MCA Doppler velocimetry for *peak systolic velocity*.

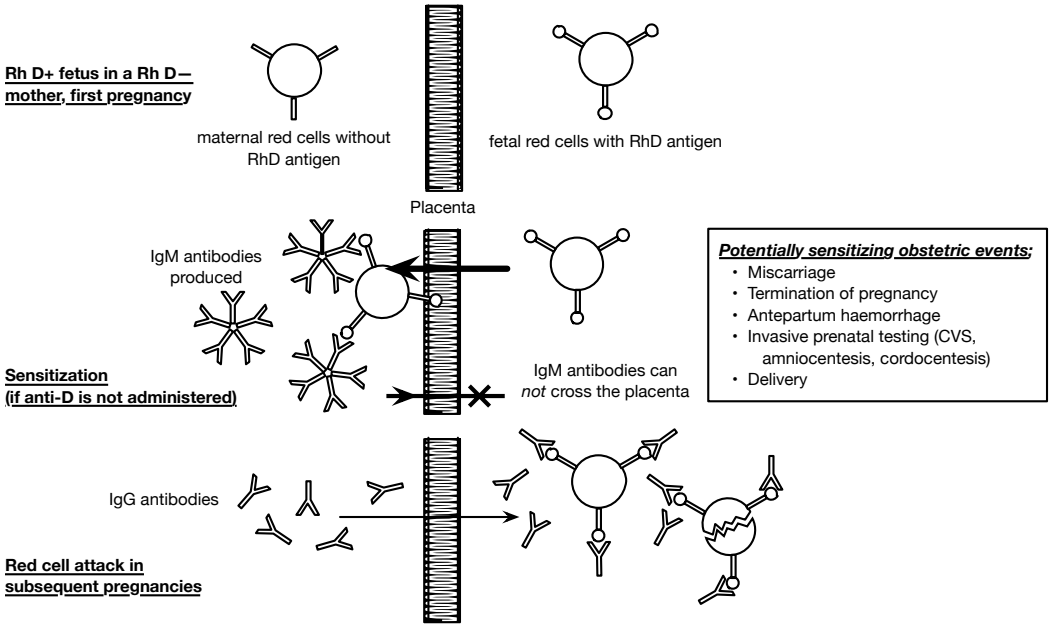


Figure. Rh isoimmunisation schematic.

Middle cerebral artery (MCA) Doppler velocimetry can detect fetal anemia if antibody levels are high. In complicated cases, delivery of the fetus or fetal blood transfusion depending on fetal maturity.

(XI) ABO isoimmunisation

ABO blood group isoimmunisation can also occur. Such is a case when the mother is blood group O and the fetus is blood group A, B, or AB.

Anti-A and Anti-B antibodies are present in the maternal circulation naturally, usually secondary to sensitization against A or B substances in food or bacteria. Because of this, ABO incompatibility can occur in a first pregnancy.

ABO incompatibility generally causes only mild haemolytic disease of the baby because;

- Most anti-A and anti-B antibodies are mainly IgM and do not cross the placenta.
- A and B antigens are not fully developed in the fetus.

(XII) Fetal anemia

Fetal anemia is a complication that is feared due to associated morbidity and mortality.

This can result from red cell alloimmunization or parvovirus infection. Parvovirus infection is an important cause and should be considered in all cases of non-immune hydrops.

In high-risk foetuses, it is recommended to check for signs of fetal anemia on ultrasound/Doppler to predict and prevent fetal hydrops (indicative of severe anemia). Previously used invasive tests are now obsolete.

Features of fetal anemia do not usually become evident until Hb level decreases by > 5g/dL from the mean for that gestational age. features are not obvious unless the fetal Hb is < 6 g/dL;

- Polyhydramnios;
- Enlarged fetal heart;
- Ascites and pericardial effusions;
- Hyperdynamic fetal circulation on Doppler (↑ peak systolic velocity on MCA Doppler velocimetry is highly sensitive for fetal anemia, see Figure);
- Reduced fetal movements;
- Abnormal CTG with reduced variability, eventually a '**sinusoidal**' pattern (see Figure).

Fetal flood transfusion is recommended in a severely anemic fetus that is premature for delivery;

- A sample to confirm the anemia is taken and fetal blood transfusion is carried out in a single prick;
- Blood for fetal transfusion can be administered into the umblical vein, intrahepatic vein, fetal heart or the peritoneal cavity;
- It is imperative to ensure that blood to be transfused **is**;
    - Densely packed (Hb usually around 30 g/dL, so that small volumes are used);
    - White cell depleted and irradiated (to reduce risk of graft-vs-host reaction);
    - Screened for infections including cytomegalovirus (CMV).

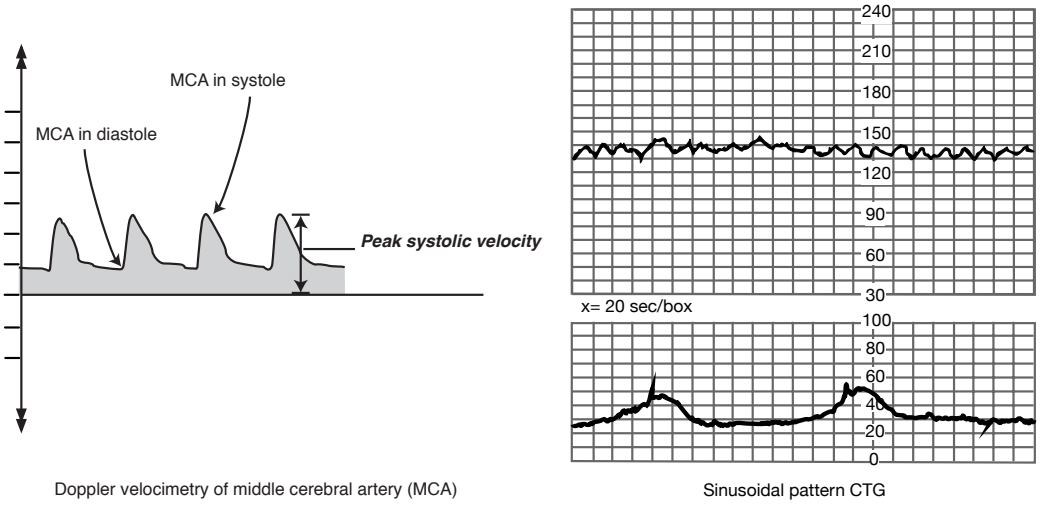


Figure. Illustrations— assessment of MCA on Doppler and sinusoidal pattern (~3 cycles/min) on CTG.

Postnatally, all babies born to Rhesus-negative women should have cord blood taken at delivery for CBC, blood grouping, indirect Coomb's test. Bilirubin levels can also be tested as an indirect measure of hemolysis.

CHAPTER 23 MULTIPLE PREGNANCY

(I) Twin pregnancy

Twins make up approx. 99% of multiple gestations. Pregnancies with three or more fetuses are referred to as '***higher multiples***'.

Increase in maternal age is associated with both— ↑ risk of chromosomal abnormalities and ↑ incidence of dizygotic twinning.

i) Classification

Depending on the age of the zygote at which it splits, there can be the different outcomes (see Figure);

- All monochorionic pregnancies are monozygotic;
- All dichorionic pregnancies are not dizygotic.

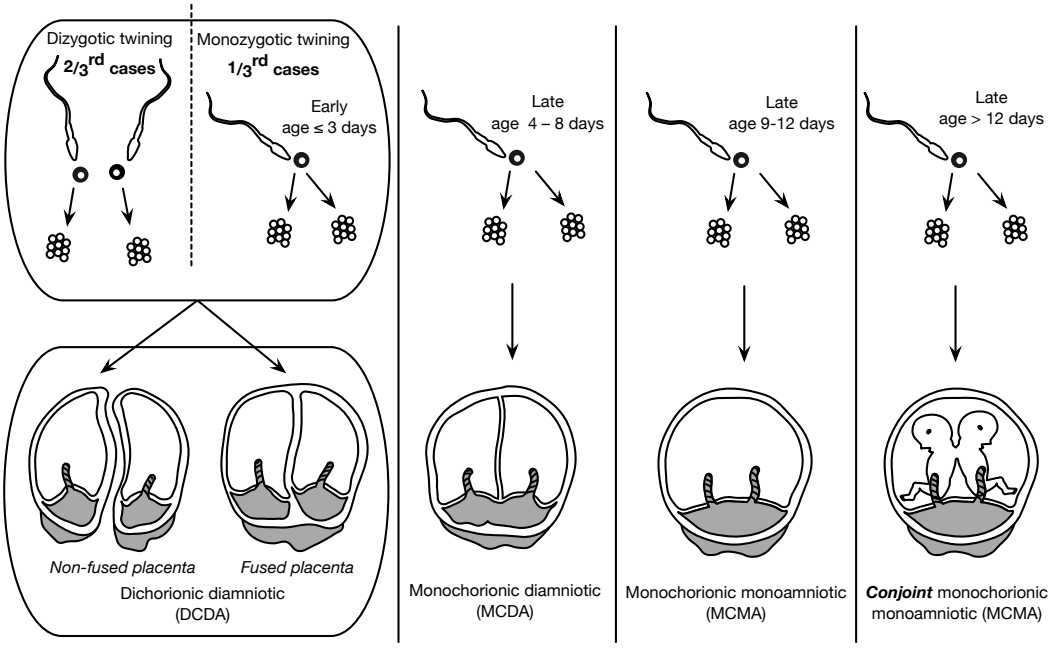


Figure. Twin pregnancy and potential outcomes.

ii) Antenatal care

a) Determination of chorionicity

In the antenatal care of twin or higher gestations, it is of significant importance to determine chorionicity. This can be done via ultrasound imaging.

Chorionicity is important to determine because twin/multiple pregnancy that shares a single placenta (~ monochorionic) are at an ↑ risk of complications and mortality.

The optimal gestation at which to perform this ultrasonic chorionicity determination is 9—10 weeks;

- A tongue of placental tissue is seen within the base of dichorionic membranes and has been termed the 'twin peak' or lambda sign;
- Dichorionic twins have a thick inter-twin separating membrane septum flanked on either side by a very thin amnion (see Figure). Monochorionic twins have a very thin inter-twin septum.

Dichorionicity may also be evident later in the gestation in the presence of different sex foetuses.

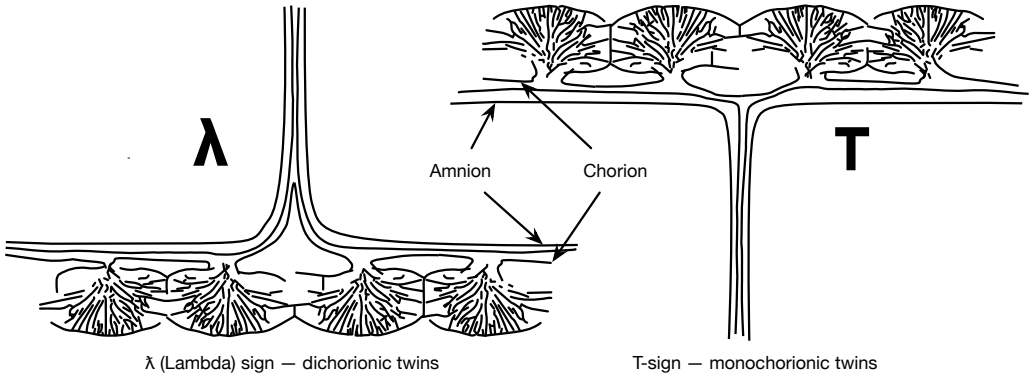


Figure. Illustration of ƛ (lambda) sign and T-sign. This can be observed on ultrasound scanning.

b) Detect fetal anomalies

Fetal screening for anomalies has optimal detection at ~20 weeks.

Maternal serum biochemistry for Down's syndrome may be of questionable value if there is multiple pregnancy. The test of choice here is by ***assessment of nuchal lucency***.

In dichorionic pregnancies, it is essential that both foetuses are sampled for karyotyping. Monochorionic twins are monozygotic and therefore only one sample is needed.

c) Fetal surveillance

Monitoring of fetal growth and well-being in twins is by ultrasound. SFH may be misleading in twin pregnancies.

It is imperative to seek features of TTTS in monochorionic twins actively. There may be discrepancy in fetal sizes, bladder volumes, amniotic fluid volumes and cardiac sizes.

d) Prevent preterm labor

Although, multiple pregnancy is associated with shorter gestational age at birth (vs. singleton pregnancies). It is important to identify pregnant women at higher risk of preterm labor.

Transvaginal cervical ultrasound is useful for *prediction* of very preterm delivery- may show shortening of cervix.

iii) Intrapartum care

- A specialized twin-CTG machine is recommended for use in monitoring during labor;
- Twins with vertex-vertex presentations are considered low-risk for vaginal delivery;
- If the second twin is breech (non-vertex), vaginal delivery can be considered safely;
    - External cephalic version can be successful in upto 70% cases if the lie is transverse to engage head of the second twin.
    - In experienced hands, internal podalic version can be undertaken if ECV is unsuccessful (see Figure). This allows for a trial of vaginal delivery.

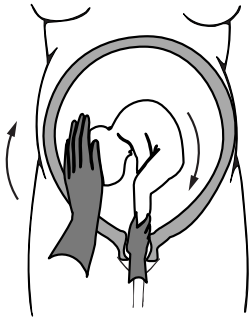


Figure. Illustration of internal podalic version— one hand enters the uterine cavity to hold both feet.

- If the first twin is breech, an elective C-section is recommended to minimize risks, including the 'locked-twin' phenomenon (see FIgure).

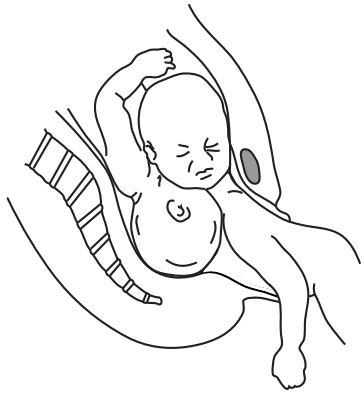


Figure. Illustration of locked-twin phenomenon. The chin of the first breech baby locks against the chin of the second cephalic twin.

iv) Complications

The risks of complications is relatively higher in individuals with twins or higher gestations, especially multiple gestations with monochorionic placentae;

- ↑ risk of miscarriage;
- ↑ risk of spontaneous preterm delivery before 37 weeks (monochorionic > dichorionic, see Figure);

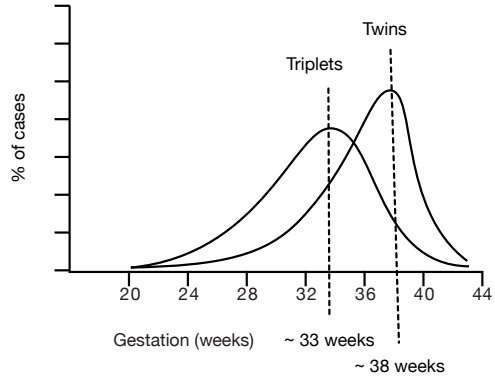


Figure. Gestational age at birth of twins and triplets with 95% CI.

- ↑ perinatal mortality rate (upto 5x times)— associated with preterm bith;
- ↑ risk of intrauterine death (IUD) of one of the twins. If this occurs, there is;
    - ↑ risk of maternal disseminated intravascular coagulation (DIC);
    - ↑ risk of early onset of labor triggered by death of one of the twins;
    - ↑ risk of neurodevelopmental complications— if monochorionic twins.
- ↑ risk of FGR (monochorionic > dichorionic);
- ↑ risk of structural anomalies (monochorionic > dichorionic).

Monochorionic twins share fetoplacental circulations through placental vascular anastomoses. Twin-to-twin transfusion syndrome (TTTS) is a complication unique to monochorionic twins;

- This can lead to oligohydramnios in donor twin (secondary to hypovolemia and ↓ urine output;
- Hypervolemia in the recipient twin— polyhydramnios, ↑ risk of myocardial damage and high output cardiac failure;

- Management of pregnancies complicated with TTTS is amniocentesis of fetus with polyhydramnios. This prolongs pregnancy and improves survival of foetuses. Other novel treatment options include fetoscopic guided laser coagulation of placental vessels.

Monoamniotic twins share a single amniotic cavity without a dividing membrane. This ↑ risk of cord accidents due to cord entanglement.

(II) Higher multiple pregnancy

- An increased rate of occurrence of higher multiple pregnancies has been observed since the introduction of assistive reproductive techniques.
- High multiple pregnancies are associated with ↑ risk miscarriage, perinatal mortality and congenital anomalies.
- The mean gestational age of higher multiple foetuses at birth is 33 weeks.
- Due to difficulty in intrapartum monitoring of all foetuses, C-section may be considered electively but is not recommended in all cases.
- Multi-fetal reduction is a procedure that in some cases may be of benefit.
    - The notion is to carry out ***selective*** iatrogenic fetal death of one of the fetuses by ultrasound-guided puncture of fetal heart and injection of potassium chloride.
    - If in consideration, it is usually delayed till 11-12 weeks gestation to allow for spontaneous reduction to occur if that is to occur. At this age, it is also possible to screen for major fetal anomalies and choromosomal defects.
    - Triplet pregnancies have a very high risk of extreme preterm delivery. Fetal reduction to twin pregnancy in these cases can improve outcome of the pregnancy.

-x-

CHAPTER 24 PLACENTATION AND RELATED DISORDERS

The placenta is a feto-maternal organ.

Pathology of early events of placental trophoblast cells invading the maternal uterine wall is of core importance in understanding clinical conditions.

Conditions associated frequently with impaired placentation include FGR, pre-eclampsia, and abruptio placenta.

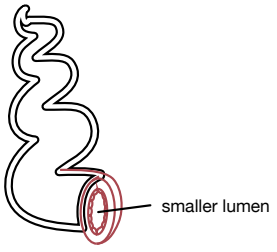
(I) The placenta

The functional unit of the placenta is the fetal cotyledon.

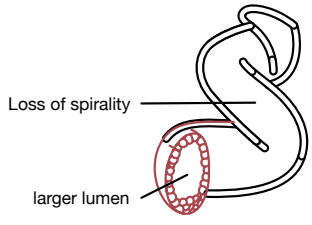
- The fetal cotyledons develop ***around*** the entries of the maternal spiral arteries from the decidual plate.
- Each cotyledon contains a primary villus stem arising from the chorionic plate and supplied by primary branches of fetal vessels.
- The terminal villi branch from the villus stems. This is where maternal–fetal exchange takes place as blood flows through the intercotyledon space.
- Maternal and fetal blood is separated by three microscopic tissue layers: trophoblastic tissue, connective tissue and the endothelium of the fetal capillaries.
- The mature human placenta has about 120 fetal cotyledons grouped into visible lobes.

The maternal blood flow to the placenta increases throughout the pregnancy.

- Trophoblast cells of the placenta keep invading the the spiral arterioles with increasing gestational age (upto 20 weeks) and replace the smooth muscle of the wall of the vessels (see Figure).
- This converts them to wide bore, low resistance, large capacitance vessels— capable of ↑ perfusion.



Spiral arteries of the uterus



Spiral arteries during pregnancy, transformation of the vessel-wall under influence of trophoblast cells

Figure. Illustration of transformation of spiral arteries of the uterus under the influence of trophoblastic tissue.

In cases of incomplete or partial trophoblast invasion of myometrial spiral arteries, there may be impaired perfusion of the fetoplacental unit;

- Affected placentae are observed to have gross morphological changes. These include **infarcts and basal hematomas;**
- A placenta with multiple infarcts is associated with FGR and risk of intrauterine fetal demise;
- Basal hematomas are a mass of blood in the centre of the fetal cotyledon due to rupture of a damaged spiral artery. These are associated with maternal hypertension and ↑ perinatal mortality.

(II) Pre-eclampsia

Pre-eclampsia is one of the leading causes of maternal death in developed countries.

Pre-eclampsia is defined as hypertension of at least 140/90 mmHg on ≥2 separate occasions and *at least* 4 hours apart and in the presence of at least 300 mg protein in a 24 hour collection of urine, arising *de novo* after the 20th week of pregnancy in a previously normotensive woman and resolving completely by the 6th postpartum week.

This differs from essential hypertension, in that it appears after 20 weeks gestation and, by definition, should resolve by 6th postpartum week.

Figure. Risk factors associated with pre-eclampsia.

Risk factors associated with pre-eclampsia
First-time mothers;
Multiparous with a previous history of pre-eclampsia;
Pre-eclampsia in a previous pregnancy;
10 years or more since last baby;
Age ≥ 40 years;
BMI ≥ 35;
Genetic predisposition in 1st degree relatives of affected women;
Diastolic blood pressure at booking visit: ≥ 80 mmHg;
Proteinuria observed in urinalysis at booking visit;
Multiple pregnancy;
Pre-existing hypertension;
Pre-existing renal disease;
Pre-existing diabetes;
Anti-phospholipid antibodies.

i) Aetiology

Although the mechanism is not very clear, but trophoblastic tissue has been implicated in studies;

- Inadequate invasion of the spiral arteries by trophoblasts and consequent uteroplacental ischemia can lead to placental infarcts and basal hematomas—seen in pre-eclampsia;
- Mediators of oxidative stress are released with continued ischemia, causing endothelial dysfunction, vasospasm and activation of coagulation system.

Because vascular endothelial cells are ubiquitous, pre-eclampsia affects multiple organ systems;

- Peripheral vasoconstriction and hypertension occurs. This combined with ↑ vascular permeability contributes to the formation of generalized oedema;
- In kidneys, ***glomeruloendotheliosis*** occurs— *a highly characteristic lesion*. Impaired glomerular filtration and proteinuria results;
- Fibrin levels and platelet counts are decreased as increasing amount of fibrin and platelets are utilized in the face of diffuse vascular damage. If this occurs in the liver, there can be elevation of liver enzymes. Together these events constitute the HELLP syndrome (hemolysis, elevation of liver enzymes, and low platelets)— a severe form of pre-eclampsia;
- The development of convulsions in a woman with pre-eclampsia *in the absence of any other identifiable cause* is defined as **eclampsia**. With *this hypertensive encephalopathy*, vasospasm, cerebral oedema, retinal hemorrhages, retinal exudates, and papilloedema are observed (unlike pre-eclampsia).

ii) Clinical features

Majority of women remain asymptomatic, but the classic symptoms, however, are frontal headache, visual disturbance, epigastric pain and edema;

- Hypertension may be mild or transiently absent in some cases;
- Progression to eclampsia is said to have occurred if convulsions occur.

Physical examination helps assessment of severe cases— ***hyperreflexia*** & ***clonus*** on neurological examination.

iii) Investigations

To diagnose and monitor the mother;

- 24 hours urine for protein— by diagnostic definition, has to have atleast 300mg of protein;
- Renal function tests with serum levels of creatinine and urea and electrolytes. Electrolytes and uric acid levels should also be measured;

- CBC— may show ↓ platelet count and ↑ haematocrit;
- Liver function tests— may show increasing trend of liver enzymes (especially with HELLP syndrome);
- Frequent repeat proteinuria quantification is probably unhelpful once a diagnosis of pre-eclampsia has been made.

Fetal assessment is preferably performed with both ultrasound and cardiotocography;

- Ultrasound for fetal size, amniotic fluid volume, maternal and fetal doppler scanning for abnormalities;
- Cardiotocography may show decelerations with fetal hypoxia/distress.

iv) Management

- There is no cure for pre-eclampsia. The notion of management here is to end the pregnancy by delivering the baby and placenta as soon as possible;
    - If the gestation is less than 34 weeks, ***maternal intramuscular steroids*** administration may be considered to reduce risk of neonatal respiratory distress syndrome;
    - Delivery in these cases, if chosen, is mostly via C-section. This is carried out under epidural anesthesia to help keep periprocedural blood pressure under control.
- If the gestation is premature, the management strategies are aimed at minimizing risk to the mother in order to permit continued fetal growth;
    - Labetalol (α- and β- receptors blocker) is recommended first line antihypertensive safe in pregnancy, and is available as both oral and IV forms (may not be considered if asthmatic);
    - Nifedipine is an oral calcium channel blocker with rapid onset of action. But it can sometimes cause severe headache *mimicking* worsening of condition;
    - Methyldopa— centrally acting antihypertensive safe in pregnancy. But only available as oral form, has slow onset of action and has side-effects like sedation and depression.
- Women diagnosed with pre-eclampsia need more frequent antenatal visits. Sometimes they may need to be admitted if clinical or lab assessment show severe features, especially with eclampsia.

Table. NICE guidelines for treatment of hypertension in pre-eclampsia.

	Mild (140/90 – 149/99)	**Moderate (150/100 – 159/109)**	**Severe (≥ 160/110)**
Admit to hospital	Yes	Yes	Yes
BP testing	Atleast 4 times/day	Atleast 4 times/day	> 4 times/day
Treat	No	With oral **labetalol** as 1st line (*if no asthma*)— Keep systolic BP <150; Keep diastolic BP between 80-100.	
Test for proteinuria	Do not repeat urine quantification of proteinuria		
Surveillance with blood tests	Check twice/week: renal function tests, electrolytes, CBC, transaminases, bilirubin.	Check thrice/week: renal function tests, electrolytes, CBC, transaminases, bilirubin.	
Only offer women with pre-eclampsia antihypertensive treatment other than labetalol after considering side-effect profiles for the woman, fetus and newborn baby. Alternatives include *methyldopa* and *nifedipine*.			

v) Complications

- The commonest cause of death in women who die of pre-eclampsia is cerebral bleeding secondary to uncontrolled systolic blood pressure.
- Eclampsia (= pre-eclampsia + convulsions)— maternal collapse may occur. Emergency management with an ABCDE structured approach should be carried out.
- HELLP syndrome is a feared complication;
    - It ia variant of pre-eclampsia with additional **h**emolysis, **e**levated **L**FTs and **l**ow **p**latelets;

- Affected individuals typically present with epigastric pain, nausea and vomiting. Hypertension may be absent in some cases;
- It is associated with a range of serious complications including acute renal failure, placental abruption and stillbirth;
- The management of HELLP syndrome involves stabilizing the mother, correcting any coagulation deficits and assessing the fetus for delivery.

vi) Screening and prevention

There is no screening test for pre-eclampsia.

In some cases, however, uterine artery doppler waveform analysis often shows a characteristic '**diastolic notch**' (see Figure). This has been associated with incomplete trophoblast remodelling of the spiral arteries.

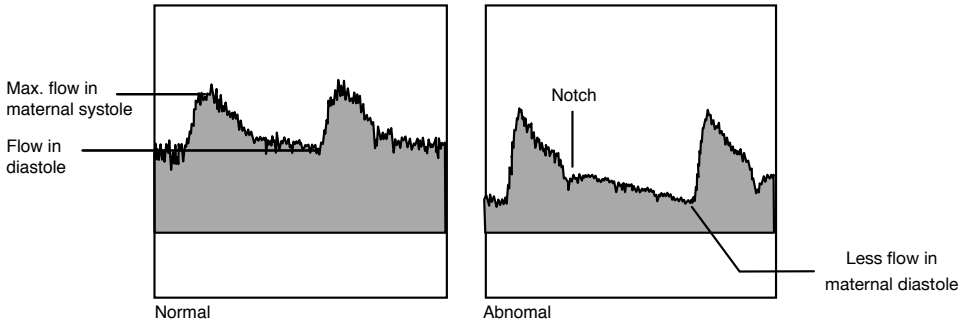


Figure. Doppler velocimetry of uterine artery— normal and ***'high-risk'*** diastolic notch.

Preventative measures may be considered in *high-risk* individuals (see Table: Risk factors associated with pre-eclampsia). These include;

- Low-dose daily 75mg aspirin orally;
- Calcium supplementation— but only in those with low dietary intake of calcium.

To prevent progression to eclampsia in severe-preeclampsia;

- Low threshold to administer magnesium sulphate as a preventive measure against pre-eclampsia;
- Magnesium sulphate is also the drug of choice for *treatment* of eclampsia;
  - A loading dose of 4 g is given followed by a maintenance infusion of 1 g/hour for 24 hours after delivery;
  - Magnesium sulphate has a narrow therapeutic range and overdose can cause respiratory depression and ultimately cardiac arrest;
  - 10 mL of 10% calcium gluconate IV slowly is an antidote to magnesium sulphate overdose.

(III) Fetal growth restriction (FGR)

Fetal growth restriction is defined as a failure of a fetus to achieve its genetic growth potential. This *results* in a small for gestational age (SGA) fetus, i.e. fetal weight < 10^{th} centile for its gestation.

It is important distinguish FGR from SGA, as most SGA foetuses may be so because of their genetic constitution. But FGR implies a pathological process restriction growth.

FGR is a major cause of neonatal and infant morbidity and mortality. There is also evidence that diabetes and hypertension are also more common in adults that were born with FGR.

i) Aetiology

The common causes of FGR can be classified into two main groups (see Table);

- Maternal under-nutrition is *globally* the major cause of FGR;
- In developed countries, the most common cause of FGR is poor placental function secondary to inadequate trophoblast invasion of the spiral arteries.

Table. Causes of fetal growth restriction.

Reduced fetal growth potential		Aneuploides, e.g. trisomy 18; Single gene defects (e.g. Seckel's syndrome); Structural abnormalities (e.g. renal agenesis); Intrauterine infections (e.g. cytomegalovirus, toxoplasmosis).
Reduced fetal growth support	*Maternal factors*	Under-nutrition, e.g. poverty, eating disorders; Maternal hypoxia e.g. living at altitude, cyanotic heart disease; Drugs, e.g. alcohol, cigarettes, cocaine.
	Placental factors	Reduced uteroplacental perfusion, e.g. inadequate trophoblast invasion, sickle cell disease, multiple gestation; Reduced fetoplacental perfusion, e.g. single umblical artery, twin-to-twin transfusion syndrome.

FGR is associated with certain maternal risk factors (see Table). These risk factors increase the suspicion of FGR as the cause if SGA is observed on surveillance testing.

Table. Pregnancies at-risk of FGR.

Multiple pregnancies; History of FGR in previous pregnancy; Current *heavy* smokers; Current drug users; Women with underlying medical conditions; • Hypertension; • Diabetes; • Antiphospholipid syndrome. Pregnancies where the SFH (symphysiofundal height) is less than expected.

ii) Pathophysiology

Based on fetal features, FGR can be classified as symmetrical or asymmetrical;

- Symmetrical FGR is associated with factors that directly impair fetal growth— e.g. chromosomal disorders and fetal infections;
- Asymmetrical FGR is classically associated with any condition that impairs uteroplacental function— ↓ oxygen transfer and excretion of CO_2;
    - In face of hypoxia, chemoreceptors trigger diversion of oxygenated blood away from liver, kidneys, and subcutaneous tissues towards the brain;
    - The result is an asymmetrical fetus with relative brain sparing, reduced abdominal girth and skin thickness. The vasoconstriction in the fetal kidneys also can result in impaired urine production and oligohydramnios.

iii) Investigations

Before FGR can be diagnosed, it is needed to establish that the fetus is SGA;

- The most precise method prenatally to detect SGA is ultrasound biometry of fetal parts ***serially at specified time intervals*** in the context of accurate fetal age;
- Due to limited resources, serial ultrasounds for SGA are preferably carried out in pregnancies at high risk for FGR (see Table: Pregnancies at risk of FGR).

When a diagnosis of SGA has been made, the next step is to clarify whether the baby is constitutionally small or has pathologic FGR;

- Ultrasound for fetal anomalies is performed to rule out fetal anomalies that may explain the smaller size.
- The suspicion of a fetal genetic defect remains high even if ultrasound shows normal fetal anatomy but

symmetrical *growth restriction* in the presence of a normal amniotic fluid volume. Useful tests here include CVS, amniocentesis, fetal karyotyping, doppler velocimetry etc.

Surveillance of the FGR fetus includes serial biometry and amniotic fluid volume measurement performed at no less than 2-weekly intervals. In addition, dynamic tests of fetal wellbeing in FGR foetuses include:

- ***Umbilical artery*** Doppler wave form analysis— absence or reversed flow of blood in the umbilical artery during fetal diastole *requires* delivery in the near future;
- Fetal cardiotocography.

iv) Management

There are no treatments for FGR related to uteroplacental insufficiency.

Management consists of stopping high-risk behaviors e.g. smoking, alcohol and drug abuse. Low-dose aspirin may have a role in the prevention of FGR in high-risk pregnancies but is as treatment of established cases.

When growth restriction is severe and the fetus is too immature to be delivered safely, bed rest in hospital is usually advised initially. Further management is individualized to the case and cause.

v) Prognosis

Prognosis of FGR varies with the pathologic cause;

- FGR secondary to congenital infection or chromosomal abnormality— depends on the abnormality and associated features;
- FGR secondary to uteroplacental insufficiency— prematurity at birth affects morbidity and mortality. However, long-term prognosis is good with ***'catch-up growth'*** *after delivery as feeding is established*;

vi) Complications

Chronic fetal hypoxia in FGR may eventually lead to fetal acidosis. These foetuses are especially at-risk from asphyxia in labour due to further compromise of the uteroplacental circulation by uterine contractions;

- Most babies suffer morbidity or mortality as a result of prematurity;
- A link has also been established between adult-onset hypertension and diabetes in FGR affected fetuses.

vii) New developments

Research has shown new developments in pre-eclampia;

- Placental growth factor (PIGF) levels inversely correlating with predicting adverse outcomes in women with pre-eclampsia. Lower levels of PIGF have a high sensitivity for predicting adverse outcomes.
- Sildenafil citrate has potential to increase uteroplacental circulation and perfusion, resulting in improved fetal growth as shown in research studies.

(IV) Placental abruption

Placental abruption is the premature separation of placenta from the uterine wall.

This results in bleeding from the site of separation and carries significant morbidity and mortality for both the mother and the fetus.

i) Aetiology

The aetiology is unknown in majority of cases. It is thought to be associated with defective trophoblastic invasion as is seen with pre-eclampsia and FGR.

Placental abruption can occur from precipitating risk factors in women (see Table).

Table. Risk factors for placental abruption.

Risk factors for placental abruption
Hypertension; Smoking; Trauma to abdomen; Cocaine use; Anticoagulant therapy; Uterine overdistention (Polyhydramnios, multiple pregnancy); FGR.

ii) Clinical features

The classical presentation is painful vaginal bleeding with tense rigid abdomen and uterine contractions (often close to term or in established labor). Fetal distress can also occur.

The bleeding in placental abruption, however, can manifest clinically in two ways; concealed or revealed vaginal bleeding in the mother (see Figure).

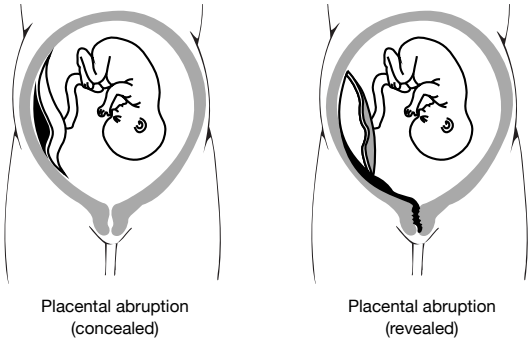


Figure. Types of bleeding in placental abruption.

Examination typically shows a tense, tender 'woody hard' uterus with difficulty palpating the fetus.

In severe cases of large abruptions, maternal shock or collapse can occur. Warning signs in such cases also include restlessness and distress, light-headedness, feeling cold and painful abdomen.

iii) Investigations

Because of variable presentation, the diagnosis is mainly clinical. Although ultrasound can demonstrate a retroplacental clot in concealed bleeding but is not a reliable diagnostic tool.

Other useful investigations include CBC, fetal cardiotocography (see Figure), amniotic fluid assessment, umblical artery doppler but these help in maternal and fetal assessment more so than in diagnosis.

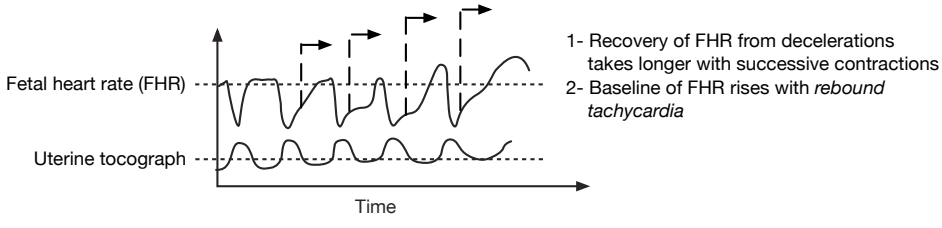


Figure. Suspicious signs of *fetal compromise* in cardiotocography.

iv) Management

A conservative approach to management may be taken in small degress of abruption. This includes hospital admission, bed rest, fetal and maternal monitoring, ultrasound and doppler scanning.

With severe cases, the decision may be weighed for the best possible outcome for baby and mother.

v) Complications

- Hypovolemic shock— if mother already has *underlying* hypertension, BP ↓ may be not be apparent in some cases. Central venous pressure monitoring is of value here as a better choice for assessment;
- Disseminated intravascular coagulation (DIC)— can occur as pathologically generalized activation of platelets unlike local activation to control bleeding;
- Acute renal failure— secondary to hypovolemia, and poor renal perfusion;
- Fetomaternal haemorrhage— in Rh D-negative mothers, a **Kleihauer test** is necessary to quantify feto-maternal haemorrhage so appropriate dose of anti-D can be given to prevent Rh isoimmunisation'
- Perinatal mortality;
- FGR— placental abruption can exacerbate pre-existing FGR.

(V) Placenta praevia

A placenta that lies implanted (partially or wholly) in the lower uterine segment is called placenta praevia.

Though such an implantation can be incidental, bleeding occurs when the lower uterine segment increases in length and resulting shearing forces between the trophoblast and maternal blood sinuses.

The risk factors for occurrence of placenta previa include;

- Multiple gestation;
- Previous C-section;
- Uterine structural anomaly;
- Assisted conception.

i) Classification

Placenta praevia is classified based on placental site as (see Figure);

- Complete placenta praevia— the placenta completely covers the internal os;
- Partial placenta praevia— the placenta covers a portion of the internal os;
- Marginal placenta praevia— the edge of placenta reaches the margin of the internal os;
- Low-lying placenta— the placenta is implanted in the lower uterine segment in close proximity but not extending to the internal os.

Previously placenta previa used to be classified into grades based on placental site (see Figure). Allocation to a particular grade may change. The degree of dilatation of the cervix at the time of assessment may alter a classification; what was type 1 at 2 cm dilatation may become type 2 at 4 or 5 cm.

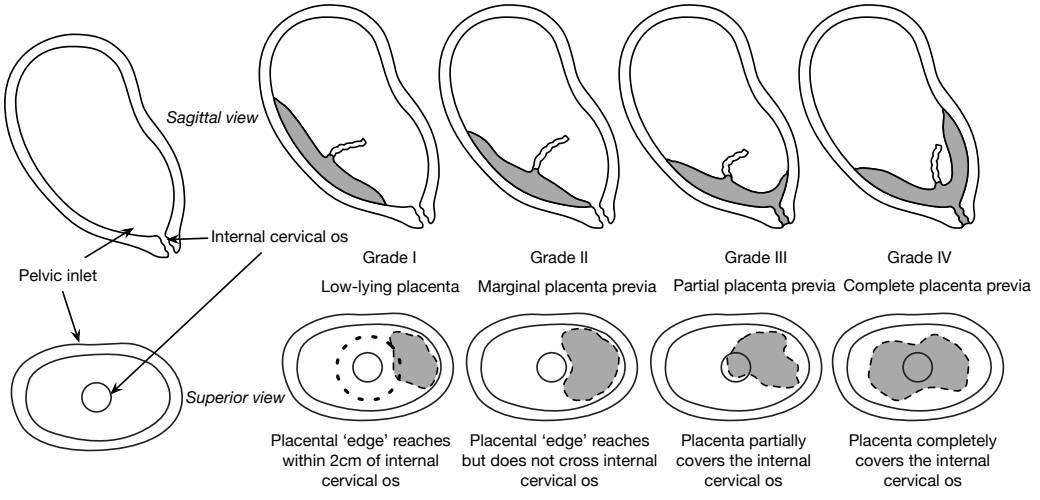


Figure. Placenta praevia and types.

ii) Clinical features

The 1st episode of bleeding occurs after 36th gestational week in upto 60% cases.

Classically, the vaginal bleeding is *painless*, causeless and often recurrent (see Table). The bleeding can be provoked (e.g. by per-vaginum examination).

Per-vaginal examination is therefore contraindicated (and can be performed if ultrasound rules out placenta praevia) as this may trigger more bleeding in a case of placenta praevia. Abdominal examination is needed to assess gestational age, lie etc.

Hemodynamic unstability (e.g. low BP, tachycardia) may point to severe bleeding, and transfusion may be required.

Table. Comparison of haemorrhage from placenta praevia with that from placental abruption.

Placenta praevia	**Placental abruption**
Painless	Painful
Patient is less distressed	Patient is distressed
Soft abdomen	Tender, tense abdomen
Abnormal lie and presentation	Normal lie and presentation
CTG usually normal	Abnormal CTG likely
No particular association with pre-eclampsia	May be associated with pre-eclampsia
No coagulation defect initially	Coagulation defect may occur early

iii) Investigations

- Ultrasound visualization of placenta remains the test of choice for diagnosis;
    - A limitation here is that a normally situated placenta may falsely appear to be a previa due to compression by a completely filled maternal bladder;
    - Therefore, it is suggested to have the bladder entirely emptied before this portion of the ultrasound scan is performed if placenta previa is a possibility.
- Hemoglobin level and cross-matching should be carried out— this helps as transfusion may be needed;
- Cardiotocography helps assess fetal activity.

iv) Management

In a non-emergency situation where ultrasound shows a low-implanted placenta, it is important to note lower uterine segment does not develop fully until late in 3rd trimester;

- Hence, a 'wait-and-watch-again' approach is taken if *a low-lying placenta* is noted in 2nd trimester scans;
- This repeat ultrasound can be done at ~ 34th week of gestation or earlier if vaginal bleeding occurs.

Materna condition should be stabilized in an acute emergency situation;

- It helps to quantify the amount of blood loss with gross assessment of clots in bleeding;
- Rest, intravenous fluids and blood transfusions as needed;
- Administration of sterioids to the mother may be considered for a premature fetus.

In cases of severe bleeding, urgent treatment to deliver the baby (and the placenta) is required, irrespective of the gestational age of the fetus. Other indications for delivery are;

- Gestational age reaching 37-38 weeks;
- A massive bleed > 1500mL, or;
- Continuing significant bleeding of lesser severity.

Delivery is by C-section in all but most minor forms of placenta praevia.

v) Complications

Placenta in the lower segment can obstruct engagement of the head and cause the lie to be non-longitudinal. There can be;

- Malpresentation;
- Preterm delivery;
- Preterm prelabor rupture of membranes.

The risk of excess bleeding is particularly great when the placenta is situated ***anteriorly***. Heavy bleeding can occur at any time and this can theoretically cause;

- Maternal collapse and hypovolemic shock— if bleeding can not be controlled despite use of oxytocics, compression by an intrauterine balloon may be considered;
- Hypoxia to the fetus, fetal morbidity and mortality;
- Post-*partum* haemorrhage— veins of the lower uterine segment are poorly supported by surrounding tissue. This makes such individuals at relatively higher risk for post-partum haemorrhage.

Fetomaternal haemorrhage— as for placental abruption needs to be assessed in Rh D-negative mothers by **Kleihauer test** and appropriate dose of anti-D given to prevent Rh isoimmunisation'.

(VI) Other variations

i) Vasa previa

Occurs when the fetal vessels to pass over the internal cervical os. It may be associated with;

- A velamentous insertion of umblical cord;
- Joining an accessory (succenturiate) placental lobe to the main disc of the placenta.

Classically, diagnosis is suspected when there is painless fresh vaginal bleeding accompanied with spontaneous or artificial rupture of the membranes.

- It occurs due to rupture of relatively less shielded fetal vessels traversing over the internal os;
- Vasa previa is associated with a very *high perinatal mortality* from **fetal blood loss**. Hence, an emergency C-section is considered promptly for alive foetuses.

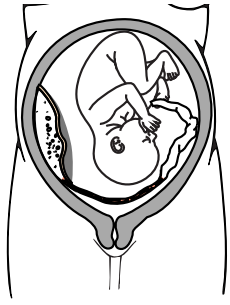


Figure. Illustration of vasa previa.

ii) Placenta accrete, increta and percreta

Haemorrhage can also occur during C-section when the placental bed may not contract or there may be morbid adherence, especially in a case of ***anterior placenta praevia over an old C-section scar***.

If placenta implants in a previous C-section scar, it may penetrate deeply into surrounding tissue (see Figure);

- Placenta accreta— placenta is abnormally adherent to the uterine wall;
- Placenta increta— placenta is abnormally invading into the uterine wall;
- Placenta percreta— placenta is invading through the uterine wall reaching upto surrounding structures.

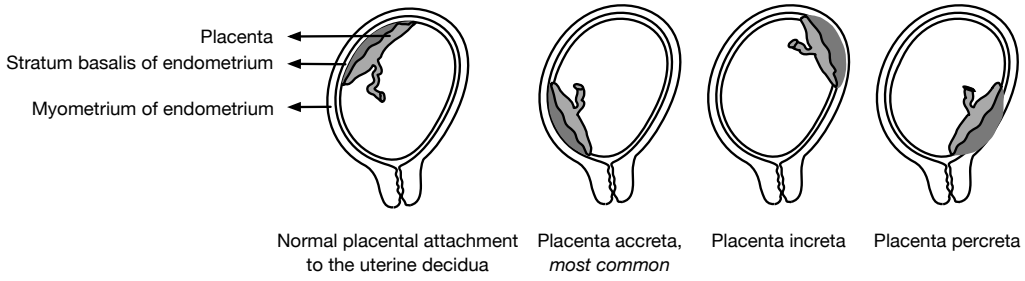


Figure. Illustration of normal placental attachment to uterus, placenta accrete, increta and percreta.

Risk of occurrence of such morbidly adherent placentae also ↑ with ↑ numbers of previous C-sections.

iii) Velamentous placenta

Occurs when blood vessels insert between the amnion and the chorion, away from the margin of the placenta, leaving the vessels largely unprotected and vulnerable to compression or injury.

iv) Succenturiate placenta

An extra lobe of the placenta that is implanted at some distance away from the rest of the placenta Fetal vessels may course between the two lobes, possibly over the cervix, leaving these blood vessels unprotected and at risk for rupture.

v) Circumvallate placenta

Occurs when the membranes double back over the edge of the placenta, forming a dense ring around the periphery of the placenta. Often considered a variant of placental abruption, it is a major cause of second-trimester haemorrhage.

CHAPTER 25 LATE MISCARRIAGE AND EARLY BIRTH

An age of 23 weeks' gestation is a grey zone for 'age of viability', as live births are only occasional at this age. A 'late' or second trimester miscarriage occurs between 12- and 23-weeks gestation.

(I) Preterm delivery

Instead of normal labor, there can premature events leading to late miscarriage or preterm delivery. These are preterm labor and preterm prelabor rupture of membranes (PPROM).

Preterm delivery (PTD) is defined as *birth before 37 weeks' gestational age*, but *after the age of viability*.

i) Classification

Based on aetiology, PTD can be categorized into;

- Spontaneous preterm labor (PTL)— upto 50% cases of PTD;
- Preterm premature rupture of membranes (PPROM);
- Delivery for maternal or fetal indications.

For reasons related to aetiology, outcome and recurrence risk, preterm births can also be divided into three gestational periods;

- Mildly preterm births at 32+0d to 36+6d weeks;
- Very preterm births at 28+0d to 31+6d weeks;
- Extremely preterm births at 24+0d to 27+6d weeks.

ii) Aetiology

Preterm birth is emphasized to be multifactorial in nature. There are genetic, environmental and other factors that are linked with its aetiology.

These risk factors associated with PTDs include (see Table);

- Intrauterine infections— subclinical or otherwise, of choriodecidual space and amniotic fluid;
- Uterine overdistention— this can be due to multiple pregnancy (*most common*), polyhydramnios, etc;
- Vascular disruption— any uteroplacental interface disturbance and consequent bleeding can irritate the uterus. This can potentially result in early uterine contractions and rupture of membranes;
- Intercurrent illnesses— e.g. pyelonephritis, appendicitis and pneumonia;
- Anatomical anomalies— uterine malformations, fibroids, *cervical incompetence*;
- Certain surgical procedures— amniocentesis, cordocentesis, LLETZ of cervix;

Table. Risk factors for preterm labour/PPROM.

Non-modifiable, major	**Non-modifiable, minor**	**Modifiable**
Last birth preterm; Twin pregnancy; Uterine abnormalities; Cervical abnormalities; Recurrent antepartum hemorrhage; Intercurrent illnesses; Surgical procedures.	Teenage or advanced old age; Teenager with 2nd or subsequent pregnancy; Parity— 0 or >5; Black ethnicity; Poor socioeconomic status; Un- or under-educated.	Smoking— 2x ↑ of PPROM; Drug abuse, e.g. cocaine; Underweight— BMI <20; Interpregnancy interval <1 year.

iii) Preterm labor

By definition, a labor at term refers to birth at gestational age from 37+0d to 41+6d weeks. While preterm labor (PTL) is the onset of *labor* before 37 weeks' gestation.

a) Clinical features

Women most commonly present with complains of abdominal pain ± pelvic pain ± contractions. There may be vaginal discharge.

Examination shows uterine tenderness. Per-vaginal examination or speculum examination aids in assessment of cervical dilatation. It can also reveal pooling of amniotic fluid, blood or abnormal discharge.

b) Investigations and diagnosis

Diagnois is centered around accurate assessment of gestational age. The criteria for diagnosis are;

- The gestational period is less than 36 completed weeks.
- Uterine contractions, preferably recorded on a tocograph, occur every 5–10 minutes, last for at least 30 seconds and persist for at least 60 minutes.
- The cervix is more than 2.5 cm dilated and more than 75% effaced.

Vaginal swab for fetal fibronectin (fFN) can be used as confirmatory test;

- Presence of fFN in cervicovaginal fluid between 22-36 weeks' has been shown to be a predictor of PTD.
- A negative test means it is very unlikely that the woman will deliver within 7 days ~ negative predictive value (NPV) approaches 100%;
- A positive test result can be if the woman has a vaginal infection, or had recent sexual intercourse, or vaginal examination.

Cervical length measurement by transvaginal ultrasound can also improve diagnostic accuracy. Significant cervical shortening is associated with preterm labour/delivery (see Figure).

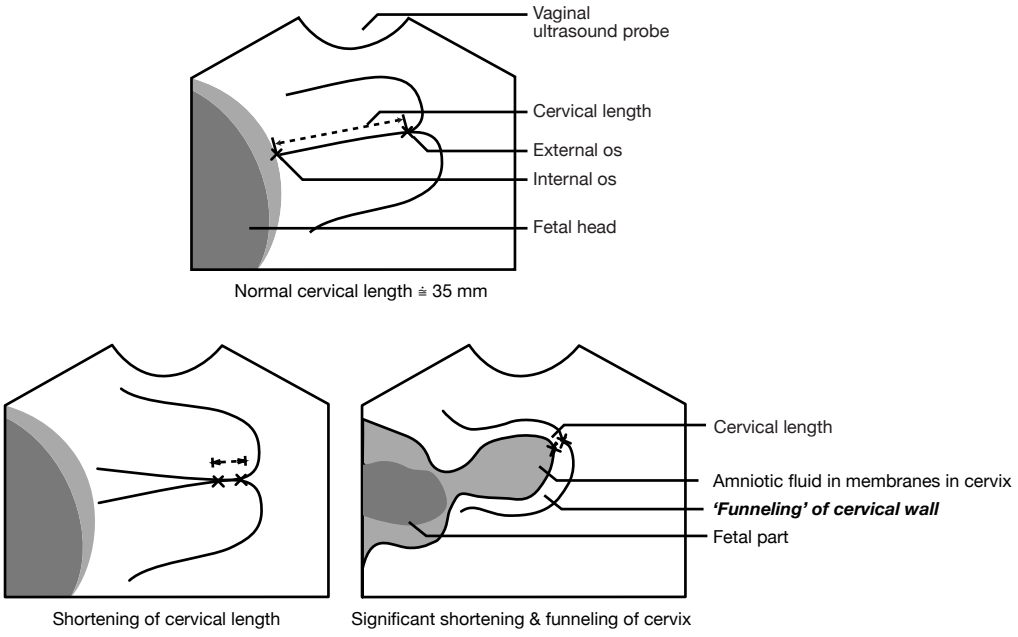


Figure. Illustration of normal, shortening and significant shortening of cervix on ultrasound.

c) Management

Given the preterm age of fetus, management of PTL is centered around achieving maximum fetal development before invasive management is carried out;

- Admission to hospital and bed rest;
- If fetus is <34 weeks' age— recommended to give 2 doses of 11.4 mg betamethasone q24h for fetal lung maturity and ↓ chance of intraventricular haemorrhage;
- The membranes should be kept intact, and when they rupture a vaginal examination is carried out to exclude a prolapsed cord.

If labour is established;

- Consider tocolytic therapy to delay delivery for atleast 24 hours for— steroid-induced lung maturation;
- Make sure neonatal ICU facilities are available.

The tocolytic drug of choice is **nifedipine** (calcium-channel blocker, CCB). Nitroglycerine or magnesium sulphate have not been shown to be effective tocolytic agents (see Table). While oxytocin antagonist **atosiban** is a new effective but expensive tocolytic.

Before starting tocolysis, make sure;

- Pregnancy is <34 weeks;
- Preterm labour has been confirmed;
- Cervix is <5 cm dilated (otherwise CCB and β-blockers are relatively ineffective at *tocolysis*);
- No evidence of abruptio placenta or chorioamnionitis;
- the fetus is alive and no potentially lethal malformations have been detected on ultrasound.

Table. Tocolytic agents in management of preterm labour.

Drug	**Dosages**	**Side-effects**
NIfedipine	20mg PO, then 10-20mg q8h to q6h daily upto 48 hours, adjusting according to uterine activity.	Headaches, hypotension, nausea, palpitations. *Less so than with β-agonists.*
Salbutamol (β-agonist)	Infused at 4 µg/min, ↑ by 4 µg/min q20min until uterine contractions suppressed; dose maintained for 6 hours and then reduced. Oral salbutamol started 8 mg q6hr for 5 days.	Tachycardia, palpitations, apprehension, anxiety, and ↑ in cardiac output.
Ritodrine (β-agonist)	Infused at 50 µg/min ↑ by 50 µg q10min until the contractions cease. Maximum dose 350 µg/min. Run for 24 hours then oral ritodrine 10–20 mg 2–6-hourly.	Hypokalaemia, pulmonary edema, fluid retention and myocardial ischaemia in 5% cases.

C-section in the management of preterm labour is controversial. If labour starts when the pregnancy is 26–31 weeks' gestation, caesarean section should be performed if;

- The fetus does not present cephalically;
- There is associated antepartum haemorrhage;
- The labour ails to progress normally;
- Fetal distress develops.

d) Complications

Early-onset neonatal sepsis, maternal postpartum endometritis and histological chorioamnionitis are significantly more common after preterm birth, particularly before 32 weeks;

Other neonatal complications associated with pre-term birth;

- Germinal matrix and intraventricular haemorrhage;
- Periventricular leukomalacia;
- Visual and auditory impairment.

e) Prevention

In addition to optimizing modifiable risk factors;

- Progesterone as a depot intramuscular injection or as pessaries reduces the recurrence fo preterm birth;
- Cervical cerclage increases the duration of pregnancy in women but only in ***diagnosed*** cases of cervical incompetence.

iv) Preterm prelabor rupture of membranes (PPROM)

PPROM is the spontaneous rupture of the fetal membranes before 37 completed weeks and *before labor onset*.

It is important to distinguish this with;

- Premature rupture of membranes (PROM)— rupture of fetal membranes before the onset of labor;
- *Prolonged* PROM refers to PROM > 24 hours and is associated with ↑ risk of intra-amniotic infection.

a) Clinical features

- Women classically present with a gush of clear fluid from the vagina, followed by leaking;
- As this event is *pre-labor*, uterine contractions are not a presenting symptom;
- On examination, fetal lie and presentation is checked. Though per-vaginal digital examination is not recommended but it is performed **if** the presentation is non-cephalic to rule out **cord prolapse**.

b) Investigations

The diagnosis of PPROM is mainly clinical through history and the demonstration of a pool of liquor in the vagina on speculum examination. Additional investigations of help here;

- **Nitrazine test**— an alkaline elevated pH of amniotic fluid in vagina (it is usually acidic) turns nitrazine stick black. Its use is, however, limited due to high false positives;
- CBC, CRP for maternal assessment;
- CTG for fetal well-being assessment— a persistent fetal tachycardia is suggestive of infection;
- Ultrasound to assess amniotic fluid— this may not be reduced as fetal urine production continues;
- Lower genital tract swabs— helpful in directing antibiotic therapy (in chorioamnionitis);
- Occasionally, amniocentesis with gram staining + culture/sensitivity may be used.

c) Management

Management of PPROM continues to be controversial;

- There appears to be shorter intervals between membrane rupture and preterm labour at *later* gestational ages— 'inverse relationship between gestational age and latency';
    - It is a norm to institute conservative management in PPROM before 34 weeks while induce labour relatively early if membrane rupture occurs after 37 weeks;
    - There is currently no good evidence as to what ideal management should be between 34 and 37 weeks.
- Conservative management should include clinical surveillance for signs of chorioamnionitis, including regular recording of maternal temperature and heart rate and CTG;
- The potential benefits of tocolytic drugs do not apply in the majority of cases of PPROM as there is time to administer steroids. Exaggerated use of tocolytics may ↑ risk of maternal and fetal infection.

To prevent infection, erythromycin is usually prescribed to women. The use of Amoxicillin/clavulanic acid is contraindicated as it ↑ risk of **neonatal necrotizing enterocolitis**.

d) Complications

- PPROM leads to PTD in most of the cases;
- Infections are common— chorioamnionitis (of fetus or placenta), or ***funisitis*** (of umblical cord). The onset of regular contractions and the establishment of preterm labour in cases of PPROM may be the first evidence of chorioamnionitis;
- Additionally, if PPROM occurs prior to 23 weeks' gestation, there may be neonatal pulmonary hypoplasia and postural deformities as there is loss of adequate amniotic fluid.

(II) Late miscarriage

Late miscarriage is a sequela of preterm events that do not lead to live birth. By definition, a 'late' or second

trimester miscarriage occurs between 12- and 23-weeks gestation.

It shares much of its typical features with miscarriages that occur early in pregnancies.

i) Aetiology of later miscarriages

The aetiological factors can be mainly grouped into two;

- Inability of uterus to hold pregnancy— e.g. congenital uterine abnormalities, cervical incompetence, submucosal fibroids.
- Poor placentatation/function— e.g. pre-eclampsia, autoimmune diseases.

Other entities that can also lead to late miscarriage;

- Syphilis infection;
- Hypothyroidism;
- Diabetes mellitus (esp. insulin-dependent);
- Iatrogenic— late miscarriage after an amniocentesis procedure.

ii) Clinical features

The presentation is similar to preterm events like PTL and PPROM. The distinct feature here is the rapid progression of events;

- There can be uterine cramping and bleeding;
- The membranes may be intact or ruptured;
- Backache, and increased vaginal discharge are also seen;

Examination should be performed to assess lie, presentation. Speculum examination to visualize the cervix is important— it may show dilatation and membranes bulging throught the external os.

Fetal heart auscultation by pinard stethoscope or doppler ultrasound may be considered.

iii) Investigations

Approach to investigations in late miscarriages is similar to that of PTL and PTD.

After 24 weeks, maternal steroid therapy can suppress both fetal activity and heart rate variability;

- A hand-held doppler may be preferred over pinard fetoscope for better auscultation of fetal heart;
- CTG assessment— has *no* role if the fetal age is pre-viability.

iv) Management

Acute management of late miscarriages is individualized— there may be acute maternal or fetal compromise;

- In some cases, it may be more appropriate to hasten delivery. This can be because of maternal and fetal risks or the 'late miscarriage' appears inevitable;
    - Before 24 weeks, induce contractions with gemeprost or misoprostol;
    - After 24 weeks induction with milder prostaglandins or conventional-dose oxytocin can be considered as an alternative to a planned C-section.
- Delay in ending pregnancy in cases complicated with chorioamnionitis may lead to worsening infection and complications. Augmenting labour may be the most appropriate management.

With a late miscarriage, vaginal delivery will almost always occur, even if there is a transverse lie or fetal malformation— due to small size of the fetus;

- Hence, C-section is usually not performed for fetal indications below 26 weeks of age;
- However, safety of preterm *breech* vaginal delivery is questioned, and C-section commonly performed;
- For C-section performed at the early gestations or if there is oligohydramnios— a vertical incision is often used. This is because the lower uterine segment is often poorly formed, but this incision carries an ↑ risk of uterine rupture in subsequent pregnancies.

The management of structural abnormalities may be delayed, and surgical team be involved;

- Uterine anomalies can be diagnosed on radiology e.g. hysterosalpingography;
- Hysteroscopic removal of submucosal fibroids may be considered;
- Tranvaginal cervical cerclage is a surgical procedure to provide structural support to a weakened cervix. It may be performed if;
    - History of multiple midtrimester (2nd) losses or PTDs— **history-indicated cerclage**;
    - Cervix shortens (usually <25 mm) after cervical surgery or previous preterm birth— **ultrasound-indicated cerclage**;
    - The cervix is dilating in the absence of contractions— **rescue cerclage**.

Cervical cerclage does not appear to reduce the risk of PTD in multiple pregnancies. The different types of cerclage are described (see Table and Figure).

Table. Types of cerclage.

McDonald transvaginal cerclage	Transvaginal purse-string suture inserted at the cervico-vaginal junction without bladder mobilization.
Shirodkar (high transvaginal) cerclage	Transvaginal purse-string suture inserted following bladder mobilization, to allow insertion above the level of cardinal ligaments.
Transabdominal cerclage	Suture inserted at the cervicoisthmic junction via laparotomy or laparoscopy. Transabdominal cerclages can either be inserted preconceptionally or in the 1st trimester.

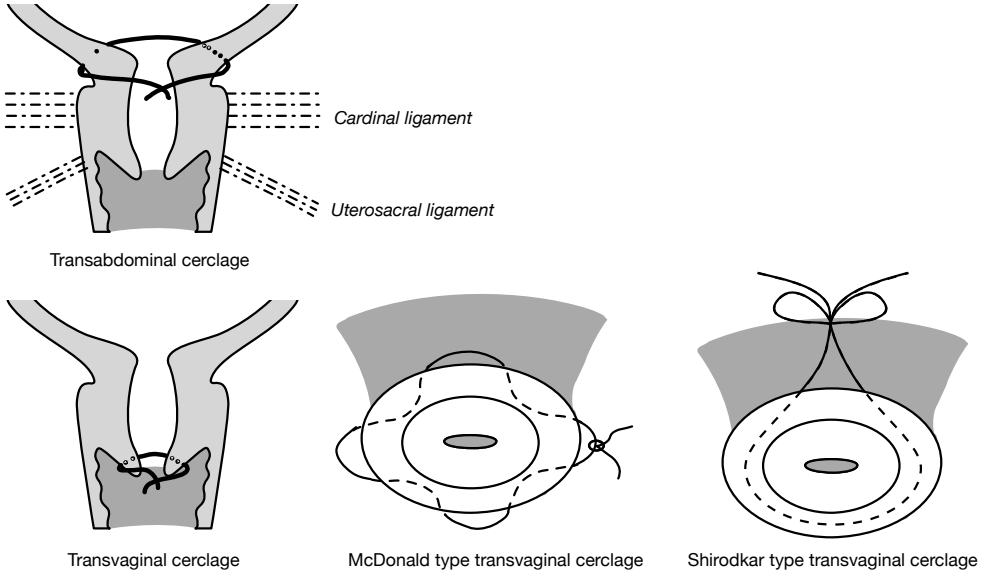


Figure. Cervical cerclage— types.

v) Complications

- Late miscarriages are associated with complications associated with blood loss, and post-miscarriage infections;
- Retention of placenta or part of it is also more common under these circumstances, and manual removal under anaesthetic may be required.

vi) Prevention

Becaue late miscarriages are commonly associated with conditions which can lead to recurrent losses, investigations to determine the cause should be done after one loss, especially if it is in the late 2nd trimester.

Investigations commonly used for this purpose include, but not limited to;

- Serology for syphilis;
- Lupus anticoagulant;
- Antinuclear factor, and;
- Hysterosonography.

-x-

CHAPTER 26 MEDICAL COMPLICATIONS IN PREGNANCY

Pre-existing medical problems can often pose complex management issues in pregnancy. It is, therefore, important to be aware of diseases and their management frequently encountered during pregnancies.

(I) Renal diseasae

i) Chronic Kidney Disease (CKD)

Renal adaptations in response to pregnancy are affected in women with chronic kidney disease (CKD).

CKD is classified into 5 stages based on level of renal function by estimated glomerular filtration rate (eGFR).

Prepregnancy counselling is recommended in all women with CKD about;

- Safe contraception until pregnancy;
- Fertility issues;
- Genetic counselling if inherited disorder;
- Risks to mother and fetus during pregnancy;
- Avoid known teratogens and contraindicated drugs;
- Treatment of blood pressure and adjustment of antihypertensives;
- Low-dose aspirin;
- Need for anticoagulation once pregnant in women with ***significant proteinuria***;
- Need for compliance with strict surveillance;
- Likelihood of prolonged admission or early delivery;
- Possibility of accelerated decline in maternal renal function;
- Need for postpartum followup.

Table. CKD stages, their effects on pregnancy and vice-versa.

CKD Stages	**Pregnancy on CKD**	**CKD on pregnancy**
Stage 1— GFR >90 Stage 2— GFR 60-89	Usually uneventful with renal outcome.	↑ incidence of FGR, preterm delivery and need for C-section to deliver.
Stage 3— GFR 30-59 Stage 4— GFR 15-29 Stage 5— <15 or dialysis	Accelerated decline of renal function especially with super-imposed pre-eclampsia, NSAIDs use, or post-partum haemorrhage.	

In pregnant women with CKD, it is recommended to monitor them with;

- Blood pressure surveillance;
- Renal function assessment by creatinine levels;
- Urine for infection/proteinuria;
- Haemoglobin and ferritin levels;
- Fetal ultrasound for anatomy, anomalies, growth and uterine artery doppler at 20-24 weeks.

If a patient with CKD stage 5 on dialysis gets pregnant. The Dialysis duration and UF must be adjusted accordingly to allow for physiological changes of pregnancy.

ii) Renal transplant recipients

Conception is observed in 2-10% of female renal transplant recipients;

- Tacrolimus, azathioprine, ciclosporin and prednisolone are generally considered safe in pregnancy and can be continued during breast-feeding;

- Screening for gestational diabetes (GDM) is necessary if prednisolone or **tacrolimus** are being used;
- Use of mycophenolate and sirolimus should be avoided in transplant recipients considering pregnancy and switch to alternatives atleast 3–6 months' prior.

(II) Diabetes mellitus (DM)

There are three scenarios for occurrence of diabetes in pregnancy;

- Individuals that have type 1 DM from before pregnancy;
- Individuals that have type 2 DM from before pregnancy;
- Individuals that develop gestational diabetes mellitus (GDM) during pregnancy.

Pre-pregnancy, women are counselled to achieve best possible glycemic control;

- Optimize glycemic control to achieve HbA_{1C} < 42 mmol/mol;
- High dose (5mg) folic acid to ↓ risk of neural tybe defects;
- Switch other medications that may be teratogenic, e.g. statins, ACE inhibitors.

Targets for therapy prepregnancy are premeal glucose levels of 4–7 mmol/l (i.e. ~ 72mg/dL to 126mg/dL). Poor glycemic control is associated with ↑ risk of;

- Congenital anomalies—
    - Neural tube defects, and cardiac anomalies— the fetal anomaly scan should focus on *cardiac outflow tracts* in these cases;
    - ↑ incidence of fetal macrosomia → subsequent shoulder dystocia and traumatic birth.
- High levels of HBA_{1C} in early pregnancy correlate with risk of early fetal loss. In contrast, there also an ↑ risk of late miscarriage/stillbirth;
- ↑ risk of worsening of diabetic retinopathy in mother antenatally and post-partum.

In general, *however*, ***maternal morbidity*** in diabetic pregnancies is related to;

- Diabetic-related vascular disease preceding pregnancy → pre-eclampsia;
- Severe hyperglycemia, or diabetic ketoacidosis.

Blood glucose monitoring is encouraged 7 times a day (before and 1 hour after meals) with targets of <5.3 mmol/l and 1-hour postprandial levels of <7.8 mmol/l.

All women should be assessed at booking for risk factors for *gestational diabetes*. This *targeted* screening helps detect previously undiagnosed type 2 diabetes and gestational diabetes;

- BMI above 30 kg/m^2;
- Previous baby weighing 4.5 kg, or above;
- Previous gestational diabetes;
- First-degree relative with diabetes;
- Family origin from high prevalence area (South Asian, black Caribbean and Middle Eastern).

If risk factors are positive, the woman should be offered testing with a glucose challenge test or more *comprehensive but longer* glucose tolerance test;

- 2-hour 75 g oral glucose tolerance test (OGTT) at 24–28 weeks gestation;
- A previous history of gestational diabetes should prompt glucose monitoring, or an OGTT, **at 16–18 weeks**. If these results are normal, the test should be **repeated at 24–28 weeks**.
- UK National Institute for Health and Care Excellence (NICE) guidelines (2015) recommend a diagnosis of GDM with a fasting glucose ≥5.6 mmol/l and/or a 2 hour (post-75 g glucose load) of ≥ 7.8 mmol/l;
- The WHO guidelines (2013) recommend a diagnosis with a fasting glucose of 5.1 mmol/l and/or a 1 hour (post 75 g glucose load) of 10.0 mmol/l or 2 hour of 8.5 mmol/l.

Table. WHO/IADPSG recommendations for diagnostic criteria for diabetes in pregnancy.

Diabetes mellitus
Fasting blood glucose ≥ 7.0 mmol/L (126 mg/dL); 2-hour post 75g oral glucose load ≥ 11.1 mmol/L (200 mg/dL); Random blood glucose ≥ 11.1 mmol/L (200 mg/dL) in presence of diabetes symptoms.
Gestational diabetes mellitus
2-hour and 75g OGTT after overnight fast, one or more of: Fasting blood glucose 5.1-6.9 mmol/L (92-125 mg/dL); 1-hour ≥ 10.0 mmol/L (180 mg/dL); 2-hour 8.5-11.0 mmol/L (153-199 mg/dL).

Management pearls—

- Insulin resistance increases during pregnancy and ↑ dosages are required in the 2nd half of pregnancy;
- In an uneventful pregnancy, the aim would be to achieve a vaginal delivery at 38-39 weeks;
- For women with type 1 diabetes and those with type 2 diabetes requiring insulin, a sliding scale of insulin and glucose should be commenced in labour, and maternal blood glucose levels maintained at 4–7 mmol/l to reduce risk of neonatal hypoglycaemia;
- Insulin requirements return to prepregnancy levels immediately post-partum and medications should be adjusted as there is ↑ risk of hypoglycaemia in the postnatal period.

Poor pregnancy outcome	**Effects of pregnancy on diabetes**	**Effects of diabetes on pregnancy**
Maternal social depriviation; No folic acid intake prepregnancy; Suboptimal— • Management of diabetes; • Preconception care; • Glycemic control *at any stage*; • Antenatal care; • Fetal surveillance of big babies.	Nausea and vomiting, particularly in early pregnancy may need medication adjustment. ↑ in insulin dose requirements in the second half of pregnancy. Increased risk of severe hypoglycaemia. Risk of worsening of pre-existing ***retinopathy*** and ***nephropathy***.	Increased risk of miscarriage. Risk of congenital malformation. Risk of macrosomia. Increased risk of pre-eclampsia. Increased risk of stillbirth. Increased risk of infection. Increased operative delivery rate.

Recommendations—

- All women with diabetes should be offered low-dose aspirin from 12 weeks' gestation to reduce the risk of pre-eclampsia;
- Women at risk of progression of diabetic retinopathy should be kept under careful surveillance— retinal screening at booking, 16–20 weeks' and 28 weeks' gestation;
- Maintain capillary blood (fingerprick) glucose levels <5.3 mmol/l before meals and postprandial levels <7.8 mmol/l 1 hour after meals. Women unable to achieve this with diet and lifestyle are treated with metformin and/or insulin as necessary;
- Individuals affected gestational diabetes should be followed to rule out type-2 diabetes after pregnancy. This screening can be done with **fasting glucose level** or **HBA_{1c}** at 6-13 weeks post-partum.

(III) Other endocrine disorders

i) Thyroid disease

New presentations of thyroid disease can be difficult to detect during pregnancy.

Due to changes in levels of binding proteins (see Figure), total T and T are not used for evaluation. Free thyroxine-4, free thyroxine-3 and thyroid-stimulating hormone (TSH) should be used **instead** for assessing thyroid function.

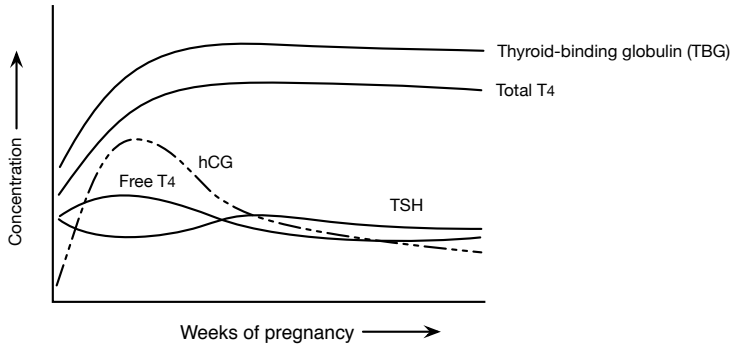


Figure. Graph illustration of changes in thyroid hormones and thyroid-binding proteins with pregnancy.

During pregnancy, there is ↑ in hepatic production of thyroxine- binding globulin (TBG) and placental chorionic gonadotropin (hCG). hCG has thyrotropin-like activity and stimulates maternal T4 secretion.

a) Hypothyroidism

The most common cause of hypothyroidism *worldwide* is iodine deficiency but in *developed world* Hashimoto's thyroiditis is more common;

- Women with hypothyroidism should continue thyroid replacement therapy during pregnancy to keep TSH <4 mmol/l;
- Thyroid function tests should be performed serially in each trimester for surveillance;
- Maternal T4 levels adequacy is **most important** in 1st trimester, failing which is associated with developmental delay and pregnancy loss in some studies.

b) Hyperthyroidism

This can occur secondary to autoimmune thyroiditis— Graves' disease, or other causes: toxic adenoma, subacute thyroiditis and toxic multinodular goitre;

- Affected women usually present with tremor, sweating, insomnia, hyperactivity and anxiety;
- On examination, goitre, Graves' ophthalmopathy, tachycardia, hypertension with a wide pulse pressure, weight loss and pretibial myxoedema may be observed;
- Treatment during pregnancy should be drug therapy, aiming to maintain maternal fT_3 and fT_4 levels in the high/normal range;
- Therapy with β-blockers for symptoms and carbimazole or propylthiouracil (PTU) using the lowest acceptable doses can be done during pregnancy;
    - Both drugs can also cause agranulocytosis, therefore regular checks of **maternal white cell count** are necessary;
    - Radioactive iodine is contraindicated during pregnancy.
- Thyroid surgery may rarely be considered if a retrosternal goitre is causing upper airways obstruction due to tracheal compression, or if there is a suspicion of malignancy or failed medical therapy;
- Uncontrolled thyrotoxicosis is associated with increased risks of miscarriage, preterm delivery and FGR.

Graves disease in some cases can have maternal high levels of anti-TSH-receptor *antibodies*. These are IgG antibodies and can cross the placenta. After birth, these neonates should be assessed for thyroid dysfunction.

c) Thyroid storm

A thyroid storm is a life-threatening event that arises in those with underlying thyroid disease and can be fatal in 20–50% of untreated cases.

It is usually seen with undertreatment of hyperthyroidism or infections.

Features include excessive sweating, pyrexia, tachycardia, atrial fibrillation, hypertension, hyperglycaemia, vomiting, agitation and cardiac failure. The diagnosis is made on clinical grounds with laboratory confirmation of hyperthyroidism.

Treatment is with PTU and high-dose corticosteroids, while beta-blockers are used to block the peripheral effect of thyroxine and supportive care with rehydration is also required.

ii) Parathyroid disease

a) Hyperparathyroidism

Hyperparathyroidism is caused by parathyroid adenomas (more common) or hyperplasia.

Due to ↑ levels of PTH, hyperparathyroidism manifests as hypercalcaemia and its associated features. The risks to the mother are from hypercalcaemic crises and complications such as acute pancreatitis, while fetal risks include ↑ rate of miscarriages, IUD, preterm labour and neonatal tetany in untreated cases.

If suspected in pregnancy, parathyroidectomy may be indicated in severe cases, but mild cases are managed conservatively through hydration and a low calcium diet.

b) Hypoparathyroidism

Hypoparathyroidism most commonly is an iatrogenic sequela of thyroid surgery. It can, however, also occur as part of autoimmune destruction of parathyroid gland.

It is diagnosed by finding ↓ serum calcium (corrected) and ↓ PTH levels and if untreated, it is associated with ↑ risks of 2nd trimester miscarriage and fetal hypocalcaemia— can lead to neonatal rickets.

The aim of treatment is to maintain normocalcemia through vitamin D and oral calcium supplements, with regular monitoring of calcium and albumin levels during pregnancy.

iii) Pituitary gland disorders

The pituitary gland enlarges by 50% during pregnancy.

If the pituitary gland has a functioning adenoma secreting prolactin, this may affect fertility drastically. Such *subfertility* is the reason, these pituitary tumors are often detected early.

There can be microadenomas or macroadenomas within the pituitary gland pre-pregnancy;

- Microadenomas do not cause symptoms unlike macroadenomas which often become symptomatic during pregnancy;
- A microadenoma is ≤ 10 mm, and a macroadenoma is > 10 mm.

These symptoms include headaches, visual field changes and MRI scanning can be used for evaluation. *Prolactin levels* are less useful because of normal increases during pregnancy.

Management of these pituitary gland disorders—

- Treatment for microadenomas is usually with bromocriptine or cabergoline (a dopamine agonist and prolactin inhibitor). It is highly effective in reducing size and restores ovulation. It is safe in pregnancy;
- For macroadenomas or non-responding microadenomas, a surgical approach for research is considered, preferably before pregnancy.

iv) Adrenal disease

Although rare, but adrenal hormonal disorders can be encountered in pregnancy.

a) Cushing's syndrome

Cushings syndrome is characterized by ↑ glucocorticoid production. It can be iatrogenic or endogenous hypersecretion of cortisol. "Cushings ***disease***" refers to hypercortisolism secondary to pituitary ACTH hypersecretion.

Cushing's syndrome is rare in pregnancy as most affected women are infertile due to feedback gonadal-axis blockade. But there is ↑ incidence of pre-eclampsia, preterm delivery and stillbirth.

- Diagnosis is difficult as symptoms mimic normal changes in pregnancy– striae, weight gain, weakness, glucose intolerance. Hypertension is a notorious feature of hypercortisolism.
- Plasma cortisol levels should be measured (although levels increase in pregnancy) and adrenal imaging with ultrasound, or MRI should be used.

b) Addison's disease

Addison's disease or *adrenal insufficiency*, most commonly, results from autoimmune adrenalitis. Individuals present with exhaustion, nausea, hypotension, hypoglycaemia and weight loss.

If untreated, Addison's disease carries a high maternal mortality rate. In autoimmune adrenalitis, antibodies can cross placenta but neonatal adrenal insufficiency secondary to maternal Addison's disease is very rare;

- When making diagnosis, it is important to adjust reference values for pregnancy. Compensatory ↑ in cortisol binding proteins can also mislead in accurate estimation of cortisol levels;
- Replacement steroids (hydrocortisone and fludrocortisone) should be continued in pregnancy and ↑ at times of stress such as hyperemesis and delivery;
- In diagnosed and adequately treated patients, the pregnancy usually continues normally.

c) Phaeochromocytoma

Phaeochromocytoma is a rare catecholamine-producing tumour.

This tumor arises from adrenal medulla in 90% of cases. It is notorious for its characteristic feature of *paroxysmal hypertension;*

- Maternal and perinatal mortality is greatly ↑, especially if the diagnosis is delayed;
- In pregnancy, it may present as a hypertensive crisis and the symptoms may be similar to those of pre-eclampsia, e.g.— headaches, blurry vision, anxiety, convulsions. There may also be palpitations;
- The diagnosis is confirmed by measurement of catecholamines in a 24-hour urine collection and in plasma, as well as by adrenal imaging;
- Treatment is by alpha- and beta-blockade with prazosin or phenoxybenzamine (alpha-blockers) and a beta-blocker (e.g. atenolol or propranolol), but surgical removal is the only cure;
- Caesarean section is the preferred mode of delivery. This ↓ likelihood of sudden surge of catecholamines associated with stress of vaginal delivery.

(IV) Heart disease

Screening for maternal heart disease is not a norm in all pregnancies, they can be considered in individuals who have never had cardiac evaluation.

Unusual cardiac findings that *may be normal* in pregnancy include;

- Bounding/collapsing pulse;
- Ejection systolic murmur all over the precordium (see in upto 90% pregnant women);
- Loud S1;
- Audible **S3**;
- Relative sinus tachycardia;
- Ectopic beats;
- Peripheral edema.

In women with known heart disease, echocardiography is non-invasive, useful and usually done at the booking visit and around 28 weeks' gestation. Additionally, worsening symptoms that need attention include;

- Breathlessness, particularly at night,
- Change in her heart rate or rhythm;
- Increased tiredness or a reduction in exercise tolerance.

Routine physical examination should include pulse rate, blood pressure, jugular venous pressure, heart sounds, ankle and sacral oedema and presence of basal crepitations.

Heart disease ↓ ability to tolerate body changes in pregnancy. This is particularly significant with high risk cardiac conditions (see Table).

Table. High-risk cardiac conditions and pre-pregnancy counselling.

High-risk cardiac conditions	Pre-pregnancy counselling
- Systemic ventricular dysfunction (EF <30%, NYHA class III-IV); - Pulmonary hypertension; - Cyanotic congenital heart disease; - Aortic pathology (dilated aortic root > 4cm, Marfan's syndrome); - Ischemic heart disease.	Risk of maternal death; Possible reduction of maternal life expectancy; Effects of pregnancy on cardiac disease; Mortality associated with high-risk conditions; Risk of fetus developing congenital heart disease; Risk of preterm labour and FGR; Need for frequent hospital attendance and possible admission; Intensive maternal and fetal monitoring during labour; Other options – contraception, adoption, surrogacy.

Amoung others, the major fetal risks with maternal cardiac disease include;

- Recurrence, leading to *congenital heart disease*;
- Maternal cyanosis, leading to *fetal hypoxia*;
- Iatrogenic premature birth, as a safeguard measure to prevent complications;
- FGR;
- Effects of maternal drugs (teratogenesis, growth restriction, fetal loss).

The aim of management, in most of the cases, is to await the onset of spontaneous labour. This minimizes need for intervention and risk thereof;

- C-section should only be performed if maternal condition is considered too unstable to tolerate the demands of labour;
- Anticoagulation is essential in patients with congenital heart disease who have pulmonary hypertension (PH) or artificial valve replacements, and in those in or at risk of atrial fibrillation. Low-molecular-weight heparin is used in place of *teratogenic warfarin*, and can be titrated using factor Xa levels.

Management of labour in women with heart disease includes;

- Avoid induction of labour if possible unless planned time with availability of resources;
- Use prophylactic antibiotics— to reduce risk of bacterial endocarditis;
- Ensure fluid balance;
- Avoid the supine position;
- Discuss anaesthesia/analgesia with senior anaesthetist. Epidural anaesthesia is often chosen but has potential to cause maternal hypotension;
- Keep the second stage short— ↓ requirement for cardiac output;
- Use Syntocinon (instead of ergometrine), preferably with low-dose infusions.

i) Treatment of heart failure in pregnancy

The principles of treatment are the same as in the non-pregnant individual.

- Once the woman is admitted and diagnosis confirmed with echocardiography, drug therapy is initiated.
- Drug therapy may include diuretics, vasodilators and digoxin. Oxygen and morphine may also be required. Arrhythmias also require urgent correction and drug therapy;
- In all cases, assessment of fetal wellbeing should be carried out serially. Premature delivery may be considered if evidence of fetal compromise is detected.

ii) Ischaemic heart disease (IHD) in pregnancy

Most pregnant women with myocardial infarction (MI) are >40 years with <1% are <35 years.

This makes IHD uncommon ***in child-bearing age***, but statistically, the peak risk of incidence of MI during pregnancy is in the 3rd trimester, in parous women older than 35 years.

The underlying pathology is frequently not atherosclerotic. ***Coronary artery dissection*** is the primary cause of MI in the postpartum period.

Percutaneous transluminal coronary angioplasty (PTCA) is now considered acceptable but should be avoided when the fetus is most susceptible to radiation (8–15 weeks). Thrombolytic therapy in pregnancy carries risks of fetal and maternal haemorrhage.

iii) Mitral stenosis (MS) and aortic stenosis (AS)

These stenoses obstruct left-heart outflow— with inability to increase cardiac output to meet the demands of pregnancy;

- Aortic stenosis (AS) observed in obstetric population is usually congenital and mild-to-moderate lesions can cope with changes of pregnancy;
- Mitral stenosis is usually rheumatic in origin and often complicates pregnancy with pulmonary edema. Maternal mortality is seen in upto 2% cases in severe lesions.

The aim of mangement of these conditions is to reduce heart rate. This reduces heart rate to allow time for ventricular filling. Recommended course of action includes;

- Bed rest;
- Oxygen inhalation, as needed;
- Beta-blockers administration;
- Diuretic therapy.

If the woman's condition deteriorates before delivery is feasible, surgical intervention such as balloon or surgical aortic valvotomy can be considered.

iv) Marfan syndrome and pregnancy

Marfan syndrome is an autosomal dominant abnormality in *fibrillin* that may lead to mitral valve prolapse and aortic regurgitation, aortic root dilatation and aortic rupture or dissection.

Pregnancy increases the risk of aortic rupture or dissection and has been associated with ↑ maternal mortality with marked aortic root dilatation.

Echocardiography is the principal investigation. It is able to determine the size of the aortic root. Dilated aortic root ***(>4 cm)*** is more likely to develop complications. Risks are considerably lower with ortic root <4 cm.

A number of other obstetric complications have also been observed in women with Marfan syndrome; early pregnancy loss, preterm labour, cervical weakness, uterine inversion and postpartum haemorrhage.

v) Pulmonary hypertension (PH) and pregnancy

PH is characterized by an increase in the pulmonary vascular resistance resulting in an increased workload placed on the right side of the heart.

The main symptoms are fatigue, breathlessness and syncope, and clinical signs are those of right heart failure.

It carries a poor prognosis but treatments shown to improve symptoms and survival include endothelin receptor blockers, such as **bosentan**, and phosphodiesterase inhibitors such as sildenafil.

Women with PH should be counselled about the significant risks of pregnancy;

- In women with PH, pregnancy is associated with a high risk of maternal death;
- Women may deteriorate in early 2nd trimester or in the immediate postpartum period;
- The demands of increasing blood volume and cardiac output may not be met by an already compromised right ventricle, increasing risks of a cardiac event.

In women continuing their pregnancy, targeted pulmonary vascular therapy is an option, with timely admission to hospital and delivery.

(V) Respiratory disorders

i) Respiratory tract infections (RTIs) and pregnancy

Women are encouraged to have a seasonal flu vaccine in pregnancy as viral pneumonia follows a more complicated course in pregnancy and women often decompensate quicker.

Table. Warning signs in pneumonia.

Warning signs in pneumonia
Respiratory rate >30/minute.
Hypoxaemia; pO 2 <7.9 kPa on room air.
Acidosis; pH <7.3.
Hypotension.
Disseminated intravascular coagulation (DIC).
Elevated blood urea.
Evidence of multiple organ failure.

During pregnancy, therapy for bacterial pneumonia should be carefully selected. Penicillin/cephalosporins are mostly 1st choice, or erythromycin if atypical organisms are suspected.

ii) Asthma and pregnancy

Asthma is a chronic airway obstructive illness characterized by airway hyperresponsiveness to certain antigens.

Women with asthma in pregnancy should be seen assessed regularly;

- This can be done by history and an objective measure of pulmonary function, e.g. spirometry or peak expiratory flow rate (PEFR) monitoring.
- This objective data can be especially helpful in determining whether dyspnea is due to *breathlessness of pregnancy* or an asthmatic exacerbation.

Table. Features of severe lifethreatening asthma.

Features of severe lifethreatening asthma
Peak expiratory flow rate <35% of predicted;
pO 2 <8 kPa. pCO 2 >4.6 kPa;
Silent chest;
Cyanosis;
Bradycardia;
Arrhythmia;
Hypotension;
Exhaustion;
Confusion.

As for asthma in general, a similar step-wise approach to therapy is taken to adjust for severity in pregnancy;

- Smoking cessation should be emphasized;
- Inhaled β-symphathomimetics like albuterol (Ventolin), long-acting β2-agonists like salmetrerol, and inhaled corticosteroids are considered safe for use during pregnancy;
- Theophylline, although safe, is observed to have altered metabolism during pregnancy. Dose adjustment and drug levels monitoring is recommended;
- Recent studies show leukotriene receptor antagonist (LRTA) ***montelukast*** are safe during pregnancy;
- Oral corticosteroids, however, have been associated with ↑ risk of cleft life or palate in 1st trimester;
- Bronchoconstrictors such as ergometrine or prostaglandin F2α should be avoided in women with severe asthma.

Asthma severity and suboptimal control are associated with adverse pregnancy outcomes;

- Prolonged maternal hypoxia can lead to FGR and ultimately to fetal brain injury;
- These exacerbations are more likely to occur during pregnancy in women with severe asthma. Asthma attacks, however, are uncommon to occur during labour;
- Most episodes occur between 24-36 weeks. Prompt and effective management improves maternal and fetal morbidity from asthma.

(VI) Neurological disorders

i) Seizures and epilepsy

Pregnancy has no consistent effect on epilepsy. Most of the women will have a decreased or no difference in frequency of seizures, but ⅓ of women do experience ↑ frequency of fits.

Altered drug metabolism in pregnancy results in ↓ in anticonvulsant drug levels, increasing risk of fits;

- There is ↑ hepatic and renal clearance of medications.
- Stress, sleep deprivation or difficulty in compliance with medication also play a role.

Table. Causes of seizures in pregnancy.

Epilepsy;
Eclampsia;
Encephalitis or meningitis;
Space-occupying lesions (e.g. tumour, tuberculoma);
Cerebral vascular accident;
Cerebral malaria or toxoplasmosis;
Thrombotic thrombocytopaenic purpura (TTP);
Drug and alcohol withdrawal;
Toxic overdose;
Metabolic abnormalities (e.g. hypoglycaemia).

Women with known epilepsy are more at risk of iatrogenic complications to the fetus;

- The major fetal abnormalities are associated with anticonvulsant drugs. These include neural tube defects, facial clefts, mid-facial abnormalities and cardiac defects;
- Sodium valproate, carbamazepine, phenytoin and phenobarbitone are commonly implicated in such teratogenesis;
- These abnormalities are detectable by ultrasound and these individuals should be offered *detailed* anomaly scanning.

Though there are risks with continuing anticonvulsants, discontinuation may lead to ↑ frequency of seizures;

- These seizures may cause both maternal and fetal hypoxia and consequent complications in pregnancy;
- Despite altered metabolism of anticonvulsants, the recommended course of action is to wait-and-watch for ↑ frequency of seizures. This is because;
    - Monitoring of drug levels is difficult;
    - In majority of cases, the prenatal dosage can be continued if there is no ↑ in seizures;
    - Exceptionally, for lamotrigine, ↑ in dose is necessary as its levels fall rapidly in pregnancy.
- An increase in seizure frequency or a recurrence of seizures, especially in the context of subtherapeutic drug levels, should prompt an increase in dosage of all anti-epileptics.

The principles of epilepsy management are to control seizures with minimum possible dose of the optimal drug while weighing risk-to-benefit;

- Polytherapy *increases* risks of congenital abnormalities with each additional medication. These women

should, *where possible*, be converted to monotherapy before pregnancy;

- Carbamazepine and lamotrigine are considered to be relatively safe drugs in pregnancy but should be used carefully;
- In the case of valproate, the risk is dose dependent (>1,000 mg/day). It should be avoided in pregnant women, except when epilepsy cannot be controlled with other AEDs.

- All epileptic women are advised to take high dose 5mg/day folic acid supplementation pre-conception;
- In women who have been free of seizures for 2 years, consideration may be given prepregnancy to discontinuing medication.

Anticonvulsant medication should be continued during labour;

- C-section is usually only reserved for women with too frequent stress-associated seizures;
- Breastfeeding is not contraindicated, but feeding is best avoided for few hours after taking medication;
- Information on safe handling of the neonate should be given to all epileptic mothers so as to prevent a traumatic injury.

ii) Multiple sclerosis (MS)

Multiple sclerosis (MS) is a *relapsing and remitting* autoimmune disease that causes disability through demyelination of nerves in the brain;

- This can lead to muscle weakness, lack of coordination, numbness in the hands or feet, blurred vision, tremor, spasticity (UMN sign) and voiding dysfunction;
- MS affects women more than men and **first** presents predominantly with visual complaints of optic neuritis (demyelinating inflammation);
- Pregnant women with MS are **not** at an ↑ risk of preterm delivery, FGR or congenital malformations.

Women with MS during pregnancy are observed to have a lower risk of progression of the condition;

- This is helpful as the 1st line treatments for MS like glatiramer, β-interferon, and dimethyl fumurate are contraindicated in pregnancy;
- Steroids or intravenous immunoglobulin remain centre of management if a flare develops weighing risk-to-benefit ratios.

iii) Migraine

Migraine often improves in pregnancy, but worsening of headaches can occur;

- Obstetric complications are not increased in migraine sufferers.
- Migraine during pregnancy should be treated with analgesics, antiemetics and, where possible, avoidance of factors that trigger the attack.
- Beta-blockers may be used to prevent attacks.

iv) Bell's palsy

Bell's palsy is an idiopathic palsy of facial nerve's lower motor neuron. It is often seen during 3rd trimester of pregnancy. It is often associated with herpes simplex virus (HSV) infection.

Affected women typically present with weakness of the ipsilateral facial expression muscles. There is mouth deviation to normal side, effaced facial creases ipsilaterally and difficulty closing ipsilateral eyelid (see Figure).

Management, as also in non-pregnant, is with corticosteroids and antivirals administration. These can be used but may only hasten recovery if given within 24 hours of onset of symptoms.

The course of the disease takes 1-8 weeks to recover completely, but uncommonly, some individuals may be left with long-term facial weakness.

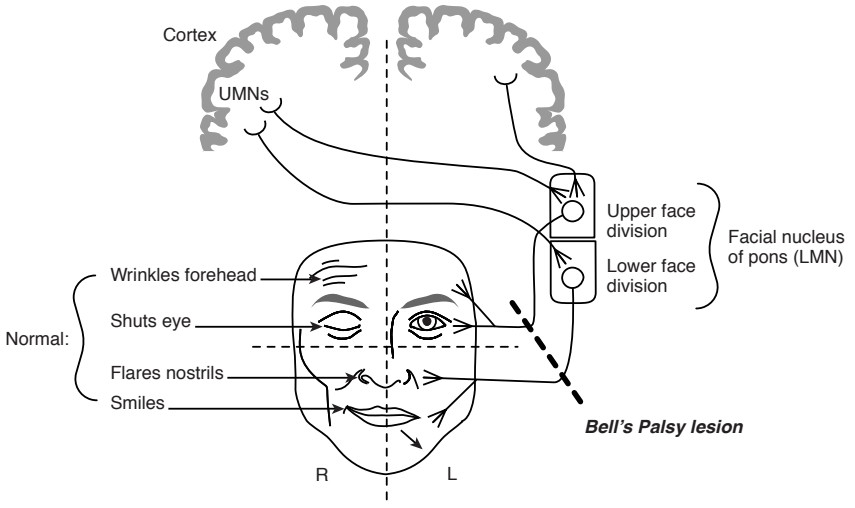


Figure. Illustration of normal facial nerve innervation and Bell's palsy lesions.

(VII) Hematological abnormalities

i) Anemia and pregnancy

Anemia is the most common haematological abnormality encountered during pregnancy.

During pregnancy, the plasma volume begins to ↑ by 6th week and while the red cell mass also ↑, it is proportionately less than the plasma volume. The relative decrease in haemoglobin concentration (and otherwise normocytosis) is often referred to as '*physiological anemia of pregnancy*'.

However, a haemoglobin concentration < 11 g/dL in the 1st trimester and <10 g/dL in the late 2nd trimester is considered as anemia and should be investigated.

ii) Iron deficiency anemia

Iron deficiency remains the most common cause of maternal microcytic anemia. This is especially common in;

- Women of childbearing age;
- Vegetarians with inadequate dietary iron intake;
- Individuals with gastrointestinal blood loss— e.g. in cases of hookworm infestation;
- Women with closely spaced pregnancies.

Diagnosis is by serum ferritin and TIBC analysis;

- Ferritin levels— best first-line test for iron deficiency. Levels < 15 µg/L indicates body iron depletion while < 12 µg/L are associated with deficiency;
- TIBC is observed to be ↑ as a compensatory response and helps in diagnosis where ferritin may be falsely elevated as an acute-phase reactant.

Pregnant women with iron deficiency should be treated with oral iron;

- The treatment of established iron deficiency is with 200 mg of elemental iron daily;
- Parental iron (*Venofer*) is not needed unless there is poor compliance with oral iron or malabsorption. But this carries additional risks of hypersensitivity reactions with IV infusions;
- Women with severe anemia who are symptomatic, blood transfusion may be considered as it is quicker in restoring haemoglobin levels.

In women considered at risk of developing iron deficiency, elemental iron 30-60 mg should be taken orally every day as prophylaxis.

iii) Haemoglobinopathies

Haemoglobin protein consists of globin subunits. Mutations in their genes result in hemoglobinopathies.

Women with hemoglobinopathies are at an ↑ risk of miscarriage, preterm birth, fetal growth restriction and perinatal morbidity.

Women with no previous evaluation can be diagnosed using Hb electrophoresis after ruling-out iron deficiency as a cause of microcytic anemia (see Figure).

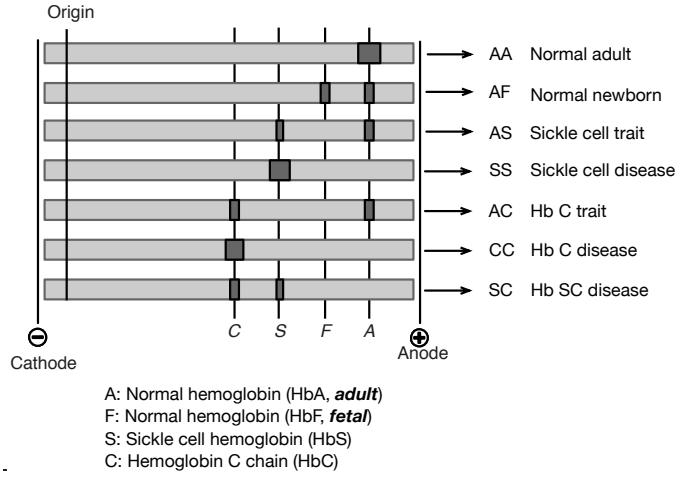


Figure. Hemoglobin electrophoresis patterns seen in a normal adult and in hemoglobinopathies.

a) Sickle-cell disease (SCD)

Sickle cell disease (SCD) is an autosomal recessive condition of abnormal haemoglobin chains. Here the haemoglobin molecule can be classified based on severity of mutation;

- Sickle cell trait (HbAS);
- Sickle cell disease (HbSS);
- Sickle cell/haemoglobin C disease (HbSC);
- Sickle cell/beta thalassaemia.

SCD haemoglobin has a propensity to precipitate when in its reduced state;

- The RBCs become sickle-shaped and often occlude small blood vessels;
- These sickling crises are more common during pregnancy and can predispose to infections.

High-dose folate supplements (5 mg daily) are recommended starting pre-conception and the majority of women are also managed from early pregnancy on low-dose 75mg aspirin.

b) Thalassaemia

The thalassaemia syndromes are the commonest genetic blood disorders. Although some of its types are more prevalent in some populations.

Here the defect is a reduced production of normal haemoglobin and the syndromes are divided into alpha and beta types, depending on which globin chain is affected;

- In alpha-thalassaemia there may be deletion of one or two of the alpha globin chains;
- In beta-thalassemia, there may be defective production of the β-chains.

Both alpha-thalassaemia and beta-thalassemia follow mendelian inheritance. If both parents have the same subtype of thalassaemia, there is a chance that the fetus may also be affected with a major form of thalassemia.

iv) Thrombocytopaenia

Thrombocytopaenia is defined as a platelet count $<150 \times 10^9$ /L. Abnormal skin and mucous membrane bleed-

ing can be observed, however, the risk of spontaneous bleeding is more of a concern if the count is < 50 x10^9 /L.

Table. Causes of thrombocytopaenia in pregnancy.

Idiopathic
Gestational thrombocytopenia; Autoimmune; Antiphospholipid syndrome; Pre-eclampsia; HELLP syndrome; Disseminated intravascular coagulation; Thrombotic thrombocytopaenic purpura; Hypersplenism.
Decreased production
Sepsis; HIV infection; Malignant marrow infiltration.

a) Gestational thrombocytopenia

Gestational thrombocytopenia is a mild form of thrombocytopenia seen during pregnancy.

The platelet count, however, remains > 70 x 10^9 /L. It is thought to be due to accelerated platelet consumption.

There is no prior history of thrombocytopaenia outside pregnancy and a normal platelet count recorded at the start of pregnancy.

The diagnosis of gestational thrombocytopaenia is a diagnosis of exclusion and can only be made when autoimmune and other causes have been excluded.

b) Autoimmune thrombocytopaenia

In immune thrombocytopaenic purpura (ITP), IgG autoantibodies (detectable) are produced against platelet surface antigens, leading to platelet destruction.

The incidence in pregnancy is rare but the maternal platelet count may fall at any stage of pregnancy and can reach levels of <50 × 10^9 /L. Additionally, there are ↑ risks of;

- Spontaneous bleeding during pregnancy— but unlikely with platelet counts < 20 x 10^9;
- *Fetal* thrombocytopaenia (<50 × 10^9 /L)— as IgG antibodies can cross the placenta. However, this *cannot* be predicted using *maternal counts* or antibody tests;
- Maternal haemorrhage at delivery is unlikely if the platelet count is >50 × 10^9 /L.

Management in pregnancy is with serial platelet levels and treatment offered at counts < 50 × 10^9 /L near term;

- Corticosteroids supress anti-platelet autoantibodies but take 2–3 weeks to have a significant effect. Hence, should be administered early as platelet levels fall below 50 × 10^9 /L;
- Intravenous immunoglobulin G (IgG)— preferred option where a rapid platelet increase is needed;
- Plasma exchange transfusion is preferred over platelet transfusions as the latter can be destroyed by anti-platelet antibodies;
- Splenectomy improves ITP but has high risks of fetal mortality if carried out during pregnancy.

Regional anaesthesia may be avoided if the platelet count is <80 × 10^9 /l.

Instrumental delivery by ventouse and fetal blood sampling in labour are best avoided because of the risk of fetal thrombocytopaenia. A cord blood sample must be collected instead for platelet count.

v) Bleeding disorders

It is generally believed that pregnancy is a hypercoagulable state of pregnancy as factors V, VII, VIII, IX, XII levels

and von Willebrand factor activity ↑ during pregnancy.

However, women with factor deficiencies do not achieve the same levels as those of women without deficiencies. Consequently, there is an ↑ risk of miscarriages, abnormal bleeding after amniocentesis, peripartum bleeding.

Table. Bleeding disorders

Inherited:
Vascular abnormalities; Platelet disorders; Coagulation disorders.
Acquired:
Thrombocytopaenia; Disseminated intravascular coagulation; Acquired coagulation disorders; Marrow disorders.

Coagulation disorders of significance in pregnancy are;

- Von Willebrand disease is the most common inherited bleeding disorder;
    - It follows autosomal dominant inheritance;
    - Von Willebrand's disease can be due to either a qualitative or quantitative defect in von Willebrand factor (VWF, see Figure).

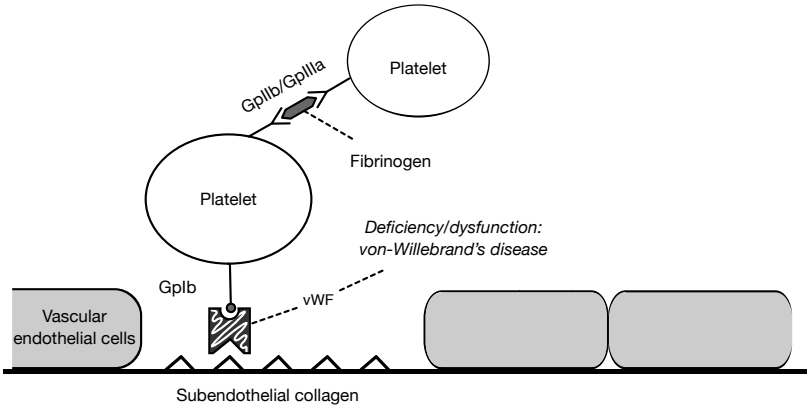


Figure. Von-Willebrand factor influencing platelet activation and adhesion.

- Haemophilia A and B— X-linked inherited disorders of clotting factors;
    - Haemophilia A is characterized by deficiency of factor VIII;
    - Haemophilia B is characterized by deficiency of factor IX.
- Factor XI deficiency is a *rare* autosomal dominant bleeding disorder. Here the bleeding risk *does not* relate to the severity of the factor deficiency.

Women with these bleeding disorders should receive pre-pregnancy counselling;

- In women with haemophilia, epidural anesthesia for labor may have ↑ risk of epidural hematoma;
- Rigorous manoeuvres during labour should be avoided as the fetus may also have bleeding disorder. This include ventuouse cup and rotational forceps;
- As it is safer, coagulation testing should be assessed from cord blood samples.

(VIII) Gastroenterological disoders

a) GERD and pregnancy

During pregnancy, under influence of estrogen and progesterone, a reduced lower esophageal sphincter (LES) is observed. It is not uncommon for women to develop GERD symptoms during pregnancy.

Treatment with antacids (e.g. ranitidine, omeprazole) is safe, although H_2-receptor blockers (e.g. ranitidine) are preferred as first line medications over proton pump inhibitors (PPIs).

ii) Inflammatory bowel disease (IBD) and pregnancy

Inflammatory bowel disease includes diseases ulcerative colitis (UC) and Crohn's disease (CD). It is often observed in women seeking obstetric care;

- Pregnancy does not usually alter course of IBD. However, IBD can have ↑ risk of adverse effects on pregnancy;
- Women with IBD have ↓ relative fertility rates;
- Disease flare during pregnancy is more likely if the disease is active at the time of conception;
- There is an ↑ incidence of preterm labour and small for gestational age (SGA) offspring;

The use of medication during *conception and pregnancy* has to be carefully considered;

- Supplementation with high-dose folic acid (5 mg daily) is recommended;
- Malabsorption of other vitamins may need replacement as well;
- Methotrexate is contraindicated throughout pregnancy. However, 5-aminosalicylates, azothiaprine, ciclosporin and corticosteroids, carry low risk of adverse effects on pregnancy;
- Infliximab— monoclonal antibody against TNF-α has also been shown to be low-risk for use during first two trimesters of pregnancy;
- A relapse of IBD in pregnancy may be treated with steroid orally, parenterally or via enemas;
- Caesarean section is considered if there is active perianal disease in Crohn's and usually if there is an ileoanal pouch.

iii) Pancreatitis and pregnancy

An episode of pancreatitis can can occur in pregnancy but is not common.

The commonest cause of pancreatitis in pregnancy is gallstones. Other aetiological factos include alcohol, hypertriglyceridemia and rarely, hyperparathyroidism;

- The clinical presentation in pregnancy does not vary from a non-pregnant woman;
- The diagnostic yield of amylase and lipase level measurement remains unchanged as well;
- Management is mainly supportive as the pancreatic inflammation resolves. Women who develop peritonitis should be referred for intensive care.

(IX) Liver diseases

i) Liver diseases specific to pregnancy

a) Intrahepatic cholestasis of pregnancy

This is a liver disorder unique to pregnancy.

It occurs most commonly in 3rd trimester and presents with symptoms of cholestasis;

- Generalized pruritus, worst on palms and soles;
- Anorexia, dark urine, pale stools and steatorrhea may develop;
- Jaundice is unusual.

It is thought to occur secondary to a genetically abnormal or exaggerated liver metabolic response to the physiologic ↑ in estrogens during pregnancy. This explains its ↑ incidence in women from Chile.

It is diagnosed in the face of mildly deranged LFTs;

- ↑ transaminases and bile acids are most sensitive. ↑ *bile acids may be the first/only abnormality*;
- CBC, clotting profile, hepatitis serology, autoimmune antibodies, renal function tests and liver ultrasound. These aid in ruling out AFLP, viral hepatitis, gallstones, autoimmune hepatitis, pre-eclampsia, HELLP syndrome, sepsis and drug-induced hepatitis.

Fetal risks can also be assessed using fetal ultrasound and CTG if indicated.

Cholestasis is not associated with major maternal complications, but fetal risks are more important (see Table);

Table. Risk of maternal and fetal complications with intrahepatic cholestasis of pregnancy.

Maternal complications	**Fetal complications**
Haemorrhage Premature labor	*Late intrauterine death*/stillbirth Intrapartum fetal distress Meconium staining of amniotic fluid

Management is centered on symptomatic relief and prevention of complications;

- Pruritus— emollient creams and antihistamines (chlorpheniramine). Ursodiol reduces itching and also improves liver function;
- Antenatally, oral vitamin K administration reduces risk of postpartum haemorrhage;
- Delivering the baby by 37-38 weeks is common— because risk of intrauterine death ↑ beyond 38 weeks.

Post-partum symptoms resolve with return of liver function. However, recurrence of intrahepatic cholestasis is higher in subsequent pregnancies.

b) Acute fatty liver of pregnancy (AFLP)

It is a rare but life-threatening complication of pregnancy that is typically observed in the 3rd trimester or within few days of a still-birth.

The aetiology is complex as it involves abnormalities in intramitochondrial fatty acid oxidation;

- Progressive insulin resistance of pregnancy leads to ↑ maternal triglyceride and fatty acid levels. Liver uses mitochondrial beta-oxidation for metabolizing these;
- Autosomally inherited heterozygous mutation of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD) enzyme in the mother has been implicated in AFLP;
- Deficiency of LCHAD in fetus and mother combined with metabolic stress of pregnancy causes hepatotoxic metabolites of LCHAD to accumulate in maternal circulation.

It is characterized by perilobular fatty infiltration in the liver. Affected pregnant women present with;

- Abdominal pain, nausea and vomiting ± jaundice;
- Hypertension, proteinuria, and edema can mimic preeclampsia;
- Progression to acute renal failure, pancreatitis, hepatic encephalopathy, and coma can occur.

Laboratory findings show;

- Elevation of liver enzymes (e.g., ALT, AST, GGT), hyperbilirubinemia;
- Hypoglycemia and ↑ serum NH_3 in severe cases.

Maternal complications associated with AFLP are those seen with hepatic dysfunction. These include hypoglycaemia, coagulopathy and hemodynamic instability.

Diagnosis is made with elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) and no direct evidence of pre-eclampsia;

- Liver biopsy is contraindicated— due to risk of bleeding;

- It is often not possible to clearly distinguish AFLP from HELLP syndrome or pre-eclampsia.

Management relies on early diagnosis;

- Supportive therapy with transfusions, vitamin K and acetyl-cysteine;
- Early delivery of the baby due to risk of mortality;
- Dialysis may be needed prior to delivery or immediately post-partum.

Liver dysfunction, however, is *not* long-term and resolves over few weeks.

ii) Hepatitis and pregnancy

Viral hepatitis is often encountered in women of childbearing age. It is the *commonest* cause of jaundice in pregnancy worldwide;

- Hepatitis A and E viruses are transmitted via feco-oral route. Hepatitis B, C and D are transmitted parenterally and have a higher risk of transplacental vertical transfer as well;
- The presentation of acute viral hepatitis in pregnancy is similar to one of a non-pregnant woman. Nausea, vomiting, dark urine and jaundice are common;
- Hepatitis serology remains the mainstay for diagnosis.

Acute episodes of viral hepatitis are associated with adverse effects on pregnancy and fetus;

- ↑ risk of spontaneous miscarriage;
- Acute hepatitis E— carries a very high risk of *fulminant hepatic failure* if it occurs in **primigravidas during 3rd trimester**. It is also associated with preterm delivery, FGR and stillbirth;
- Herpes simplex hepatitis— is rare but carries a high risk of perinatal mortality. Use of acyclovir in these cases has been shown to improve outcomes.
- Vertical transmission of hepatitis viruses;
    - It has been observed that risk of vertical transmission is ↑ if the viremic period is present during last several weeks of pregnancy or in the few weeks after delivery;
    - In acute hepatitis A, vertical transmission is rare as the viremic period is short. However;
        - Infected babies seem to recover well;
        - Hepatitis A vaccine or serum immune globulin administration is also possible.
    - In acute hepatitis E, vertical transmission occrs at a higher rate. Hepatitis E immune globulin can be administered but there is ***no*** hepatitis E vaccine available;
    - Vertical transmission of Hepatitis B can occur in both acutely-infected and chronically-infected mothers— based on viral load of the virus at the time of birth. Hepatitis B vaccine has proven to be extremely effective in preventing vertical transmission.
    - Hepatitis D is an RNA virus— a parasite on hepatitis B as HBsAg also serves as the coat protein for the hepatitis D virus;
        - Women who are infected with both hepatitis B and D can pass one or both viruses to their infants;
        - Babies of mothers with hepatitis D should be administered HBIG and hepatitis B vaccine, just as for babies born to women carrying only Hepatitis B.

Women with chronic viral hepatitis appear to tolerate pregnancy well, as long as liver function is normal;

- Hepatitis B surface antigen (HBsAg) testing *recommended at booking visit* can detect pregnant women infected with Hepatitis B;
    - It is recommended that **babies born to** HBsAg-positive women receive hepatitis B vaccine and one dose of hepatitis B immunoglobulin (HBIG) with 12 hours of birth and booster doses later in life;
    - Women with extremely high hepatitis B viral DNA load (HBV DNA PCR assay ≥ 10^8 IU/mL) may benefit from additional treatment with antiviral agents (e.g. Tenofovir) to reduce viral load before delivery. Therefore, women who are HBsAg-positive should also have a quantitative hepatitis B DNA viral load measured in the 2nd or 3rd trimester (see Figure). Reduc-

tion in maternal viral load also ↓ the probability of transmission;

- ***Amniocentesis***, ***vaginal delivery*** (compared to C-section), and ***breast feeding*** of vaccinated infants **do not** appear to increase the rate of vertical transmission of hepatitis B;
- Women with chronic hepatitis B are observed to have relatively higher incidence of liver injury post-partum— possibly due to rapid ↓ in cortisol levels post-partum and is analogous to hepatitis B flares that occur after withdrawal of immunosuppressive drugs in a non-pregnant woman;
- Due to ↑ incidence of liver-injury post-partum, it is prudent to monitor women with chronic hepatitis B for several months post-partum.

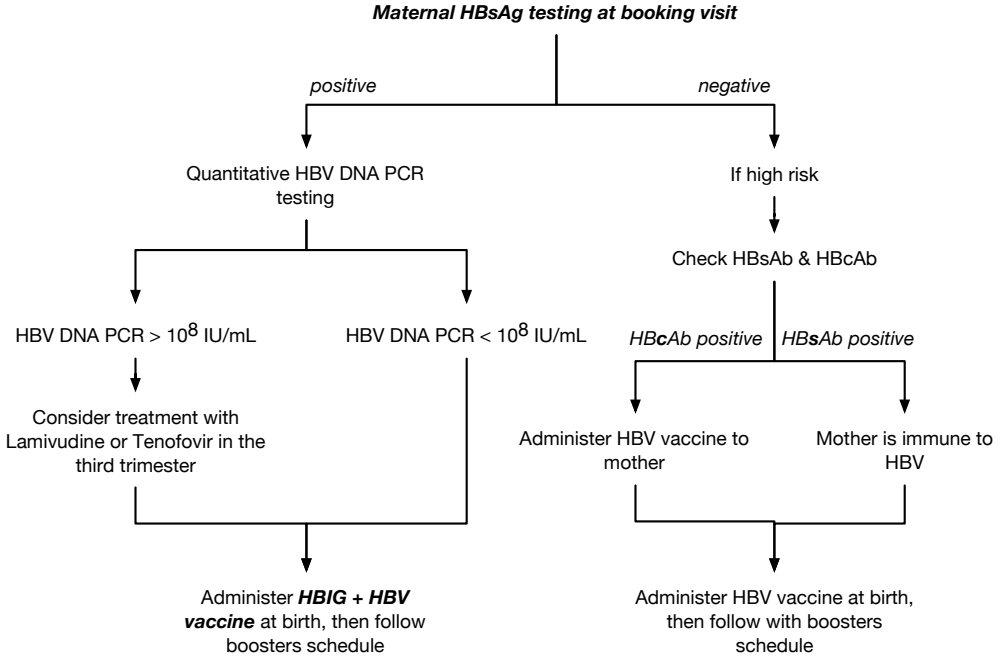


Figure. Algorithm of Hepatitis B management in pregnancy.

- Most individuals infected with **hepatitis C** are unaware of their infection. But these individuals are observed to have an ↑ in serum viral load with ↓ in ALT levels. These changes reverse post-partum and are usually asymptomatic. However, there is ↑ risk of;
  - Preterm rupture of membranes;
  - Gestational diabetes mellitus (GDM);
  - Low birthweight neonate;
  - Maternal cholestasis during pregnancy;
  - Vertically transmission— ↑ if the mother is also carrying the human immunodeficiency virus (HIV). Unfortunately, no effective vaccine is available for hepatitis C, and neither serum immune globulin nor C-section is thought to be protective.

iii) Autoimmune hepatitis

Autoimmune hepatitis (chronic active hepatitis) is characterized by progressive hepatic parenchymal destruction, eventually leading to cirrhosis;

- It is diagnosed on liver biopsy and in association with anti-smooth muscle antibodies and anti-nuclear antibodies;
- Its course in pregnancy is variable, with flares reported throughout gestation and postpartum. These flares are often complicated by fetal loss;
- Immunosuppressive therapy should be continued during pregnancy according to disease activity.

iv) Gallstones and pregnancy

A typical patient with cholelithiasis is often referred to with "***the Four Fs***", i.e. **f**at, **f**emale, **f**ertile and in her **f**our-ties. In pregnancy, the aetiology of ↑ biliary sludge and gallstones is multifactorial with roles of;

- ↑ oestrogen levels leading to ↑ cholesterol secretion and *supersaturation* of bile, while;
- ↑ progesterone levels leading to a *relative* ↓ in small intestinal motility.

Despite the multi-factorial propensity to develop ↑ biliary sludge during pregnancy, *acute cholecystitis* remains less common during pregnancy.

For acute cholecystitis, conservative medical management is recommended initially with;

- Bowel rest, IV fluids, correction of electrolytes;
- Prophylactic broad-spectrum antibiotics are often indicated;
- Surgical intervention carries a higher risk of miscarriage or premature labor.

Relapse rates of acute cholecystitis are high during pregnancy. If surgical intervention is needed, it is mostly performed in the 2nd trimester.

v) Primary biliary cirrhosis (PBC) and pregnancy

Primary biliary cirrhosis (PBC) is an autoimmune disorder of the liver.

It is characterized by progressive destruction of intrahepatic bile ducts leading to portal hypertension and liver failure. Pregnancy in individuals with PBC is uncommon due to associated ↓ fertility.

Ursodeoxycholic acid (UDCA or Ursodiol) is a bile-acid with hydrophilic properties;

- It has been approved in management of PBC as it delays progression of resultant cirrhosis;
- It should be used with care during pregnancy for its side effects. Although, it has been shown to have a favourable risk-to-benefit profile.

vi) Cirrhosis and pregnancy

Individuals affected by cirrhosis are of the older age.

It is rare to observe cirrhosis in a pregnant woman and women of child-bearing age are adviced to to avoid pregnancy for its ↑ risk of complications. These include;

- Bleeding from esophageal varices;
- Jaundice;
- Malnutrition;
- Hepatic failure and encephalopathy.

All pregnant women with cirrhosis should be screened using endoscopy from the 2nd trimester for esophageal varices and potential management options.

(X) Connective tissue diseases

i) Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease more prevalent in women of black Caribbean ethnicity.

There is antibody production against nuclear antigens. Antigen-antibody complex deposition in various tissues also results in a type 3 hypersensitivity reaction;

- It may cause disease in any organ system, but principally it affects the joints (90%), skin (80%), lungs, nervous system, kidneys and heart;
- It is not uncommon during pregnancy. Its variable presentation, flares and remissions may mislead;
- Acute flares of SLE also can share certain features with pre-eclampsia (see Table).

Table. Distinguishing features of an SLE flare over those of pre-eclampsia.

***Overlapping features* of Pre-eclampsia and SLE flare**	**SLE flare only**
Hypertension; Proteinuria; Thrombocytopaenia; Renal impairment.	Rising anti-DNA titers; Fall in complement levels; No increase in serum uric acid; No abnormal liver function.

The American College of Rheumatology (ACR) diagnostic criteria requires 4 out of 11 points for diagnosis (see Table).

Table. ACR diagnostic criteria for diagnosis of SLE.

ACR diagnostic criteria (4 out of 11 should be present for diagnosis) *Aide mémoire: "4-RASHES"*		**Points**
4 Rashes	Malar rash	1
	Discoid rash	1
	Photosensitivity	1
	Oral ulcers	1
Renal proteinuria > 0.5g/day or ≥ 3+ on dipstick		1
Arthritis ≥ 2 joints		1
Serositis, pleuritis, or pericarditis		1
Hemolytic anemia, leucopenia, lymphopenia, thrombocytopenia, or LE cell		1
Excitation— seizures, psychosis.		1
Serology	ANA	1
	Anti-dsDNA, Anti-smith, APLA, false-positive VDRL	1

Lab tests that aid in suspicion and diagnosis are;

- Antinuclear antibodies (ANA)— highly ***sensitive*** for autoimmune diseases;
- Anti-dsDNA assays— highly ***specific*** for SLE.

SLE is associated with significant risks in mother, pregnancy and fetus. These include;

- Miscarriages, and pre-eclampsia;
- FGR, fetal death, and preterm delivery;
- SLE with renal involvement (lupus nephritis) is associated with the *greatest risk* of adverse outcomes in pregnancy. *On the other hand*, pregnancy does not seem to alter renal function in the long term;
- *Pre-existing hypertension*;
- Presence of *antiphospholipid antibodies (APLA)*.
- Upto 30% of mothers with SLE also have anti-Ro and anti-La antibodies;
    - These auto-antibodies can cross placenta and occasionally result in fetal morbidity;
    - Congenital heart block— permanent and difficult to treat. Over 50% need pacemakers in early infancy;
    - Congenital lupus— manifests as cutaneous lesions 2–3 weeks after birth, disappearing spontaneously without scarring within 6 months.

a) Antiphospholipid syndrome (APS)

APS is an autoimmune condition characterized by ↑ tendency to thrombosis (blood clotting) and is associated with adverse pregnancy complications.

APS may be primary or found in association with SLE. Diagnosis requires that at least **one clinical and one laboratory criterion** (see Table).

Table. Clinical and laboratory criteria for diagnosis of APS.

Clinical criteria	Laboratory criteria
Thrombosis— 1 or more clinical thrombotic episodes (arterial, venous, or small vessel)	≥1 of the following 3 **anti-phospholipid antibodies (APLA)** must be positive on ≥2 occasions at least *8-12* weeks apart; • LA (lupus anticoagulant); • aCL (anticardiolipin antibodies)— high titer; • Anti-β_2-glycoprotein 1— >12 weeks apart
Pregnancy morbidity (unexplained)— • Fetal death >10 weeks; • Preterm birth <35 weeks due to severe pre-eclampsia or growth restriction; • 3 or more unexplained miscarriages <10 weeks.	

Like SLE, APS is also associated with both maternal and fetal adverse effects;

- Early-onset pre-eclampsia;
- Intrauterine growth restriction (IUGR);
- Preterm birth;
- *Recurrent* miscarriages;
- Fetal death;
- Venous thromboembolism (VTE).

b) Management

Due to aforementioned significant risks, pregnant women with SLE and APS require intensive monitoring for both maternal and fetal indications;

- Maternal BP monitoring— due to ↑ risk of pre-eclampsia;
- Maternal baseline renal studies, including a 24-hour urine collection for protein (aids in GFR estimation and measuring proteinuria);
- Fetal growth assessment should be carried out serially by;
    - Serial ultrasonography;
    - Umbilical artery Doppler;
    - Amniotic fluid volume.

Anticoagulation is recommended to be started antenatally.

- APS with prior recurrent miscarriages or poor obstetric history— low-dose aspirin + heparin ↓ **risk of pregnancy loss**;
- No anticoagulation intrapartum due to risk of bleeding;
- Postpartum anticoagulation for 6 weeks— prevents venous thromboembolism. Heparin is safe for breastfeeding mothers.

Most immunosuppressive drugs are considered safe in pregnancy. Their use is to ensure disease quiescence;

- Monitoring treatment is necessary as infection and flares need to be identified prompty and treated;
- The best approach is to maintain treatment and ensure disease quiescence;
- If antenatal treatment is required for SLE— steroids, azathioprine and hydroxychloroquine can be used safely.

ii) Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease affecting *primarily* the synovial joints.

RA is often encountered during pregnancy;

- Most women with RA (upto 75%) experience improvement during pregnancy. But it is very common to observe a flare post-partum in these individuals;
- Unlike other connective tissue diseases— no adverse effects of RA on pregnancy are reported.

The main concern of RA patients is the safety of medication used to control the disease;

- Paracetamol/acetaminophen analgesics are first line for pain control;
- Corticosteroids are preferred over NSAIDs (due to risk of adverse effects). NSAIDs can be used for up to 32 weeks' gestational age if needed;
- Azathioprine and hydroxychloroquine can be used in pregnancy.

If severe RA limits *hip abduction* and vaginal delivery is not possible— C-section may be needed.

iii) Scleroderma

Scleroderma is a *very rare* autoimmune connective tissue disease;

- It may manifest as either a localized cutaneous condition or *more widespread* systemic sclerosis;
- Systemic sclerosis is characterized by progressive fibrosis of skin, oesophagus, lungs, heart and kidneys.

No treatment has been shown to influence the course of scleroderma and treatment is usually symptomatic;

- Those with multiorgan involvement are often advised against pregnancy;
    - Venous access, BP monitoring is difficult due to skin and blood vessel involvement;
    - There is ↑ risk of deterioration of sclerosis during pregnancy;
    - Risks are highest for those recently diagnosed with pulmonary hypertension (secondary to lung fibrosis) or renal disease— rapid decompensation can occur.
- Systemic sclerosis is also associated with risk of adverse fetal outcomes;
    - Preterm delivery;
    - Pre-eclampsia;
    - Fetal growth restriction;
    - Perinatal mortality.

(XI) Skin disorders

Many physiological changes affect skin during pregnancy (*see also Chapter 17: Physiologic changes in pregnancy*). These are thought to occur secondary to hormonal effects.

Pruritus *without a rash* affects up to 20% of normal pregnancies, but liver function tests are needed to exclude *obstetric cholestasis.*

i) Pre-existing skin diseases in pregnancy

Some pre-existing eczematous skin conditions worsen in pregnancy.

Atopic eczema is a common pruritic skin condition;

- It causes the commonest pregnancy rash;
- Management is with emollients and bath additives. Hand and nipple eczema are common postpartum.

Acne vulgaris—

- Though acne usually improves in pregnancy, its flares are more common in the 3rd trimester;
- Oral or topical erythromycin can be used in severe cases;
- **Retinoids are contraindicated during pregnancy**.
- Though acne usually improves in pregnancy, acne rosacea, an acneiform eruption often worsens.

Psoriasis is a chronic autoimmune disease. Based on the subtype of psoriasis, it can be characterized by a variety

of skin lesions;

- It remains unchanged in around 40% of patients, improves in another 40% and worsens in around 20%;
- Topical steroids can be used for skin lesions;
- **Methotrexate is contraindicated during pregnancy**.

ii) Dermatoses unique to pregnancy

a) Polymorphic eruption of pregnancy (PEP)

Polymorphic eruption of pregnancy (PEP) is a self-limiting pruritic inflammatory disorder.

It is the most common pregnancy associated dermatosis.

It usually presents in the 3rd trimester and/or immediately postpartum and upto 75% of affected pregnancies are *primagravida*;

- PEP begins on the lower abdomen involving striae gravidarum as a maculopapular rash;
- It extends to thighs, buttocks, legs and arms, but ***spares the umbilicus*** and rarely involves the face, hands and feet;
- The lesions become confluent into plaques and spread, often resembling a *toxic erythema*.

No effect has been observed on pregnancy or fetus. But skin biopsy and *direct immunofluorescence* and is often needed— aids in ruling out other skin conditions with more adverse effects on pregnancy, e.g. PG (see below).

Symptomatic management is sufficient;

- Topical emollients and oral antihistamines may be used;
- Topical steroid creams or, in severe cases, systemic steroids may be used.

The rash resolves rapidly after delivery. The tendency for the rash to recur in subsequent pregnancies is ***low***.

b) Pemphigoid gestationis (PG)

Pemphigoid gestationis (PG) is a rare pruritic autoimmune bullous disorder.

It most commonly presents in the late 2nd or 3rd trimester with itchy skin-lesions;

- These begin on the abdomen mostly as papules and plaques that coalesce spreading to limbs, palms and soles *sparing* mucuous membranes and face;
- Unlike PEP, these lesions ***do not*** spare the umbilicus;
- These lesions develop into vesicles and ***pemphigoid-like tense bullae*** after ≥ 2 weeks;
- Due to morphologic similarity of skin lesions, PG was previously called "***herpes gestationis***". But is not associated with any active or previous herpes virus infection;
- Exacerbations and remissions are common in pregnancy, and so are flares *postpartum*.

Diagnosis is made by the clinical appearance and by direct immunofluorescence on skin biopsy samples— shows C3 complement deposition;

- Linear C3 complement deposition along the basement membrane zone (with concomitant IgG deposition in some cases). This confirms;
    - Autoimmune nature of lesions;
    - Distinguishes PG from PEP— direct immunofluorescence is **negative** in PEP.
- The IgG antibody targets the "*bullous pemphigoid 180-kd hemidesmosomal glycoprotein*" antigen of the basement membrane zone (*see Figure*)— explains resemblance to bullous pemphigoid.

Management aims to relieve pruritus and prevent new blister formation. Topical ± oral steroids may be needed in addition to anti-histamines.

It is important to note—

- The lesions heal post-pregnancy *without scarring* unless they get infected;

- PG is associated with preterm delivery and small for gestational age births, but no increase in pregnancy loss has been reported. These autoantibodies are also observed to cross-react with basement membrane of amnion/placenta on indirect immunofluorescence;
- Mild neonatal pemphigoid-like lesions can develop due to transplacental IgG antibody transfer. But the condition resolves spontaneously;
- PG recurs in most subsequent pregnancies.

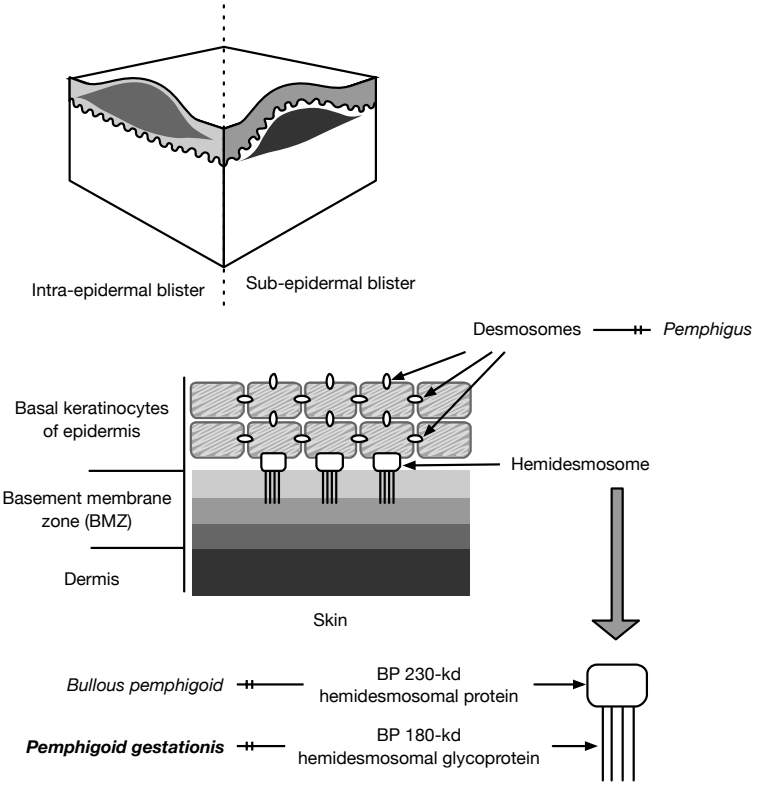


Figure. Illustration of pemphigus, bullous pemphigoid, and pemphigoid gestationis pathophysiology.

c) Prurigo of pregnancy

Prurigo of pregnancy is a common pruritic disorder.

Affected women develop itchy papules on **extensor surfaces** of limbs, shoulders and abdomen— these lesions excoriate and are thought to be associated with previous atopic tendency;

- It starts around the 3rd trimester and resolves post-partum;
- Management is symptomatic with emollients and topical steroids;
- No adverse effects on mother or baby have been observed.

It should be distinguished from ***pruritic folliculitis***— *an acneiform eruption* also be observed during pregnancy.

d) Pruritic folliculitis (PF) of pregnancy

PF is an uncommon pruritic ***follicular*** eruption seen in pregnancy.

- It presents with papules and pustules that mainly affect the trunk and sometimes limbs. Because of similar appearance to acne lesion, PF is often considered a subtype of hormonally-induced acne;
- These start in the 2nd and 3rd trimester, and resolve after delivery.
- Topical steroid treatment is effective.

Biopsy tends to be reserved for severe cases or those that fail to respond to topical steroids.

CHAPTER 27 INFECTIONS IN PREGNANCY

Pregnancy does not alter a woman's resistance to infection.

The severity of any infection correlates with its effect on pregnancy—

- More severe the infection and earlier in pregnancy it occurs— ↑ is the risk of miscarriage or IUD;
- Infections can have a direct effect as well as an indirect effect on the fetus;
    - The indirect effect occurs by ↓ oxygenation of placental blood and by altering the nutrient exchange through the placenta;
    - The direct effect depends on the ability of the invading organism to penetrate the placenta and infect the fetus— viruses have more direct effect than bacteria because of their size.
- Most viral infections do not affect the fetus *unless the mother's infection is very severe*;
    - Three exceptions to this are **rubella, CMV and herpes simplex** infections—These may cause congenital defects (see Table);
    - Microcephaly, congenital heart disease, eye damage (e.g. cataract), deafness, hepatosplenomegaly (with jaundice), purpura and in childhood— mental impairment may be seen.

As maternal antibodies cross the placenta they offer the fetus some degree of immunity;

- But this immunity is not able to counter *primary infections*;
- The fetus becomes immunologically competent by itself from about 14th week of gestation, but this protection is not very effective.

Table. Specific infections that adversely affect a fetus, neonate or pregnant woman— *Aide mémoire: STORCH*[5].

Acronym	Infection
S	Syphilis
T	Toxoplasmosis
O	Other
	Bacterial vaginosis
	Trichomonas vaginalis
	Group B streptococcus
	E. coli
	Ureaplasma urelyticum
	Haemophilus influenza
	Varicella
	Listeria monocytogenes
R	Rubella
C	Cytomegalovirus
H[5]	Herpes
	Human immunodeficiency virus (HIV)
	Hepatitis B
	Human papillomavirus
	Human parvovirus

(I) Infections causing congenital abnormalities

TORCHS is an acronym for organisms that are notoriously associated with congenital abnormalities (see Figure).

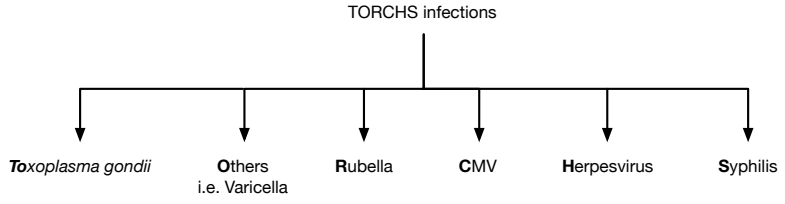


Figure. TORCHS infections associated with congenital abnormalities.

i) Toxoplasmosis and pregnancy

Toxoplasma gondii is a protozoan parasite. It is often found in cat faeces, soil or uncooked meat.

Exposure can cause *toxoplasmosis* in an adult. Infections acquired in pregnancy may lead to a miscarriage or adverse effects *in utero*.

Maternal infection occurs by ingestion of the parasite from undercooked meat or from unwashed hands;

- The initial infection is usually asymptomatic, or may be a glandular fever-like illness with occasional tender lymph nodes;
- Parasitaemia usually occurs within 3 weeks of infection;
- Exposure to toxoplasma leads to lifelong immunity in immunocompetent individuals.

Vertical transmission from mother to fetus or neonate can only occur during the parasitemia of a primary infection— as this leads to immunity afterwards;

- Exposure early in pregnancy has a relatively low-risk of vertical transmission but is more likely to cause fetal damage;
    - These include IUD, miscarriage, or serious birth defects such as chorioretinitis, microcephaly, hydrocephalus, intracranial calcifications, hepatosplenomegaly and severe FGR;
    - Congenital toxoplasmosis is rare but potentially serious infection— infants present with tetrad of chorioretinitis, hydrocephalus, intracranial calcifications and convulsions (see Figure).
- In the 3rd trimester, 85% of infections are vertically transmitted, but risk of fetal damage is relatively low;
    - Most infected infants (at later gestations) are asymptomatic at birth;
    - But these individuals develop long-term sequelae including chorioretinitis, severe visual impairment, hearing loss or neurological abnormalities after several years.

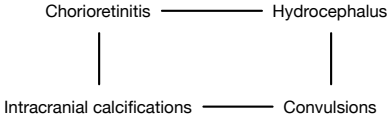


Figure. Tetrad of congenital toxoplasmosis.

Screening tests for maternal toxoplasmosis are available but have not been shown to conclusively identify if the infection is acute or chronic;

- Enzyme-linked immunosorbant assays (ELISAs) are available for IgM antibody— often serial testing for rising titres is necessary.
- The gold-standard of diagnosis for primary infection with toxoplasma during pregnancy is made by the Sabin-Feldman dye test— a serologic test but is not widely available.

If suspicion of congenital toxoplasmosis has arisen because of an abnormal ultrasound scan of the fetus, an amniocentesis can be performed;

- Polymerase chain reaction (PCR) analysis of amniotic fluid is highly accurate for the identification of *Toxoplasma gondii*;
- If toxoplasmosis is found to be the cause of abnormalities detected on ultrasound scan of the fetus, then termination of pregnancy can be offered.

Less treatment options are available based on severity of manifestations;

- Spiramycin treatment is safe in pregnancy (3-week course of 2–3 g per day);
    - It has been shown to reduce *incidence* of vertical transmission;
    - But has not been shown to definitively ↓ the incidence of clinical congenital disease.
- Congenital toxoplasmosis— may often consider use of pyrimethamine + sulfadiazine, with supplementary folic acid to counteract their antifolate activity.

Preventative measures are recommended in all pregnant women;

- Avoid eating less-cooked meat, e.g. *rare-done steaks*;
- Avoid handling cats and cat litter;
- Avoid touching eyes or mouth while handling raw meat;
- Hand hygiene.

ii) Varicella zoster virus and pregnancy

Varicella zoster virus (VZV) belongs to herpes-virus family. It is transmitted by droplet spread and direct personal contact.

In non-pregnant individuals, it causes the common chicken-pox;

- Following the primary infection, the virus remains dormant in sensory nerve root ganglia.
- Sometimes, the dormant virus reactivates to cause a vesicular erythematous skin rash in a dermatomal distribution— called herpes zoster (HZ) or 'shingles' rash.

It is transmitted by;

- Droplet spread and direct personal contact with individuals with active chickenpox lesions;
- Infection can also be acquired by direct contact with lesions of an individual with HZ.

Pregnant women are observed to have a complicated course with VZV infection;

- Non-immune pregnant women may develop a serious pneumonia, hepatitis or encephalitis;
- Miscarriage, however, *does not appear to be increased* if infection occurs in the 1st trimester;
- Pregnant women may also vertically transmit the virus to the fetus.

Diagnosis is mostly clinical and confirmation utilizes serologic testing;

- VZV IgM antibodies are most frequently tested but these may be negative in acute presentation— as there is a time lag between infection and production of antibodies;
- VZV IgG antibody positivity is indicative of immunity.

Once infected, the fetus may manifest the infection variably;

- Fetus develops viral vesicles that lead to a wide spectrum of abnormalities;
- This leads to **fetal varicella syndrome (FVS)** or manifest as **varicella infection of the newborn**;
    - FVS is characterized by one or more of the following;
        - Skin scarring in a dermatomal distribution;
        - Eye defects (microphthalmia, chorioretinitis, cataracts);
        - Hypoplasia of the limbs;
        - Neurological abnormalities (microcephaly, cortical atrophy, mental restriction and dysfunction of bowel and bladder sphincters).
    - If the maternal infection appears 7 days *before* or 7 days after *delivery*— the infection may disseminate as *varicella infection of the newborn* (see Figure). This occurs due to lack of maternal antibody production and transfer to fetus.

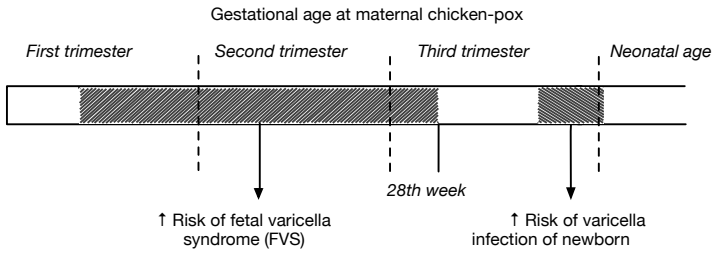


Figure. Illustration of maternal chicken-pox infection and fetal risks with reference to gestational age.

Women should be asked whether they have had chickenpox— at the initial booking visit. They should be advised to avoid exposure to if they have no history of previous infection.

If contact occurs with chickenpox, it is imperative to determine;

- Significance of the contact;
    - Significant contact is defined as being in the same room as someone for ≥15 minutes, or face-to-face contact;
    - Individuals with the virus are infectious for 48 hours prior to the appearance of the rash and until the vesicles crust over (usually 5 days).
- Susceptibility of the patient;
    - Blood test for confirmation of VZV immunity, by testing for VZV IgG;
    - This can give results within 24–48 hours.

If immunity is not confirmed and there has been significant exposure;

- Women should be given varicella zoster immunoglobulin (VZIG);
- VZIG is effective when given up to 10 days after contact and may prevent or **attenuate** the disease.

If the mother has developed chickenpox during pregnancy, she should be offered;

- Oral acyclovir— if they present within 24 hours of the onset of the rash and if they are more than 20 weeks' gestation;
- Detailed ultrasound examination at 16–20 weeks or 5 weeks after infection;
    - This is because features of fetal infection may not be detected before atleast 5 weeks;
    - Ultrasound may detect limb deformities, microcephaly, hydrocephalus, soft-tissue calcification and FGR.
- VZIG has no therapeutic benefit once chickenpox has developed.

If maternal infection occurs at term— i.e maternal rash appears ± 7 days from EDD;

- Delivery during this *phase of viremia* carries ↑ risk of complications. These include;
    - Maternal bleeding;
    - Thrombocytopenia;
    - Disseminated intravascular coagulation (DIC);
    - Hepatitis.
- There is a significant risk of varicella of the newborn;
    - Elective delivery should be avoided until 5–7 days after the onset of maternal rash;
    - This allows passive transfer of antibodies from mother to the fetus;
    - The neonate should be given VZIG and monitored for symptoms upto 4 weeks.
- If neonatal chickenpox has developed;
    - VZIG is of no benefit;
    - In these cases, treatment with acyclovir is considered instead.

Women with chickenpox should avoid contact with other pregnant women and neonates until the lesions have crusted over.

Varicella zoster vaccination is available and can be used in seronegative women before conception.

iii) Rubella virus in pregnancy

Rubella virus is a togavirus spread by droplet transmission. *Chikungunya virus also belongs to the togavirus family (but is spread via mosquitos);*

- Rubella virus causes rubella (previously known as *german measles* or *3-day measles*);
- Congenital rubella syndrome (**CRS**) *may be* observed in the newborn when exposure to a non-immune mother occurs during pregnancy.

Measles, mumps, and rubella (MMR) vaccine has made rubella a rare infection;

- Vaccination of children after birth with booster doses is sufficient in most cases for life-long immunity;
- This life-long immunity also is protective towards the fetus when these individuals conceive.

Most cases of rubella occur where vaccination regimens are not followed. Exposure to rubella virus may manifest in one of two ways;

- A non-immune mother's reaction to exposure is a fever with a rash that lasts few days. It may be subclinical in many cases (upto 50%);
- CRS of the fetus may occur— **this risk ↓ with ↑ gestational age**;
    - CRS is characterized by congenital defects like sensorineural deafness, congenital cataracts, blindness, encephalitis and endocrine disorders;
    - These defects can occur in upto 100% infants infected during first 11 weeks of pregnancy;
    - Rubella infection prior to the estimated date of conception or after 20 weeks' gestation carries no documented risk to the fetus.

If infection during pregnancy is confirmed, the risk of CRS should be assessed;

- If infection occurred prior to 16 weeks' gestation— termination of pregnancy should be offered;
- If the infection occured later in pregnancy— reassurance is often offered as evidence shows low-risk.

Screening is recommended at booking for all pregnanct women— to detect immunity to rubella using serology;

- This identifies susceptible women to rubella infection during pregnancy and its effects;
- Non-immune individuals should receive *postpartum vaccination* to protect future pregnancies. Due to the theoretical risk of viral reactivation associated with live-virus vaccines;
    - It is recommended that women *avoid pregnancy* upto 3-months after vaccination;
    - Vaccine administration is ***contraindicated in pregnancy***.

iv) Cytomegalovirus and pregnancy

Cytomegalovirus (CMV) is a DNA virus. It also belongs to herpesvirus family.

- It is transmitted by respiratory droplet transmission and is *excreted in high levels in the urine*.
- Like other herpes viruses, CMV has the capacity to establish latency and reactivation;
    - It persists in the lymphocytes throughout life and can be transmitted by blood transfusion or transplantation.
    - Reactivation occurs intermittently, with shedding in the genito-urinary or respiratory tract.

It is a common virus and about 60% of women are already seropositive for CMV before pregnancy;

- During pregnancy, if it occurs— primary infection usually manifests mild non-specific flu-like symptoms in the mother;
- Vertical transmission from mother to fetus *or neonate* occurs mainly during viremic phase;
    - Viremia of a primary infection has a ↑ risk of vertical transmission;

    - Fetal infection can also occur with reactivation— as primary infection leads to a predisposition of *residual lifelong latency*.
- Primary infection is more likely to cause— symptomatic congenital CMV and long-term sequelae compared to risks with reactivation of infection.

Diagnosis is with serologic testing—

- Development of CMV antibodies in a seronegative woman, who initially develops CMV IgM antibody and subsequently IgG antibody;
    - Since IgM can be secreted for several months, it is not sufficient to simply demonstrate IgM in a sample at the time of presentation;
    - It has to be a new finding in a woman who was negative for IgM at the time of booking.
- Although it may be difficult in some cases to obtain blood samples from before the illness.

The diagnosis is often made after abnormalities are seen in the fetus on ultrasound scan;

- These occur as a result of vertical transmission of the fetus and include;
    - FGR;
    - Microcephaly;
    - Intracranial calcification;
    - Ventriculomegaly;
    - Ascites or hydrops.
- If there is a suspicion that the fetus is infected by CMV— amniotic fluid can be tested for the virus by PCR. (***as the virus is excreted in fetal urine***);
- Sometimes, antenatal ultrasound may not detect abnormalities. But affected infants may later be found to have neurological damage such as blindness, deafness or developmental delay;
- If abnormalities are detected on ultrasound and correlate with congenital CMV infection, termination of pregnancy should be discussed;
- If CMV infection is known to have occurred, but the fetus appears normal on ultrasound— there still remains a 20% chance of neurological abnormality in this fetus.

Most of the infants (upto 90%) born are asymptomatic;

- But in rare severe cases, neonate may have anaemia and thrombocytopaenia with purpural rash, hepatosplenomegaly, and jaundice;
- CMV is the most common cause of *sensorineural deafness* in children.

Routine screening has proved to be of no value as there is no vaccine or preventative therapies. Antiviral therapy with ganciclovir may be considered for treatment in some cases.

v) Genital herpes in pregnancy

Herpes simplex virus (HSV) is a double-stranded DNA virus. It has two viral subtypes, HSV-1 and HSV-2.

In non-pregnant individuals;

- HSV-1 is notoriously known for causing the common orolabial herpetic lesions. These infections are usually acquired during childhood through direct physical contact.
- Genital herpes is an STI most commonly caused by HSV-2 (occasionally by HSV-1);
    - Genital herpes is the most common ulcerative sexually-transmitted infection (STI);
    - It manifests mostly as mild ulcerative lesions on vulva, vagina or cervix which sometimes may be preceeded by viremia associated with systemic manifestations— fever, malaise and adenopathy.
- HSV infection predisposes to a residual lifelong latency with periodic recurrent attacks. HSV lies dormant in dorsal root ganglion of sensory nerves.

In pregnant individuals, however, there are certain risks with maternal genital herpes (not specifically HSV 1 or HSV 2)— whether it is primary infection or secondary recurrence;

- A primary infection during pregnancy may be associated with systemic symptoms and may cause urinary retention in the mother;
- Very rarely, herpes simplex virus (HSV) may cross the placental barrier to infect the fetus *in utero*;
    - Although rare, the likelihood of such an occurrence is associated with;
        - Infection early in pregnancy;
        - Primary infections— especially *viremic phase of primary infection*.
    - This **congenital herpes** is associated with micro-ophthalmia, chorioretinitis and microcephaly and cerebral calcifications if the fetus survives risk of spontaneous abortion.
- If genital herpes occurs **near delivery**— this can lead to potentially fatal **neonatal herpes**;
    - Almost all cases of neonatal herpes result from contact with *infected* maternal secretions;
    - Factors influencing ↑ risk of such direct transmission include—
        - Primary infection;
        - Lack of transplacental transmission of maternal neutralizing antibodies;
        - >8–12 hours since the rupture of membranes before delivery;
        - The use of fetal scalp electrodes;
        - Vaginal delivery during *active viral shedding*.
    - Neonatal herpes is classified into three subgroups;
        - Disease localized to skin, eye and/mouth;
        - Disease localized to central nervous system— e.g. encephalitis;
        - Dissemination with multiple organ involvement— *highest risk of neonatal death*.
    - Those who survive have severe sequelae— meningoencephalitis, mental retardation, pneumonia, hepatosplenomegaly, jaundice, and petechiae.

Diagnosis of genital herpes is mostly clinical, but confirmation requires specialized testing;

- In order to determine *mode of delivery*, it is also important to determine;
    - Viral shedding in infections close to term;
    - Whether infection is *primary or secondary*.
- Tzanck smear (=staining with Wright or Giemsa) of lesions shows multinucleated giant cells;
- 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);
- Testing by polymerase chain reaction (PCR) on lesions is more sensitive— in those at risk, it is *best for detection of viral shedding*;
- HSV type-specific IgG antibodies, i.e. anti-HSV1 or anti-HSV2 IgG are also gaining widespread use;
    - 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**.

Management—

- For maternal genital herpes, use of PO acyclovir is recommended;
    - This is associated with a ↓ in the duration and severity of symptoms;
    - This also ↓ the duration of viral shedding;
    - It is well tolerated and considered safe in pregnancy *after 20 week's gestation*;
    - If delivery **does not ensue within next 6 weeks**, vaginal delivery is expected *without risks*.
- If delivery is to occur **within 6 weeks** of active genital lesions or positively shedding the virus;
    - A cesarean section should be performed— if the initial event was a primary infection, be-

cause the risk of *neonatal transmission* is very high;

- However, if the initial event was a recurrent episode of genital herpes—C- section is **not** necessary and vaginal delivery can be planned, as;
  - The risk of neonatal transmission is very low (1-3%);
  - Recurrence in these cases can be confirmed with relative surety using HSV type-specific IgG antibodies and virology/PCR correlation;
  - Oral acyclovir administration from 36 weeks' gestation— to ↓ lesions and need for C-section;
  - However, during vaginal delivery, all *factors influencing direct transmission* should still be optimized (see above).

- If membranes have been ruptured for > 8–12 hours before birth;
  - The virus may already have infected the fetus and cesarean delivery would be of no value;
  - Acyclovir given intrapartum to the mother and later to the neonate may be considered.

vi) Syphilis in pregnancy

Syphilis is a sexually-transmitted infection (STI) caused by bacterium *Treponema pallidum*.

The 'infection screen' at booking can lead to detection of maternal syphilis— primary, secondary, latent or tertiary syphilis (see Figure).

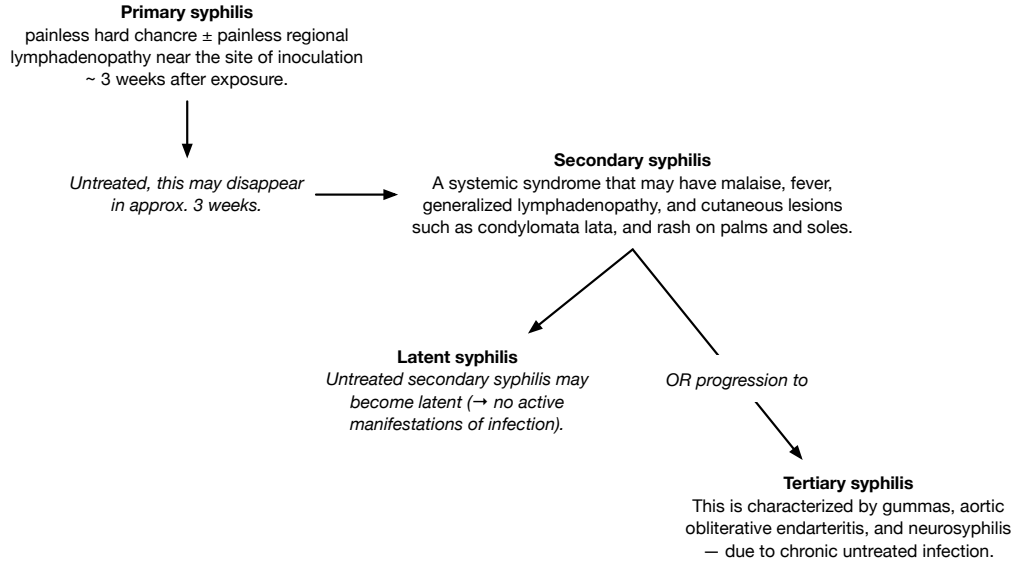


Figure. Primary, secondary, latent and tertiary stages syphilis.

Maternal syphilis infection can result in a range of adverse pregnancy and neonatal outcomes;

- It can lead to late miscarriage in pregnancy or cause fetal exposure to infection;
- Fetal exposure to infection can occur vertically by trans-placental transmission or during labor if fetus comes in contact with an active syphilis lesion (e.g. on the cervix).

Most fetal risk is with vertical transmission of infection;

- This risk of vertical transmission ↓ with ↑ duration of maternal syphilis prior to pregnancy;
- Early, untreated primary or secondary syphilis in mother has **highest risk** of vertical transmission.

Vertical transmission of syphilis in pregnancy is associated with;

- Fetal growth restriction (FGR);
- Fetal hydrops;

- Preterm birth;
- Neonatal death;
- Congenital syphilis— If the fetus survives initial infection, it is in the 2nd stage of syphilis at birth.

Once infected, the fetus may manifest the congenital syphilis infection variably;

- A severe fetal infection can cause intrauterine death;
- A neonate manifesting symptoms early in life— *early congenital syphilis*;
- A child who eventually develops the stigmata of congenital syphilis— *late congenital syphilis*;
- A child who is asymptomatically infected.

Because of available effective treatment that ↓ fetal morbidity, syphilis screening is *recommended in all pregnant women as part of 'infection screen' at booking*;

- For screening individuals, Enzyme Immunoassays (EIAs) that detect specific IgG and IgM antibodies is gaining popularity;
    - EIAs are replacing the previous *non-specific antibodies + treponemal specific antibodies testing combination* for syphilis screening;
    - This is because 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.
- Other testing options are;
    - Dark-field microscopic detection of treponemes— most accurate test but requires microscopy of lesions;
    - The 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).

The initial step is to confirm the diagnosis and to test for any other sexually transmitted diseases;

- Contact tracing of sexual partners and their treatment is indicated;
- Other older children may also need to be screened for congenital infection.

Antibiotic therapy is the mainstay of treatment for both mother and child;

- Benzathine penicillin is safe in pregnancy— it is highly effective in preventing congenital syphilis;
- A ***Jarish–Herxheimer reaction*** may occur with treatment;
    - This is a result of release of proinflammatory cytokines in response to dying organisms;
    - Worsening of symptoms, and fever for 12–24 hours after commencement of treatment— is often suggestive of this reaction;
    - It may be associated with uterine contractions and fetal distress. Hospital admission for monitoring aids in management.
- An infected baby may be born without signs or symptoms of disease;
    - But if not treated immediately, may develop serious problems within a few weeks;
    - Developmental delay, seizures or death can occur in untreated infants.

(II) Infections associated with pregnancy loss and preterm birth

i) Parvovirus in pregnancy

Parvovirus B19 (PVB19) is a relatively common virus;

- It is transmitted through respiratory droplets;
- Upto 50% women in childbearing age are seropositive for previous exposure to parvovirus B19;
- It is observed most commonly in pregnant women who work with children, e.g. school teachers.

a) Clinical features

In children it is notorious for causing the classic rash which gives its name— slapped cheek syndrome (also known as ***erythema infectiosum*** or ***fifth disease***).

In adults, many cases are asymptomatic or produce symptoms of a mild flu-like illness ± arthropathy.

Exposure to an un-immune pregnant woman is associated with ↑ risk of vertical transmission to the fetus and subsequent ***pregnancy loss or preterm birth***;

- This risk is highest if infection occurs in the second trimester;
- In most fetuses infected with PVB19, there is spontaneous resolution without complications;
- In others, aplastic anaemia leading to **non-immune hydrops fetalis** (NIHF) can occur;
- A hydropic fetus may recover spontaneously as the mother and fetus recover from the virus, or may require treatment by *in-utero* transfusion.

b) Diagnosis

Most cases are detected on fetal ultrasound— as fetus develops hydrops due to high output cardiac failure and liver congestion secondary to fetal anemia.

If a fetus is hydropic, the velocity of blood flow in the fetal middle cerebral artery should be measured. If the velocity is high, it is suggestive of anaemia, and PVB19 would be one of several differential diagnoses.

However, diagnosis in mother is made by demonstrating seroconversion of the mother;

- This is done by detection of anti-PVB19 IgM antibodies previously tested negative in the mother;
- It may be false-negative as there is often a time lag between infection and production of antibodies;
- Although it may be difficult to obtain a maternal blood sample from before the illness.

Viral DNA detection using PCR in maternal and fetal serum or amniotic fluid, is the **most sensitive and accurate** diagnostic test.

c) Management

Infection in the first 20 weeks of pregnancy may lead to hydrops fetalis and intrauterine death;

- As treatment by intrauterine transfusion is not possible at early gestations. Prior to 20 weeks, the fetal loss rate is approximately 10%;
- After 20 weeks' gestation, in utero intrauterine transfusion (IUT) is a treatment option;
- Unlike *immune-mediated hydrops fetalis*, the prognosis is very good in these cases with most cases often requiring only one session of *in utero* transfusion.

If the fetus survives the anaemia, the outcome is usually normal.

Routine screening in pregnancy is not currently recommended as there is no treatment or prevention to protect the baby from being infected.

ii) *Listeria monocytogenes* infection in pregnancy

Listeria monocytogenes is an aerobic and facultatively anaerobic motile gram-positive bacillus.

a) Pathogenesis

It has two major virulence factors and an unusual lifecycle (see Figure);

- It possesses Listeriolysin O (**LLO**)— a β-hemolysin toxin. LLO permits L. monocytogenes to escape from phagosomes into the cytosol without damaging the plasma membrane of the infected cell;
    - Escape from phagosomes into the cytosol allows the listeria to live intracellularly. Here they are protected from extracellular immune system factors i.e. complement system and antibodies;
    - Thus, those with ↓ cell-mediated immunity (CMI), e.g. the elderly and pregnant women-- are at ↑ risk.
- Actin assembly-inducing protein (ActA)— helps listeria spread cell-to-cell.

L. monocytogenes is ubiquitous in nature and infection is mostly foodborne. However;

- It is not transmitted through hot well-cooked foods;
- Althought, it does not multiply in the freezer, it can be transmitted in chilled foods— as it multiplies at refrigerator/fridge temperatures.

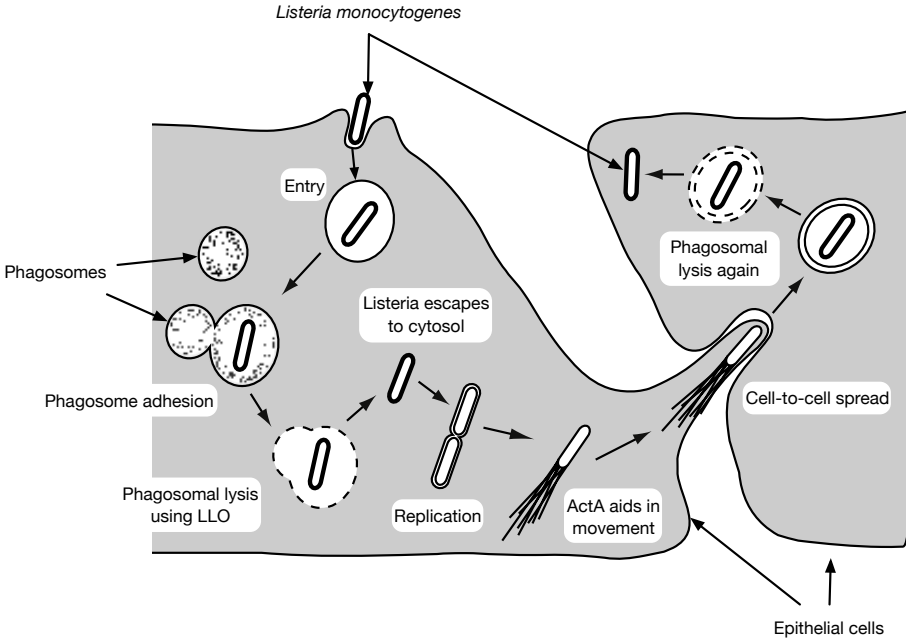


Figure. Illustration of pathogenic virulence factors aiding in listerial infection and spread.

b) Manifestation of clinical disease

In healthy adults and children;

- Listeria infection is generally asymptomatic or may manifest as diarrhea;
- Often there is a transient asymptomatic carrier state.

In pregnant women, symptomatic infection is more common as a febrile illness;

- Bacteremic phase is associated with transplacental transmission to fetus and amnionitis may occur—
    - There is ↑ risk of spontaneous abortion, premature delivery, or stillbirth;
    - Transplacental infection may cause early neonatal death or granulomatosis infantiseptica;
    - **Granulomatosis infantisepticum** presents in infants as a febrile illness with organ abscesses and erythematous rash (small, pale nodules or granulomas).
- The newborn can also be affected by following descent through the cervix ***during labour***. In these cases, infection often manifests 2-3 weeks after birth with meningitis.

c) Diagnosis

The diagnosis of listeriosis is based on;

- Clinical suspicion and isolation of the organism from blood, vaginal swabs or the placenta;
- Meconium staining of the amniotic fluid in a preterm fetus may increase clinical suspicion for listeriosis.

d) Treatment and prevention

For women with listeriosis during pregnancy, intravenous antibiotic treatment is indicated;

- This includes ampicillin 2g given q6hourly;
- Gentamicin addition may be considered to ↑ efficacy (but potentially riske should also be considered).

Prevention involves educating pregnant women of high-risk foods in pregnancy;

- Avoid soft and blue cheeses, patés and uncooked, partially cooked or prepared food;
- Drink only pasteurized or UHT milk;
- Avoiding contaminated cabbage (coleslaw)— this has also been cited as source of infection.

Screening remains impractical.

iii) Malaria in pregnancy

Malaria refers to a protozoan-parasite infection transmitted by the female anopheles mosquito.

It is endemic in sub-Saharan Africa, South Asia and parts of South America.

Malaria can be caused by 4 species of plasmodium;

- Plasmodium falciparum— malignant tertian malaria; it carries worst prognosis in pregnancy relative to other species;
- Plasmodium vivax— bening tertian malaria;
- Plasmodium ovale— milder form of tertian malaria;
- Plasmodium malariae— quartan malaria.

a) Clinical features

In non-pregnant individuals, infection manifests with cyclical fever spikes. Most manifestations of malaria are secondary to sequestration of parasitized erythrocytes in vasculature of organs.

Similarly, in pregnant women there is cyclical spiking pyrexia. Severity is also based on preexisting level of immunity (secondary to previous infection and treatment) of the mother. She may develop;

- Severe anaemia;
- Hypoglycaemia— may be severe in pregnancy;
- Pulmonary oedema— due to abnormal capillary permeability;
- Haemolysis— leading to jaundice and renal failure;
- Malarial parasitemia.

Infection during pregnancy is associated with effects on both mother and fetus;

- ↑ risk of miscarriage and preterm labour, especially with exacerbation of malaria.
- Most severe maternal complications (cerebral malaria, pulmonary edema and renal failure) occur with *P. falciparum*;
    - In some cases of *Plasmodium falciparum*, malarial parasites may even be found sequestrated in the **intervillous space of placenta** (see Figure);
    - This space is thought to be a relatively protected site for parasite sequestration, replication and *vertical transmission of plasmodia*;
    - Placental infection may alter placental function and ↓ oxygen and nutrient transport;
    - This is associated with FGR, ↓ birth weight and premature birth.
- Both P. falciparum and P. vivax infection during pregnancy are associated with ↓ weight at birth;
- Vertical transmission of both malaria and HIV to the fetus *is more likely* if the two infections coexist.

The neonates born with congenital malaria manifest fever, respiratory distress, pallor, anemia, hepatomegaly, jaundice, and diarrhea. An ↑ fetal/neonatal mortality rate with congenital infection is also observed.

b) Diagnosis

In endemic areas, any pregnant woman with cyclic fever spikes should be suspected of having the infection;

- Diagnosis is made by microscopic examination of thick- and thin-blood films;
- Antigen-detection by rapid diagnostic kits is gaining popularity;

- Serology is often not helpful in distinguishing current from previous infections.

Placental sequestration of parasites is associated with abnormal uteroplacental Doppler wave forms— ↑ ***resistance index (RI) ± diastolic notch*** in umblical artery may be observed.

For neonatal detection, microscopic examination may be carried out on cord blood for plasmodia.

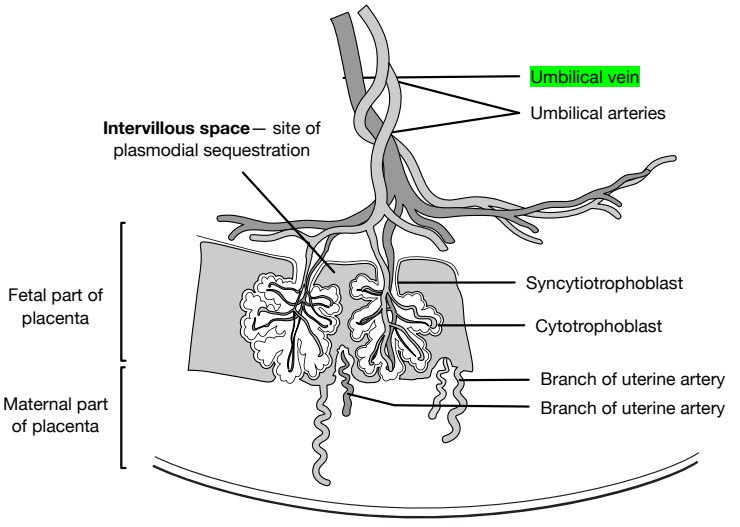


Figure. Illustration of intervillous space in placenta— *site of sequestration of plasmodia*.

c) Management

If malaria is suspected, prompt symptomatic and supportive treatment with appropriate antimalarial therapy is important.

The choice of antimalarial varies;

- Historically, chloroquine is the safest antimalarial;
- It is also the drug of choice for the prevention and treatment of malaria in pregnancy in **non-chloroquine-resistant regions;**
- Treatment of malaria in chloroquine-resistant regions varies;
    - Current WHO recommendations for treatment of malaria in pregnancy in resistant regions includes quinine + clindamycin during the first trimester;
    - If this treatment fails, artemisinin-based combination therapy (ACT) is indicated.

d) Prevention

Malaria is one of the few preventable causes of low-birth weight.

The WHO has updated prevention guidelines for high-risk in endemic areas **in Africa**. It recommends *intermittent preventive treatment in pregnancy* (IPTp) after the first trimester in that region;

- IPTp involves dosing of a safe antimalarial starting in the 2nd trimester;
- Atleast 3 doses should be given, with ≥ 1 month between doses;
- IPTp ↓ risk of neonatal mortality and placental malaria.

Universal preventive strategies include;

- Use of insecticide-treated bed nets;
- Appropriate clothing to ↓ mosquito bites;
- Insect repellent creams— **DEET**-containing insect-repellents are **safe** for use in pregnancy.

Pregnant women travelling to an area where malaria is endemic should take prophylactic antimalarial drugs;

- If the risk of chloroquine resistance is low, chloroquine + proguanil (+ folic acid) is used;
- If the risk of chloroquine resistance is high, after the 1st trimester mefloquine is the prophylactic drug of choice. However, *other non-drug preventative measures should also be used in 1st trimester*.

(III) Peripartum infections with serious neonatal consequences

i) GBS infection and pregnancy

Group B streptococcus (*Streptococcus agalactiae*, GBS) is a gram-positive coccus. It is a common vaginal commensal organism.

a) Clinical features

In an adult female, infection rarely produces any symptoms.

However, vaginal colonization in a pregnant woman can lead to colonization on the fetus during labor;

- This form of infection can manifest as **early-onset group-B streptococcus (EOGBS) infection**;
- Traditionally, EOGBS is defined as neonatal disease that occurs within 7 days of birth. Infected neonate may demonstrate signs of neonatal sepsis including sudden collapse, tachypnoea, nasal flaring, poor tone, jaundice, etc;
- EOGBS carries a **high risk of neonatal mortality**.

Not all neonates born to colonized women develop EOGBS. Other risk factors associated with neonatal EOGBS include;

- Intrapartum fever (>38°C);
- Prolonged rupture of membranes greater than 18 hours;
- Prematurity less than 37 weeks;
- Previous infant with GBS;
- Incidental detection of GBS in current pregnancy;
- GBS bacteruria— this is thought to reflect concomitant vaginal colonization.

b) Diagnosis

- In pregnant women, screening with vaginal and rectal swabs for GBS is effective for colonization status.
- In neonates, diagnosis is often made on GBS detection in blood culture. Although in some cases CSF culture may be considered.

c) Management and treatment

Antenatal management— If GBS is detected incidentally, antenatal treatment is **not recommended** as it does *not reduce the likelihood of GBS colonization at the time of delivery*.

Intrapartum antibiotic prophylaxis (IAP)— It is during labour that exposure to fetus occurs and IAP is a preventive strategy that addresses this transmission of GBS to the newborn;

- The Royal College of Obstetricians and Gynaecologists (RCOG) recommends IAP to be discussed with the pregnant women if GBS is detected;
- However, there should be a low threshold for administering IAP in those with;
    - More than 1 risk factor for EOGBS (*as described above*);
    - Previous baby with neonatal GBS;
    - GBS bacteriuria in this pregnancy.
- IAP involves administering IV Penicillin 3g to the mother soon after onset of labour (or after development of a risk factor) followed by 1.5g q4h until delivery. IV Clindamycin 900mg q8h in those allergic to penicillin may be used alternatively;

- However, if maternal chorioamnionitis is suspected clinically, it is better to choose ***broad-spectrum antibiotic therapy*** over an GBS-specific-antibiotic.
- IAP administeration is not recommended in those with;
    - GBS carriage detected in a previous pregnancy;
    - Planned C-section delivery in the absence of labour or membrane rupture— regardless of GBS colonization status.

Any newborn infant with clinical signs compatible with infection should be treated promptly with **broad-spectrum antibiotics**, which provide cover against *early-onset GBS disease and other common pathogens.* This is recommended whether *mother received intrapartum antibiotics or not.*

d) Prevention and screening

- Universal screening of pregnant women using vaginal and rectal swabs for GBS is recommended in USA but not in the UK.
- Assess, anticipate and treat those with risk factors *early using IAP*— is a widely accepted and acceptable strategy for ↓ the risk of EOGBS.

ii) Chlamydia and gonorrhoea and pregnancy

These are sexually transmitted infections (STIs).

Neisseria gonorrhoea and Chlamydia trachomatis are notorious for causing pelvic inflammatory disease (PID) in women.

a) Neisseria gonorrhoea

Neisseria gonorrhoeae is a gram-negative diplococcus.

Gonococcal infection in women is often asymptomatic. But most women present with mucopurulent vaginal discharge ± dysuria within 5 days of sexual intercourse;

- Rarely disseminated gonorrhoea may cause low-grade fever, a rash and polyarthritis;
- Infection in pregnancy is associated with ↑ risk of preterm rupture of membranes and preterm birth;
- Transmission to the fetus occurs at the time of delivery and can cause **ophthalmia neonatorum**.

b) Chlamydia trachomatis

Chlamydia trachomatis is an obligate intracellular organism. It has an unusual life cycle (see Figure) and shares certain bacterial as well as virus-like characteristics.

It infects the epithelium of the lower genital tract;

- Chlamydia is often asymptomatic in the pregnant woman.
- Infection in pregnancy is associated with preterm rupture of membranes, preterm delivery and ↓ birthweight.
- Transmission to the fetus occurs at the time of delivery and can cause **conjunctivitis** (often leading to *trachoma*) and **pneumonia**.

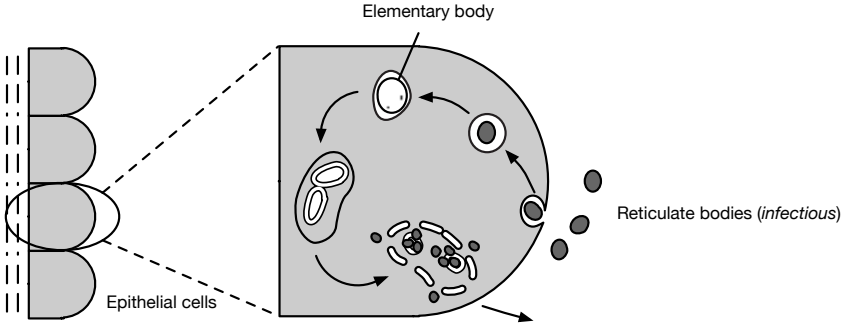


Figure. Life cycle of chlamydia— elementary bodies undergo binary fission and condense into reticulate bodies.

c) Diagnosis

If the symptoms suggest, or if the woman's sexual behaviour suggests that she may have gonorrhoea;

- Cervical and urethral swabs should be taken.
- Neisseria gonorrhoea is detected with growth on Thayer–Martin medium. On gram-staining, it appears as gram-negative diplococci.
- Chlamydia as it is too small to be seen on microscopy. Here, the use of nucleic acid amplification tests (NAAT) is sensitive for chlamydia and can also be used on *first-pass* urine samples.

d) Treatment

- Cephalosporins are effective against gonococcus, but empirical treatment for chlamydia should also be considered;
- Treatment with azithromicin or erythromycin is recommended for chlamydia;
- Tetracyclines such as doxycycline should be avoided, if possible, during pregnancy.

e) Screening and prevention

Screening cultures for chlamydia and gonorrhea aid in identifying if the fetus is at risk from delivery through an infected birth canal.

In the UK, NICE recommends that all women booking for antenatal care, who are younger than 25 years, are informed of the National Screening Programme.

(IV) Perinatal infections causing long-term disease in newborn

i) HIV and pregnancy

The human immunodeficiency virus (HIV) is a ribonucleic acid (RNA) retrovirus.

It can be transmitted through;

- Unprotected sexual contact;
- Blood products;
- Sharing IV needles;
- Transplacentally from mother to fetus;
- Contact with infected genital secretions at the time of vaginal delivery;
- Breast-feeding (potentially).

a) Clinical features

In adults, primary exposure manifests with flu-like symptoms and lymphadenopathy which often passes unnoticed. Infection progresses from asymptomatic stage to gradual immunocompromise eventually leading to acquired immunodeficiency syndrome (**AIDS**).

HIV infection has no adverse effect on pregnancy, nor any adverse effect on the progress of pregnancy been detected in evidence-based medicine.

However in infected-newborns, HIV has a similar course as chronic illness with significant morbidity. Thus, management of HIV in pregnancy is centered on preventing transmission to fetus and later, the newborn.

b) Maternal diagnosis

Early diagnosis is important, and it is recommended to screen all pregnant women at booking visit;

- ELISA testing for presence of antibodies to HIV antigens— is the recommended screening test;
- A 3-month window period is seen between HIV infection and a positive ELISA test. In these cases, detection of viral p24 **antigen** is helpful;
- Historically, confirmation of a positive ELISA was with western blot. The CDC, USA now also recommends HIV-1 and HIV-2 antibody differentiation immunoassays to confirm diagnosis and subtyping.

c) Management in pregnancy

Infected women who become pregnant have a *30% risk of transmitting the virus to the fetus/newborn*. If infected, all newborns develop HIV/AIDS over time.

The principal risks associated with mother-to-child (vertical) transmission are related to maternal plasma viral load, obstetric factors and infant feeding.

However, **implementation of these 3 interventions combined ↓ the transmission rate to < 2%**;

- Antiretroviral therapy given antenatally, intrapartum and later to neonate for the first 4–6 weeks of life.
    - Aim of anti-retroviral therapy is to ↓ the viral load to <50 copies/ml (***i.e. undetectable***);
    - Antiretroviral therapy is recommended in pregnancy. But the choice and dosing is decided with potential side effect profiles.
- Delivery by elective C-section if there is *high viral load*;
- Avoidance of breastfeeding— HIV-infected breast milk can potentially transmit HIV to newborn.

d) Peripartum management

- A planned vaginal delivery is an option for women who have an undetectable viral load (<50 copies/ml) at or beyond 36 weeks' gestation;
- In women with an undetectable viral load (<50 copies/ml)— there is no evidence to support an increased risk of transmission associated with interventions like amniotomy, use of fetal scalp electrodes, fetal blood sampling, and instrumental delivery;
- Maternal intravenous anti-retroviral (usually *azidothymidine*) administration should be considered during labor in women who have a high viral load (>1,000 copies/ml) at the time of delivery;
- Coexisting sexually transmitted infections (STIs), chorioamnionitis and ruptured membranes for >4 hours increase the risks of infection to the baby.

e) Management of infants

- The cord should be clamped as early as possible after delivery and the baby should be bathed immediately after the birth;
- The decision on whether or not to breastfeed is controversial. If safe infant feeding alternatives are **available**, all women who are HIV positive should be advised not to breastfeed;
- Infants born to women with HIV should be covered with oral azidothymidine for 4–6 weeks and follow routine vaccination programmes.

f) Diagnosis of infection in newborns

- Maternal IgG antibodies crossing the placenta are detectable in most neonates of mothers who are HIV positive— hence, the diagnosis of infection can not be made with antibody detection serologic tests;
- Direct viral amplification by PCR is used ***instead*** for the diagnosis in newborns. Typically, tests are carried out at birth, then at 3 weeks, 6 weeks and 6 months of age.

g) Other preventative measures

- Sexual partners of infected women should be traced and managed;
- Insemination may be considered if an individual in a couple is HIV-positive to prevent transmission to the partner;
- As the HIV infects the amniotic fluid as well as the women's blood, full infectious disease control precautions should be taken by attendant medical staff during labour and childbirth.

ii) Hepatitis B and pregnancy

The hepatitis B virus (HBV) is a DNA virus. It is transmitted mainly via blood and sexual contact but can also potentially transmit via other body fluids e.g. saliva.

Population groups which use intravenous recreational drugs are at especially high-risk of transmission.

HBV primarily infects the liver. The HBV has an incubation period of 6 weeks to 6 months.

The clinical presentation of primary infection varies;

- Asymptomatic or mild flu-like illness which may go unnoticed;
- Other affected individuals may present with a febrile illness together with jaundice and elevated transaminases (ALAT and ASOT).

Chronic infections or carrier-states may present with slowly progressing cirrhosis and deranged LFTs.

The diagnosis is with hepatitis B surface antigen (HBsAg) serology, which is highly effective as a screening test;

- During the 'window period' of primary infection, however, hepatitis B core IgM antibody (HBcAb IgM) is the only positive serologic test (see Figure);
- Hepatitis B e-antigen (HBeAg) on serology and/or HBV DNA positivity on polymerase chain reaction (PCR) indicates active viral replication and risk of ***both horizontal and vertical transmission***;
- Anti-hepatitis B surface-antibodies (HBsAb) confirms immunity. This may occur after primary infection as a *natural course of disease* or after vaccination with hepatitis B recombinant DNA vaccine.

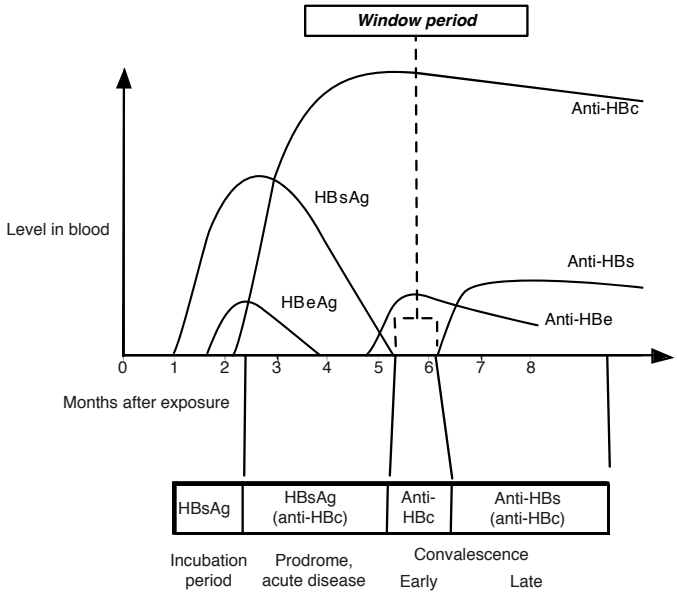


Figure. Illustration of positivity in hepatitis B serologic tests in an adult.

Pregnant females infected or exposed to hepatitis B have ↑ risk of;

- Acute viral hepatitis;
- Miscarriage or pre-term labor;
- Maternal fulminant hepatic failure— more likely if infected with hepatitis E in pregnancy;
- Chronic hepatitis B and later cirrhosis;
- Mother-to-child vertical transmission— this exposure to neonate is predominantly at the time of vaginal delivery. Transplacental fetal exposure is possible but is **rare**.

Pregnant females who are positive for HBsAg and HBeAg carry a 95% risk of vertical transmission to the baby at the time of vaginal delivery. This mother-to-child vertical transmission is especially important to note because;

- It can be fatal for the baby;
- The risks chronic carrier state after vertical transmission are particularly high. And thus, the neonate is predisposed to life-long risk of cirrhosis and hepatocellular carcinoma.

Mother-to-child transmission of HBV is approximately preventable in upto 95% cases. Factors that ↓ risk of vertical transmission include;

- Identification of high-risk individuals and prompt vaccination before pregnancy;
- Early screening and detection of infected pregnant females;

- Active immunization of mother in pregnancy— this is safe because the vaccine contains killed virus;
- Consideration to mode of delivery— however, current evidence-based guidelines ***do not recommend*** C-section without additional obstetric indications.
- Administration of HBV vaccine ± immunoglobulins to the baby at birth;
    - The expanded program on immunization (EPI) in Pakistan recommends HBV vaccination to all newborns at age 6, 10 and 14 weeks;
    - If mother is infected (HBsAg positive) ± HBeAg positivity (for active viral replication)— postexposure prophylaxis is recommended. This include an additional dose of HBV vaccine + HBV immune globulin (HBIG) within 24 h after delivery;
    - This *combined post-exposure prophylaxis* provides better protection than either alone.

Breastfeeding is acceptable after neonate has received immunization.

Serological screening for HBV should be offered to all pregnant women at the 'booking-visit'.

The management of infected females in pregnancy is mainly conservative and supportive as there are no anti-virals available for this period. Women who screen positive for hepatitis B should also be referred to a hepatologist for ongoing monitoring for the long-term consequences of chronic infection.

iii) Hepatitis C and pregnancy

The hepatitis C virus (HCV) is an RNA virus. It is transmitted through infected blood products and IV recreational drug abuse. It can also occur with infected tattooing and body piercing instruments. Sexual transmission is relatively rare but can occur.

Hepatitis C is well-known for its lack of a significant acute-clinical syndrome with primary infections. Individuals presenting with HCV are found to have slow-fluctuating LFTs long after primary infection.

On the other hand, chronic HCV infections are a major cause of liver cirrhosis, hepatocellular carcinoma and liver failure.

Following initial infection upto 80% of females of child-bearing age are found asymptomatic;

- This is explained by the relatively slow progression of infection and clinical manifestations;
- The majority of pregnant women with hepatitis C will not have reached the phase of having chronic disease in their child-bearing age.

Testing for HCV involves anti-HCV antibodies' serology in serum as an effective screening test. Confirmatory testing is by PCR for HCV RNA, if a positive result is obtained.

In non-pregnant adults, interferon and ribavirin can be used to treat hepatitis C infection, but these are contra-indicated in pregnancy.

Mother-to-child transmission of HCV can occur due to contact with infected maternal blood around the time of delivery;

- The risk of mother-to-child transmission of HCV increases with increasing maternal viral load;
- The risk is higher in those also coinfected with HIV.

Infants infected with hepatitis C are generally asymptomatic, but may have;

- Mild nonspecific malaise, anorexia, or abdominal pain;
- Hepatomegaly— most frequent sign of disease in young children.

There is no strong evidence regarding the mode of delivery in women with hepatitis C. The only ***recommendation for C-section is if the woman is also HIV positive***.

There is also *not sufficient evidence regarding increased risk of transmission with breastfeeding* in HCV.

Due to lack of evidence-based effective interventions in ↓ HCV mother-to-child transmission and treatment of HCV in pregnancy— pregnant women should not be offered routine screening for HCV although this may be debated for individuals having higher-risk history.

The infected should also be referred to a hepatologist for management and treatment of infection.

CHAPTER 28 LABOUR

Labour can be defined as the process by which regular contractions bring about effacement and dilatation of the cervix and descent of the presenting part, ultimately leading to expulsion of the fetus and placenta from the mother.

This results in birth of a baby, delivery of the placenta and signals for lactation to begin.

(I) Anatomy relevant to labour

i) Maternal anatomy relevant to labour

a) Maternal pelvis

The female pelvis can be divided obstetrically into 2 broad areas;

- The false pelvis— lies above the pelvic inlet and has no obstetric importance;
- The true pelvis— lies below the pelvic inlet and is related to childbirth.

The true pelvis can be divided anatomically into pelvic inlet (brim), mid-pelvis and pelvic outlet (see Figure).

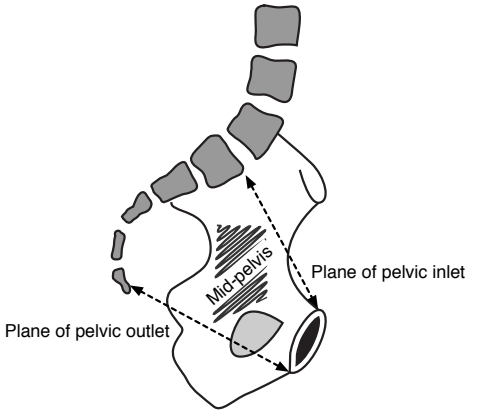


Figure. The maternal pelvis and its anatomic divisions (sagittal section view).

Based on obstetric significance, certain pelvic shapes have also been described. These are gynaecoid, android, anthropoid and platypelloid pelvises (see Figure).

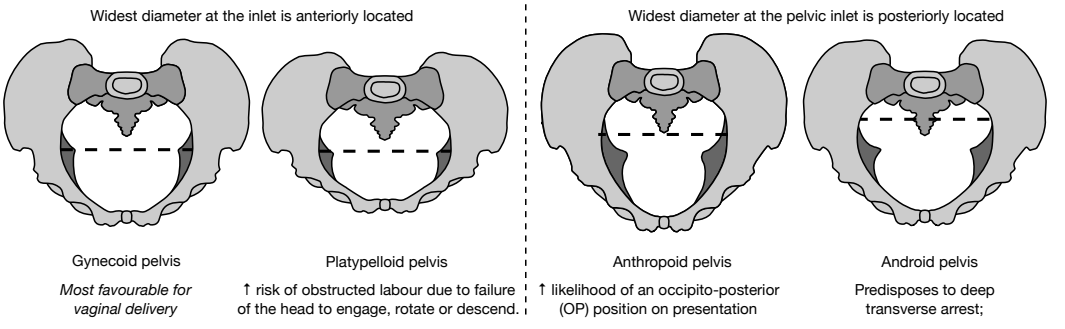


Figure. Types of female pelvis— *dashed lines indicate widest diameter at the pelvic inlet.*

The pelvic measurements hereforth are average values and relate to bony points in a common gynecoid pelvis.

It is uncommon to perform x-rays pelvimetry, computed tomography (CT) or magnetic resonance imaging (MRI) scans to measure the pelvic dimensions as they have little use in predicting the outcome of labour.

But pelvic ligaments at the pubic ramus and the sacroiliac joints loosen in late 3rd trimester, the pelvis becomes more flexible and these diameters may increase during labour.

b) Pelvic inlet (brim)

The pelvic inlet or pelvic brim is the inlet to the true pelvis (see Figures).

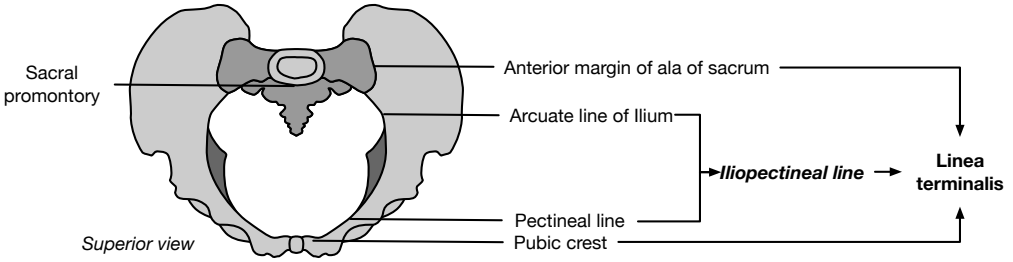


Figure. The pelvic inlet boundaries.

The boundary of pelvic inlet consists of the linea terminalis anterolaterally and sacral promontory posteriorly;

- The linea terminalis spans bilaterally from the anterior margin of the ala of the sacrum including the iliopectineal line and ends at pubic crest;
- The iliopectineal line can be anatomically divided into the arcuate line of the ilium and the pectineal line of the superior ramus of pubis.

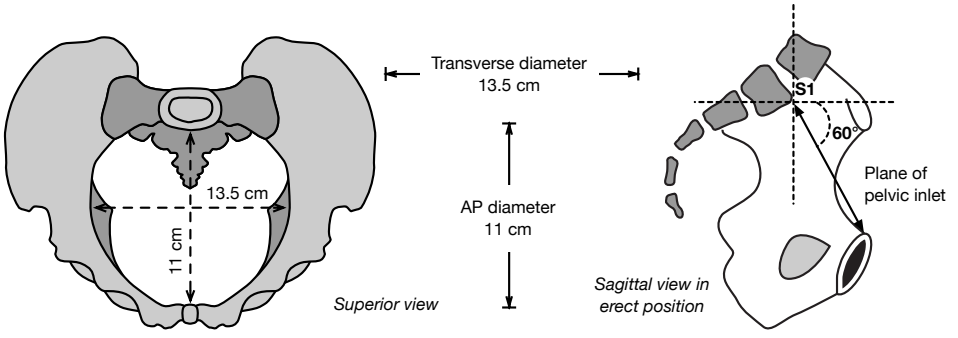


Figure. Dimensions and angle of plane of pelvic inlet with the horizontal axis.

c) The mid-pelvis

The mid-pelvis is also known as the midcavity of pelvis. This cavity is almost round, as the transverse and anterior diameters are similar at 12 cm (see Figure). Its boundaries are;

- Anteriorly by mid-symphysis pubis;
- Bilaterally by the pubic bones, obturator fascia and inner aspect of the ischial bones and spines;
- Posteriorly by the junction of the 2nd and 3rd sections of the sacrum.

The ischial spines in the mid-pelvis are palpable per-vaginum;

- Here, they are used as reference points to determine the **station** of descent (see Figure);
    - Station aids in an objective assessment of descent of the presenting part *per-vaginum*. Station-zero is at the level of the ischial spines, –1 is 1 cm above the spines and +1 is 1 cm below the spines;
    - **Station-zero** is an important clinically because instrumental delivery can only be performed if the presenting part has reached the level of the ischial spines or below.
- They are also used as reference points to administer local anaesthetic— pudendal nerve block. The pudendal nerve passes behind and below the ischial spine on each side. A pudendal nerve block may be used for a vacuum or forceps-assisted delivery.

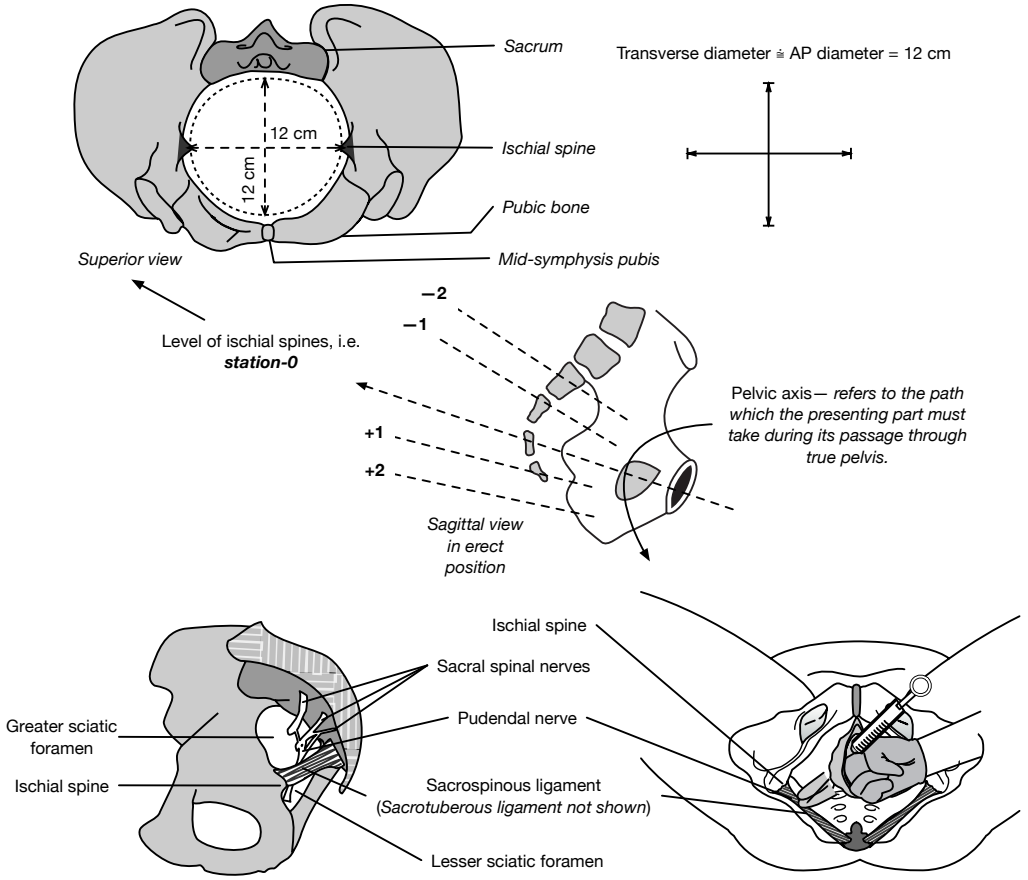


Figure. The mid-pelvis, the pelvic axis, station assessment during labor and pudendal nerve block.

d) The pelvic outlet

The pelvic outlet lies inferior to the mid-pelvis.

The boundaries of pelvic outlet—

- Anteriorly by the lower margin of the symphysis pubis;
- Laterally by descending ramus of the pubic bone, the ischial tuberosity and the sacrotuberous ligament;
- Posteriorly by the *inferiormost* sacrum.

The AP diameter of the pelvic outlet is 13.5 cm and the transverse diameter is 11 cm (see Figure).

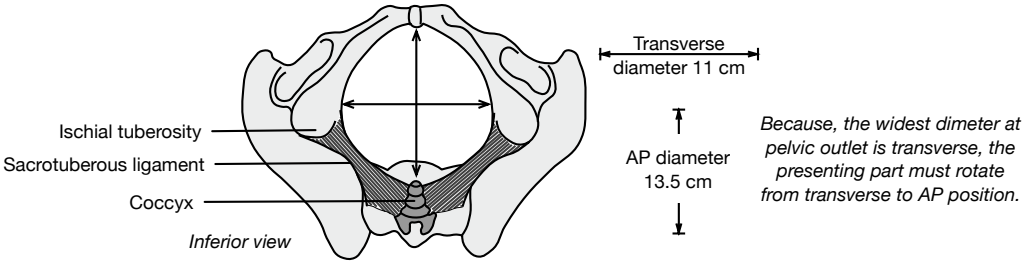


Figure. The pelvic outlet— inferior view.

e) Pelvic floor

Most of the pelvic floor ***relevant to labour*** is formed by the levator ani muscles.

The levator ani muscles and their fascia form a musculofascial gutter giving way to the presenting part towards perineum during labour (see Figure). This aids in rotation of the presenting part with descent through midpelvis.

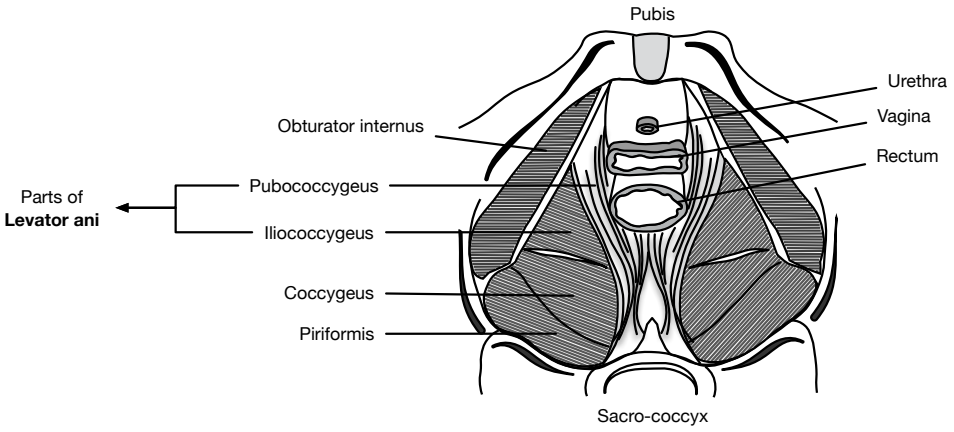


Figure. Pelvic floor musculature— superior view.

f) Perineum

The perineum is the final obstacle for the fetus during labour.

Vaginal birth may result in tearing of the perineum and pelvic floor muscles;

Unlike multiparous women, the perineum is taut and relatively resistant in the nulliparas. Episiotomy (surgical cut) is often considered to ease passage of fetus through the perineum.

The perineal body has a central role in support of perineum *relevant to labour*. It is a condensation of fibrous and muscular that receives attachments from (see Figure);

- Posterior ends of the bulbocavernous muscles;
- Medial ends of the superficial and deep transverse perineal muscles;
- Anterior fibres of the external anal sphincter.

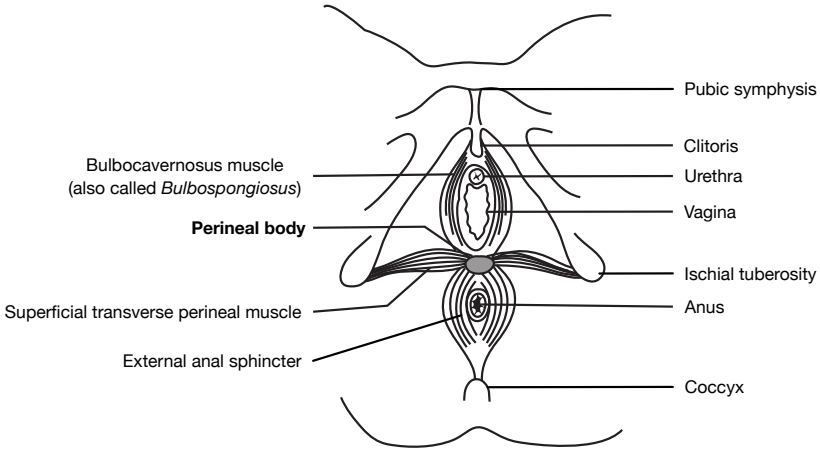


Figure. Perineal body and the perineum— inferior view.

ii) Fetal anatomy relevant to labour

a) Fetal skull bones

The fetal skull is made up of the vault, the face and the base;

- The vault of the skull is formed by parietal bones and parts of occipital, frontal and temporal bones;
- Between these bones there are four membranous sutures— the sagittal, frontal, coronal and lambdoidal sutures (see Figure).

On vaginal examination, suture lines can be felt. **Fontanelles** are the junctions of the various sutures;

- The anterior fontanelle— is at the junction of the sagittal, frontal and coronal sutures;
    - It is diamond-shaped. The area around the anterior fontanelle is called **'bregma'**;
    - On vaginal examination— **4** suture lines can be felt.

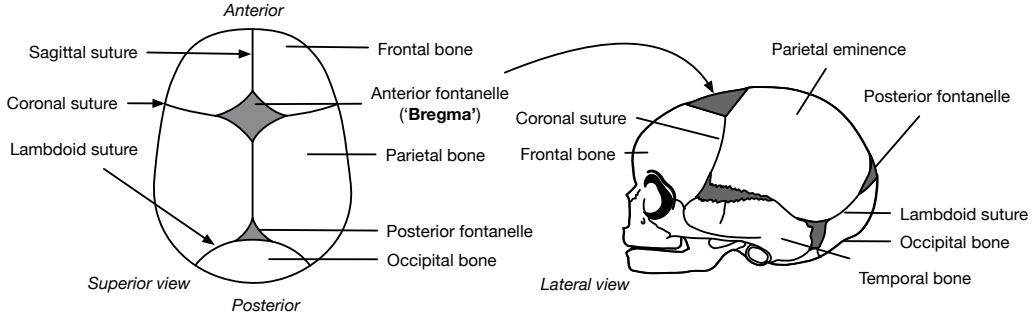


Figure. The fetal skull— superior and lateral views.

- The posterior fontanelle— lies at the junction of sagittal suture and lambdoidal sutures.
    - It is smaller than anterior fontanelle and is **triangular** shaped.
    - On vaginal examination— **3** suture lines can be felt.
- The anatomical differences between the anterior and posterior fontanelles on vaginal examination facilitate correct diagnosis of the fetal head position in labours where fetal head is the presenting part.

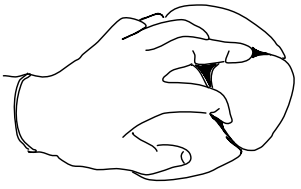


Figure. Illustration showing palpatory assessment of fetal skull fontanelles for diagnosis of position.

Regions of the fetal skull have been designated to aid in the description of the presenting part felt at vaginal examination during labour (see Figure);

- The area of the fetal skull bounded by the two parietal eminences and the anterior and posterior fontanelles is termed the 'vertex';
- The occiput is the area lying behind the posterior fontanelle;
- The sinciput is the area lying in front of the anterior fontanelle. It can be divided into two parts;
    - Brow— the area between the anterior fontanelle and the root of the nose;
    - Face— the area below the root of the nose.

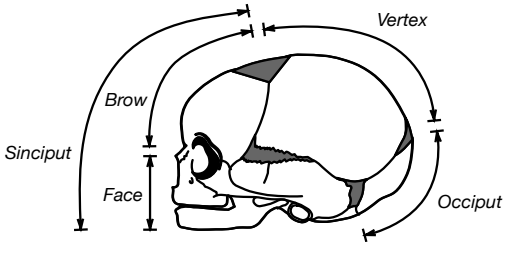


Figure. Designated regions of the fetal skull.

At the time of labour, the fetal skull bones have a special characteristic;

- The sutures joining the bones of the vault (unlike the face and skull base) tend to slide over each other. These bones are also compressible.
- This enables the fetal skull to reduce its diameters and ease its passage through the maternal pelvis. This is referred to as '**moulding**'.

b) Dimensions of fetal skull

The fetal head is ovoid in shape.

The longitudinal diameter of fetal skull on presentation depends on its relative attitude (see Figure). The **attitude** of the fetal head refers to the degree of *its* flexion and extension at the upper cervical spine;

- With a well-flexed fetal head (~ chin on chest), the longitudinal diameter that presents is the **suboccipito-bregmatic** ~9.5 cm. It is measured from suboccput to centre of the anterior fontanelle (bregma).

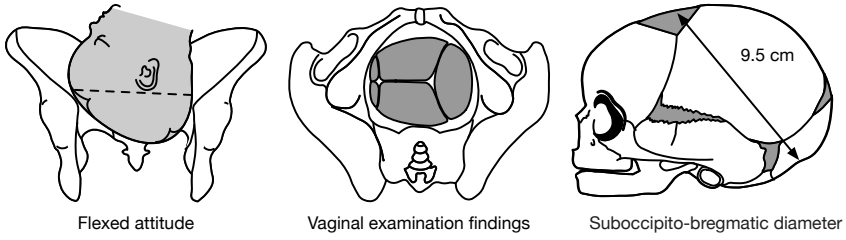


Figure. Flexed attitude and corresponding longitudinal diameter.

- In a less well-flexed head (such as is found in the occiput-posterior positions), **suboccipito-frontal** diameter ~ 10 cm is observed. It is measured from the suboccipital region to prominence of forehead.

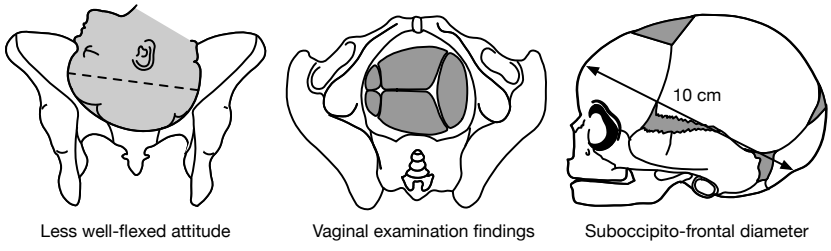


Figure. Less well-flexed attitude and corresponding longitudinal dimeter.

- With further extension of the head, the **occipito-frontal** diameter presents. This is measured from the *root of the nose* to the posterior fontanelle and is 11.5 cm.

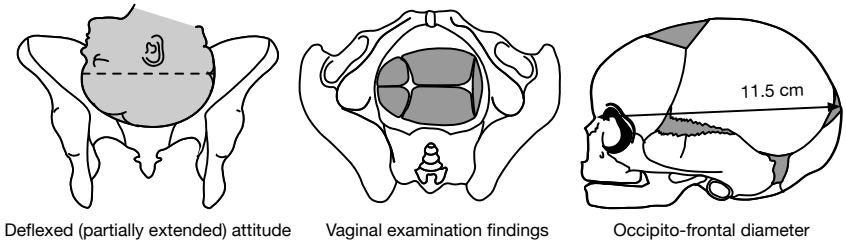


Figure. Deflexed (partially extended) attitude and corresponding longitudinal diameter.

- **Mento-vertical** diameter is the greatest longitudinal diameter which is seen with brow presentation of fetal head. It measures 13 cm from chin to furthest point of the vertex. It is usually too large to pass through maternal pelvis.

Figure. Extended attitude of fetal head with 'brow presentation' and corresponding longitudinal diameter.

- Extension of the fetal head beyond this point results in a ↓ **submento-bregmatic** diameter of face presentation. It is measured from below the chin to the anterior fontanelle and is 9.5 cm. This is termed a face presentation. A face presentation can deliver vaginally when the chin is anterior (mento-anterior position).

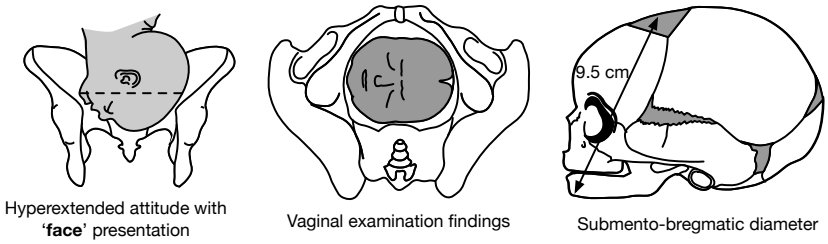


Figure. Hyperextended attitude with 'face presentation' and corresponding longitudinal diameter.

(II) Orientations *in-utero*

Many variations are observed between different pregnancies. These are referred in terms of lie, presentation and position. Assessment and detection of certain orientations is important for better management and outcome in labour.

- Lie— referes to the relation between long axis of fetus to long axis of the uterus/mother;
    - A lie may be longitudinal, oblique or transverse;
    - A lie is said to **unstable** if it is alternating between transverse, oblique and longitudinal.

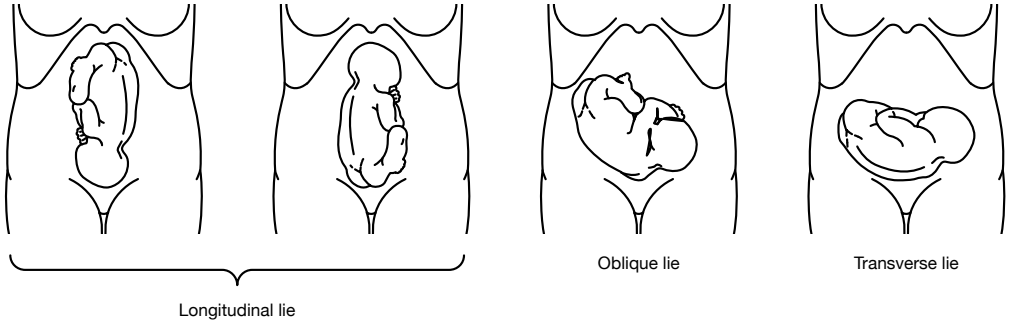


Figure. Illustration of different forms of fetal lie *in utero*.

- Presentation— refers to portion of fetus overlying the pelvic inlet.

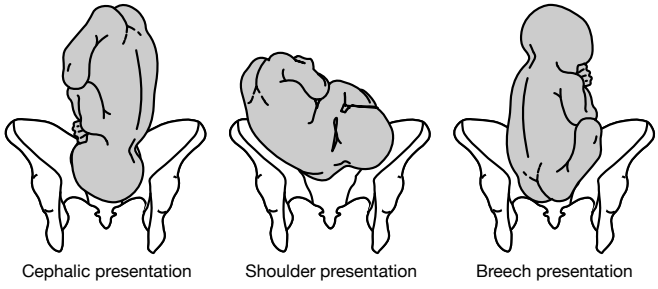


Figure. Cephalic, shoulder and breech presentations of fetus at labour.

- Position— refers to the relation of a definite fetal part to the maternal pelvis;
    - In cephalic presentations, fetal position is referred with relation of the fetal occiput to maternal axis (see Figure);
    - E.g. occiput anterior (OA), occiput transverse (OP) and occiput transverse (OT) positions.

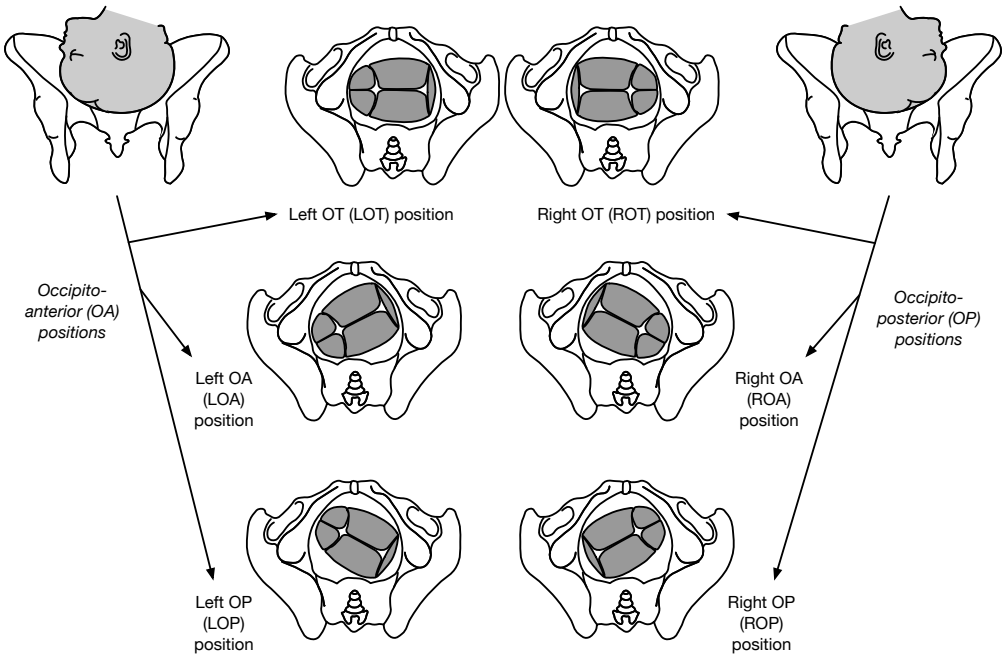


Figure. Illustration of fetal positions in labour.

(III) Physiology relevant to labour

i) Hormonal control

- Progesterone maintains uterine relaxation by;
    - Suppressing prostaglandin production;
    - Inhibiting communication between myometrial cells;
    - Preventing oxytocin release.
- Prior to labour, there is ↓ in progesterone receptors and ↑ in the concentration of oestrogen *relatively*. This leads to;
    - ↑ in Ca^{2+} influx into the myometrial cells;
    - ↑ gap junction formation between myometrial cells— for coordinated uterine activity;
    - Estrogen *opposes* the action of progesterone on uterus.
- As labour becomes established, oxytocin ↑ through the '**Fergusson reflex**'— pressure from fetus against the maternal cervix is relayed via a *reflex arc* involving maternal spinal cord and results in— ↑ oxytocin release from the maternal posterior pituitary gland.

ii) Uterus

Myometrium consists of smooth muscle fibers and contractions are involuntary in nature. The uterus must change its state from relaxation to regular, strong, frequent contractions for labour.

Unlike any other muscle of the body, actin–myosin interaction occurs along the full length of the filaments. Gap junction formation between myometrial cells are aid in coordinated uterine activity. A degree of shortening with each successive interaction is observed;

- This progressive shortening of the uterine smooth muscle cells is called **retraction**;
- As a result, a thicker, actively contracting 'upper segment' develops;
- The lower segment of the uterus becomes thinner and stretched. Eventually, this results in the cervix being 'taken up' (effacement) into the lower segment of the uterus. The cervix effaces and dilates giving way to the fetus for transit.

iii) Cervix

The cervix during pregnancy is relatively long, firm, and *closed with a protective mucus plug*.

Interactions between collagen, fibronectin and dermatan sulphate during the earlier stages of pregnancy keep the cervix firm and closed. Contractions at these stages do not bring about effacement or dilatation.

It must soften, shorten, thin out (effacement) and dilate for labour to progress.

Under the influence of prostaglandins, and other humoral mediators, there is;

- ↑ in proteolytic activity and a reduction in collagen and elastin;
- ↑ proinflammatory change with a significant invasion by neutrophils under influence of interleukins.

Dermatan sulphate is replaced by the more hydrophilic hyaluronic acid, which results in an increase in water content of the cervix. This causes *cervical softening or '**ripening**'*. This softening eases effacement and dilatation.

iv) Labour

The onset of labour occurs when the factors that inhibit contractions and maintain a closed cervix diminish. Both mother and fetus appear to contribute to this process.

It is essential that the myocytes of the uterus contract in a coordinated way for labour;

- However, during each contraction, the placenta is temporarily deprived of blood flow, and consequently the fetus of its oxygen supply;
- Thus, each contraction must be followed by a resting phase in order to maintain placental blood flow and adequate perfusion of the fetus.

The frequency of contractions may vary during labour and with parity;

- Throughout the majority of labour, contractions occur at intervals of 2–4 minutes and are described in terms of the frequency within a 10-minute period (i.e. 2 in 10 ↑ to 4–5 in 10 in *advanced labour*). Their duration also varies during labour, from 30 to 60 seconds or occasionally longer;
- The intensity or amplitude of the intrauterine pressure generated with each contraction averages between 30 and 60 mmHg.

The *frequency* of contractions can be recorded on a cardiotocograph (CTG) using a pressure transducer (tocodynamometer) positioned over the abdomen at the uterine fundus.

(IV) Course of labour

i) Onset of labour

The first important step is to recognize when labour has started.

Throughout pregnancy, uterine contractions are observed. These are usually painless and are referred to as **Braxton-Hicks** contractions. In late pregnancy, these ↑ in frequency and duration and the fetal head moves further down into the pelvis.

ii) False labour

Near term, women complain of painful uterine contractions, which may seem to indicate the onset of labour;

- This is termed 'false labour' if there is no concomitant *progressive dilation* of cervix;
- Unlike contractions of true labour, the lower part of the uterus is observed to contract as strongly as its upper part. Consequently, cervical dilatation fails to occur;
- Additionally, contractions of false labour *do not increase* in frequency and intensity.

Management is symptomatic but vaginal examination is necessary to rule out true labour.

iii) True labour

The onset of labour can be defined as the presence of strong *regular* painful contractions resulting in *progressive cervical change*.

The transition into labour is gradual, but labour may be said to have begun when;

- Cervical dilates at least 2 cm;
- Uterine contractions become painful and regular and coordinated, with *decreasing* intervals in-between.

Uterine contractions of normal labor are characterized by a gradient of myometrial activity. These forces are greatest and last longest at the fundus and diminish towards the cervix—called ***triple descending gradient with fundal dominance.***

- The cervix shortens, effaces and dilates gradually;
    - Effacement and dilation of the cervix also brings about expulsion of '*the cervical plug*'— mucus-like fluid *per vaginum*;
    - Occasionally, small amount of blood is observed *per vaginum* with loss of cervical plug— this is referred to as a **'bloody show'**.
- There may also be spontaneous rupture of the membranes (SROM, or laymen: *breaking of water*).

However, loss of a 'show' or SROM **does not** define the onset of labour, although these events may or may not occur around the same time.

(V) The three stages of labour

Labour is arbitrarily divided into three stages;

- The 1st stage spans from the diagnosis of onset of labour till full cervical dilatation;
- The 2nd stage spans from full cervical dilatation and ends with birth of the baby;
- The 3rd stage refers to the time after birth of the baby till complete delivery of the placenta.

Defining the three stages of labour is more relevant if labour is not progressing normally.

i) First stage of labour

This describes the time from the diagnosis of labour to full dilatation of the cervix (10 cm). The first stage of labour can be divided into *two phases*;

The '**latent phase**'— time between the onset of regular painful contractions and 3–4 cm cervical dilatation;

- During this time, the cervix becomes 'fully effaced' (see Figure). **Effacement** is the process by which the cervix shortens in length as it incorporates into the lower segment of the uterus;
- The process of effacement may begin during the weeks *preceding the onset of labour* but will be complete by the end of the latent phase;
- The *duration of the latent phase is* ***variable***, but it usually lasts between 3 and 8 hours, being shorter in multiparous women.

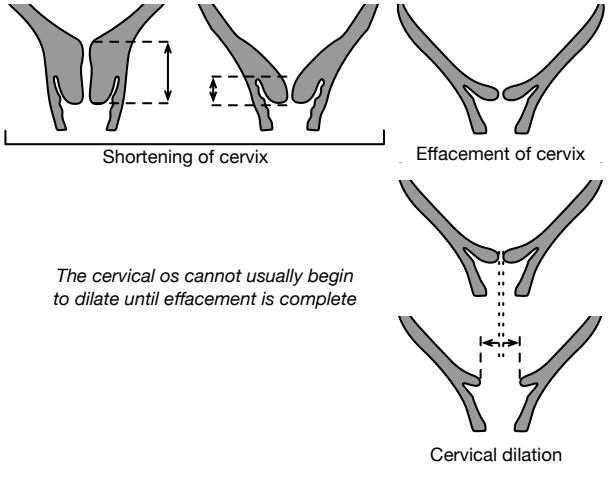


Figure. Cervical changes in stage of labour— shortening, effacement and dilation.

The '**active phase**'— the time between end of latent phase (3–4 cm dilation) till full cervical dilatation (10 cm);

- Cervical dilatation during the active phase occurs typically at **1 cm/hour** or more in a normal labour;
- It is considered abnormal if it occurs at **less than 1 cm in 2 hours**;
- It is **variable** in length, usually lasting between 2 and 6 hours, shorter in multiparous women.

ii) Second stage of labour

This refers to the time from full dilatation of the cervix to delivery of the fetus *or fetuses*.

The second stage of labour is also subdivided into two phases;

The '**passive phase**'— the time between full dilatation and the onset of involuntary expulsive contractions;

- There is no maternal urge to push;
- The fetal head is still relatively high in the pelvis;
- Use of epidural anaesthesia influences the length of the second stage of labour. A passive second stage of 1-2 hours is usually recommended to allow head to rotate and descend prior to active pushing.

The '**active second stage**'— time between onset of involuntary expulsive contractions till delivery of the fetus;

- There is a maternal urge to push;
- The fetal head is low (often visible), causing a reflex need to 'bear down';
- Normally, active second stage should not last longer than 2 hours in nulliparas and 1 hour in women who have delivered vaginally before.

The second stage is often diagnosed at the *active second stage of labour* because the maternal urge to push prompts the obstetrician to perform a vaginal examination— *shows a low fetal presenting part*.

If a woman never reaches a point of involuntary pushing, the active second stage is said to begin when she starts making voluntary pushing efforts directed by her obstetrician.

Evidence shows— a second stage of labour lasting > 3 hours is associated with ↑ ***maternal and fetal morbidity***.

iii) Third stage of labour

This is the time from delivery of the fetus or fetuses until complete delivery of the placenta and membranes.

The placenta is usually delivered within a few minutes of the birth of the baby.

A third stage lasting more than 30 minutes is defined as abnormal, unless the 'physiological management of 3rd stage of labour' is carried out. In these cases, it is reasonable to extend this limit upto **60 minutes**.

iv) Duration of labour

The average duration of a first labour is 8 hours, and that of a subsequent labour is 5 hours;

- First labour rarely lasts more than 18 hours;
- Subsequent labours usually last not more than 12 hours;
- Prolonged labour is classically defined as lasting > 12 hours in nulliparas and > 8 hours in multiparas;
- Precipitous labour is defined as expulsion of the fetus within < 3 hours of onset of regular contractions.

Table. Range of durations of stages of labour.

Stages		**Primiparas**	**Multiparas**
1st stage		3 - 8 hours	< 3 - 8 hours
2nd stage	*Without epidural*	2 hours	1 hour
	With epidural	3 hours (2 + 1)	2 hours (1 + 1)
3rd stage	*With **active** management*	30 minutes	30 minutes
	*With **physiological** management*	60 minutes	60 minutes

(VI) The mechanism of labour

This refers to the series of changes in position and attitude that the fetus undergoes during its passage through the birth canal.

- It is described here for the *vertex presentation* in a *gynaecoid pelvis*.
- The relation of the fetal head and body to the maternal pelvis changes as the fetus descends through the pelvis.

i) Engagement

Engagement is said to have occured when the widest diameter of the presenting part has passed successfully through the inlet;

- Usually, by 37 weeks' in nuliparas, engagement has occurred.
- Engagement can be assessed by palpating abdomen.

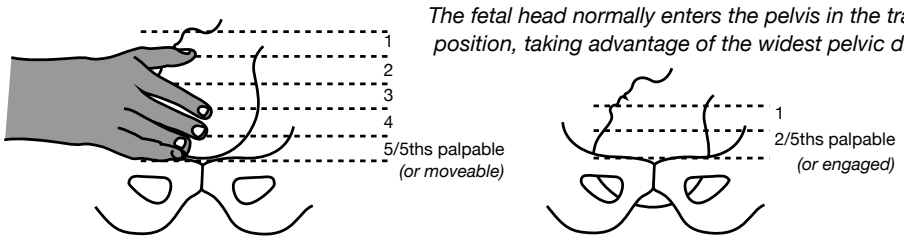


Figure. Engagement can be assessed by palpating the abdomen.

ii) Descent

Fetal head descends further down into the pelvis. This occurs with the aid of;

- Uterine contractions— during the 1st stage of labour and passive phase of 2nd stage of labour;
- Voluntary pushing efforts (valsalva manoeuvring)— during the active phase of 2nd stage of labour.

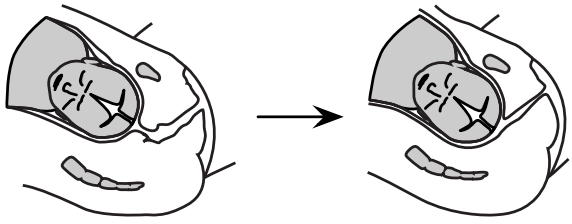


Figure. Illustration of descent of fetal head.

iii) Flexion

The fetal head is not always completely flexed when it enters the pelvis;

- The fetal head undergoes flexion as it descends into the relatively narrower mid-pelvis.
- This passive flexion aids in ↓ the presenting diameter of the fetal head.

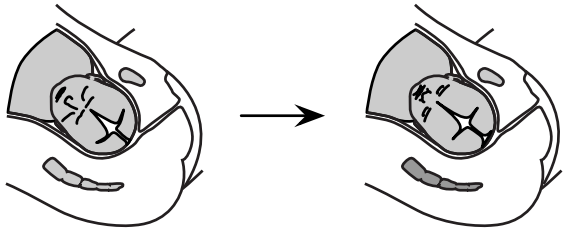


Figure. Illustration of fetal head flexion.

iv) Internal rotation

The flexed fetal head then undergoes internal rotation. This occurs due the sloping shape of pelvis.

If the fetal head engaged in OA position, then internal rotation results in fetal head's sagittal suture to lie in the AP diameter of the maternal pelvic outlet (i.e. the widest diameter, see Figure).

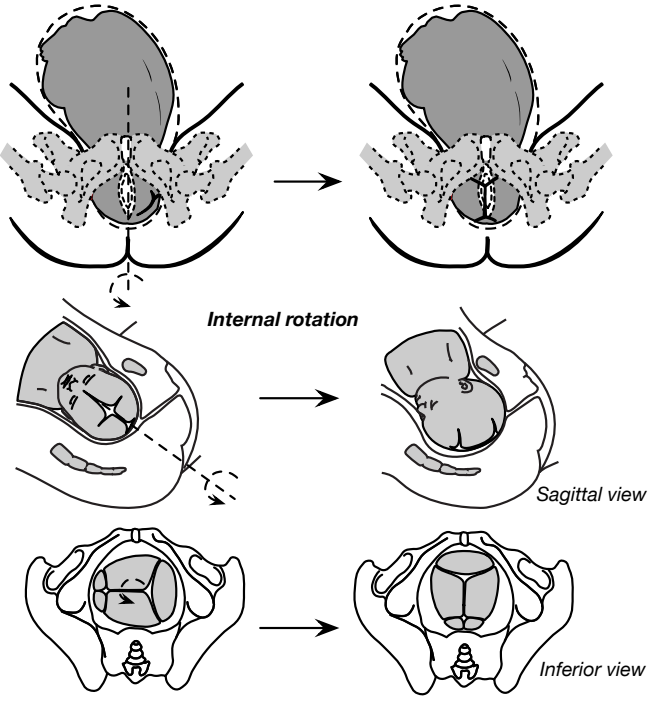


Figure. Illustration of fetal internal rotation.

v) Extension and crowning

Following completion of internal rotation, the occiput is beneath the symphysis pubis and the bregma is near the lower border of the sacrum.

The well-flexed head now;

- Extends and the occiput escapes from underneath the symphysis pubis to distend the perineum;
- The fetal occiput becomes visible through the vagina— this is referred to as **'crowning'** of the head;
    - Between contractions, the elastic tone of the perineal muscles push the presenting part back towards the pelvic cavity;
    - When the head no longer recedes between contractions— crowning has occured.
- First appears the bregma and then fetal face and chin.

The soft tissues of the perineum are resistant to distention, and perineal tearing may occur in first births.

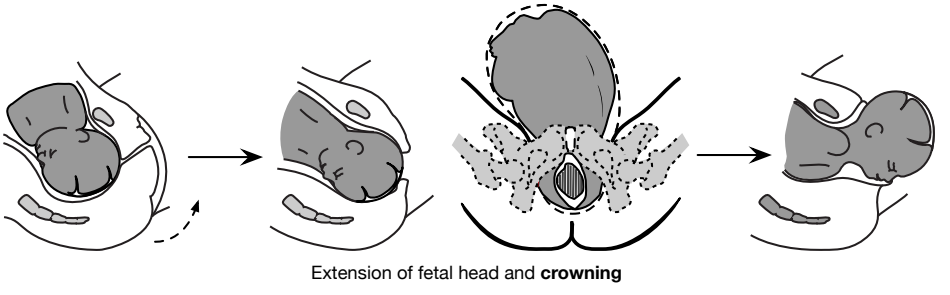


Figure. Illustration of fetal head extension.

vi) Restitution

- When the head is delivering, the occiput is directly anterior;
- With transit through the perineum, fetal head aligns itself with shoulders (which have entered the pelvis in an oblique position). This slight rotation of occiput through 1/8th of a circle is called '**restitution**'.

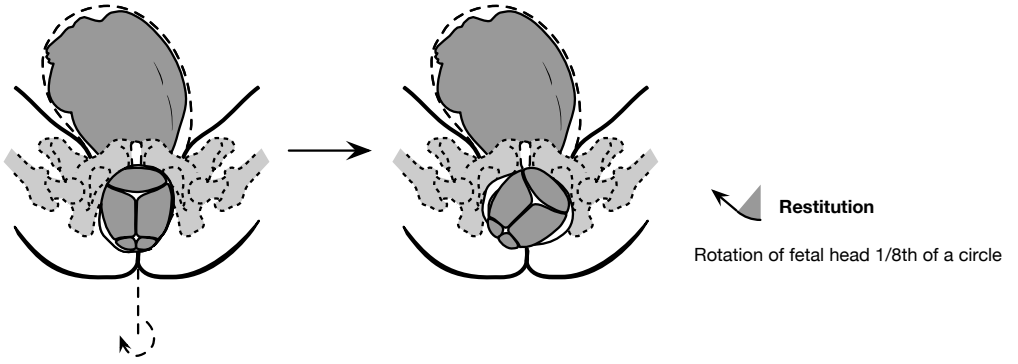


Figure. Illustration of restitution.

vii) External rotation

- To be delivered, the shoulders have to rotate into the AP plane (widest diameter at pelvic outlet);
- When this occurs, the occiput also rotates through a *further 1/8th of a circle* to the transverse position. This is called ***external rotation***.

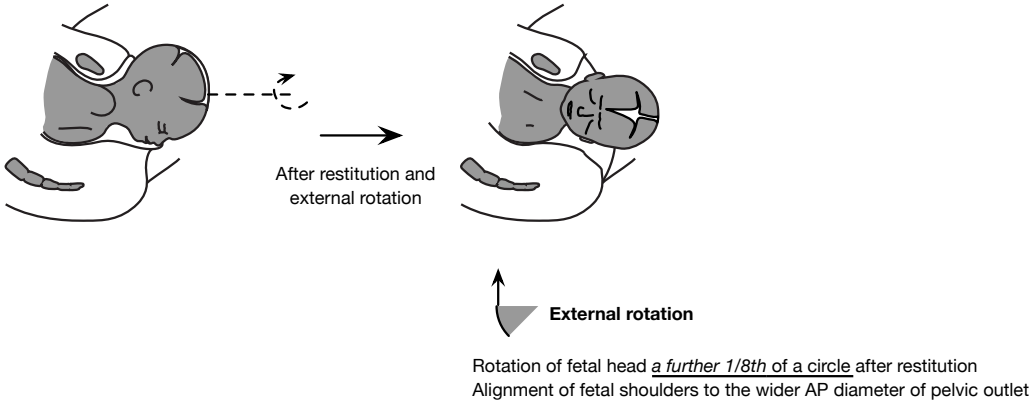


Figure. Illustration of sagittal view of external rotation.

viii) Delivery of the fetal shoulders and body

- When restitution and external rotation have occurred, the shoulders will be in the AP position;
- The anterior shoulder is under the symphysis pubis and delivers first and then posterior shoulder;
- The fetal body then delivers easily.

ix) Delivery of placenta

Signs of placental separation are important as they guide initiation of controlled cord traction by obstetrician during **active management** of 3rd stage of labour (see below);

- Apparent lengthening of the cord;
- A small gush of blood from the placental bed;
- Rising of the uterine fundus to above the umbilicus— *uterus feels firm and globular on palpation*.

(VII) Approach to management of normal labour

- Women are advised to watch-out for signs and symptoms of labour;
    - Symptoms of rupture of membranes (SROM), or;
    - When their contractions start occurring *regularly* every 5 minutes or more.
- Obtain obstetric history in detail.
- Examination relevant to labour includes;
    - Perform abdominal examination to assess;
        - Symphysiofundal height (SFH);
        - Lie of the fetus (longitudinal, transverse or oblique);
        - Presenting part (cephalic, breech or shoulder);
        - Degree of *engagement*, in terms of finger-bredths palpable *abdominally*;
        - Contractions— by palpating uterus directly (atleast 10 min, without tocography).

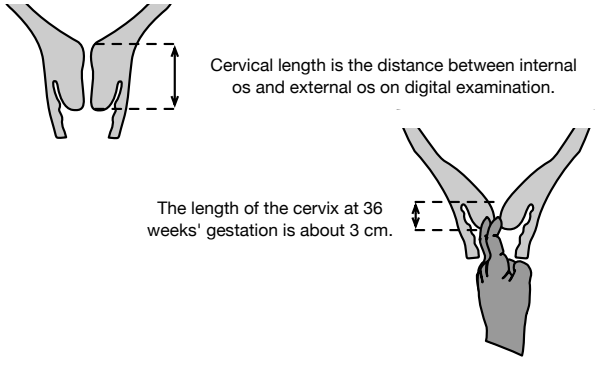


Figure. Cervical assessment on vaginal examination.

    - Vaginal examination— the index and middle fingers are passed to the cervix;
        - Cervix is examined for consistency, position, length, effacement and dilatation;
            - Cervical length and dilatation are estimated digitally in centimetres;
            - At about 4 cm of dilatation, the cervix should be fully effaced;
            - When no cervix can be felt, this means the cervix is fully dilated (10 cm).
        - Providing the cervix is at least 4 cm dilated, it should be possible to determine both the position and the station of the presenting part;
            - Assess the fetal head position, station, attitude and the presence of caput or moulding;
                - Usually, vertex is the presenting part;
                - Locating the occiput using palpation for suture lines and fontanelles aids in identifying fetal position;
                - The occiput is usually in OT or OA position.
            - Assess the fetal station with reference to the maternal ischial spines.
        - Note condition of membranes. With their rupture, a generous amount of clear fluid is a *good prognostic feature*.

Purpose of examination is to rule out abnormalities in labour;

- A head that remains high (5/5ths palpable) or unengaged (> 2/5ths palpable) is a *poor prognostic sign* for successful vaginal delivery;
- Failure to feel the posterior fontanelle may be because the head is **deflexed** (abnormal attitude), the **occiput is posterior** (malposition) or there is *significant caput + moulding* that sutures cannot be felt;

- If there is doubt, an ultrasound scan can confirm malpresentrations and malpositions;
- Scant, densely blood- or meconium-stained amniotic fluid may be a warning sign of fetal compromise.

Women who are found not to be in established labour should be offered;

- Analgesia;
- Counselling— most can safely go home and return when the contractions ↑ in strength and frequency.

i) Maternal assessment in labour

Assessment of maternal condition in labour is mainly with hemodynamic parameters;

- Before 2nd stage of labour— checking pulse q1hour, BP q4hours and temperature q4hours is sufficient;
- During 2nd stage of labour— it is recommended to check BP and pulse q4hours.

Women who chose epidural analgesia need to be urethral catheterized.

ii) Fetal assessment in labour

A healthy term fetus is usually able to withstand the demands of a normal labour although placental blood flow and oxygen transfer are temporarily interrupted with each uterine contraction;

- Such interruption, if severe, can lead to hypoxia and anaerobic metabolism ± metabolic acidosis— reflecting in abnormal FHR patterns;
- Meconium (fetal stool) passage may also occur and stain the amniotic fluid.

Fetal assessment in labour may be performed by;

- Inspection of amniotic fluid;
- Intermittent auscultation of the fetal heart using;
- Pinard stethoscope;
- Handheld Doppler ultrasound;
- CTG electrode *over the abdomen* for **external** continuous electronic fetal monitoring (EFM)/FHR;
- *Fetal scalp electrode* (FSE) for EFM/FHR **internally** (see Figure);
    - Internal EFM may be chosen for CTG monitoring if the quality of external EFM is poor;
    - This involves fixing a FSE over fetal scalp skin to assess FHR directly;
    - It, however, requires ruptured membranes and cervical dilatation for fixation;
    - It is contraindicated in presence of significant maternal infection (e.g. HIV or hepatitis C).

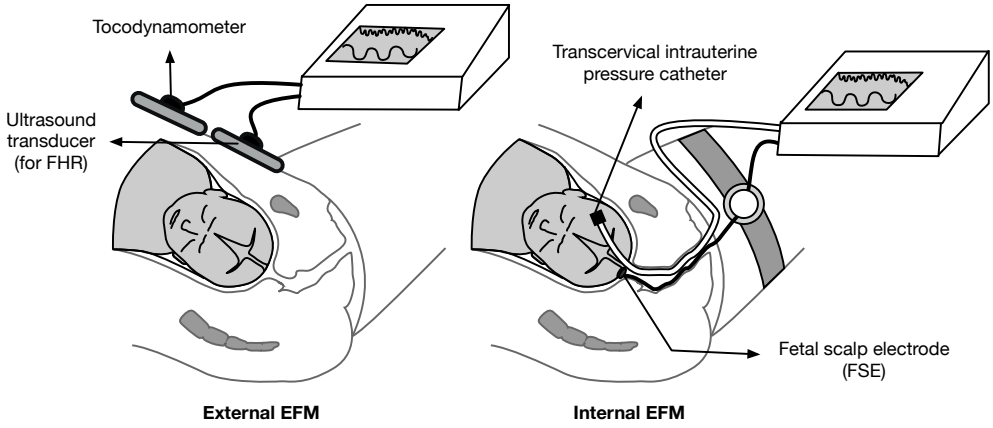


Figure. Illustration of internal and external EFM.

- Fetal scalp blood sampling (FBS)— if there are persistent non-reassuring features on CTG (see Figure);
    - This provides a sample of fetal blood to measure fetal pH and base excess directly;
    - If parameters on FBS are normal, labour can continue with close monitoring.

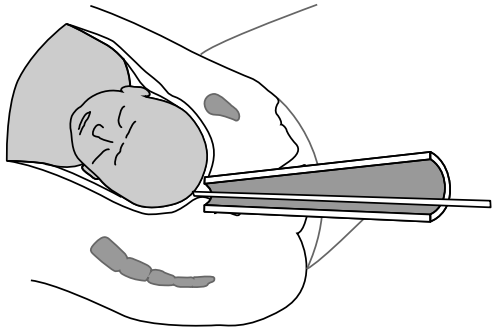


Figure. Illustration of fetal scalp blood sampling.

Each feature of CTG may be classified reassuring, non-reassuring or abnormal (see Table). Because of repetitive uterine contractions, interpreting some features in labour may vary from that of an antenatal CTG;

- The absence of accelerations is of uncertain significance during labour;
- The presence of early or variable decelerations in labour is extremely common and usually not a sign of significant fetal compromise.

Table. RCOG classification of CTG.

FHR Features	**Baseline (bpm)**	**Variability (bpm)**	**Decelerations**	**Accelerations**
Reassuring	110-160	≥5	None	Present
Non-reassuring	Either 100-109 or 161-180	<5 for ≥40 but <90 min	-- Early --Variable --Single, prolonged for upto 3 minutes	Absent (*CTG is of uncertain importance if absent accelerations but otherwise normal*)
Abnormal	Either <100 or >180, or sinusoidal pattern for ≥10 min	<5 for >90 min	--Atypical --Late --Single, prolonged for >3 minutes	
The RCOG classification of CTG is as follows: Normal— a CTG with all 4 features are in reassuring category. Suspicious— a CTG with 1 feature non-reassuring but remainder 3 features reassuring. Pathological— a CTG with either ≥2 features non-reassuring or ≥1 features abnormal.				

iii) Partogram as a record of labour

The partogram is a *graphic* record of labour (see Figure).

This record allows a visual assessment of the progress of labour based on the rate of cervical dilatation compared with an *expected 'normal'— according to the parity of the woman*. This helps recognize slow or abnormal progress in labour.

Observations charted over a partogram include (but not limited to);

- Frequency and strength of uterine contractions;
- Descent of the fetal presenting part (in finger bredths and station);
- Amount and colour of amniotic fluid.

PARTOGRAPH

Name Gravida Para Hospital no.

Date of admission Time of admission Ruptured membranes hours

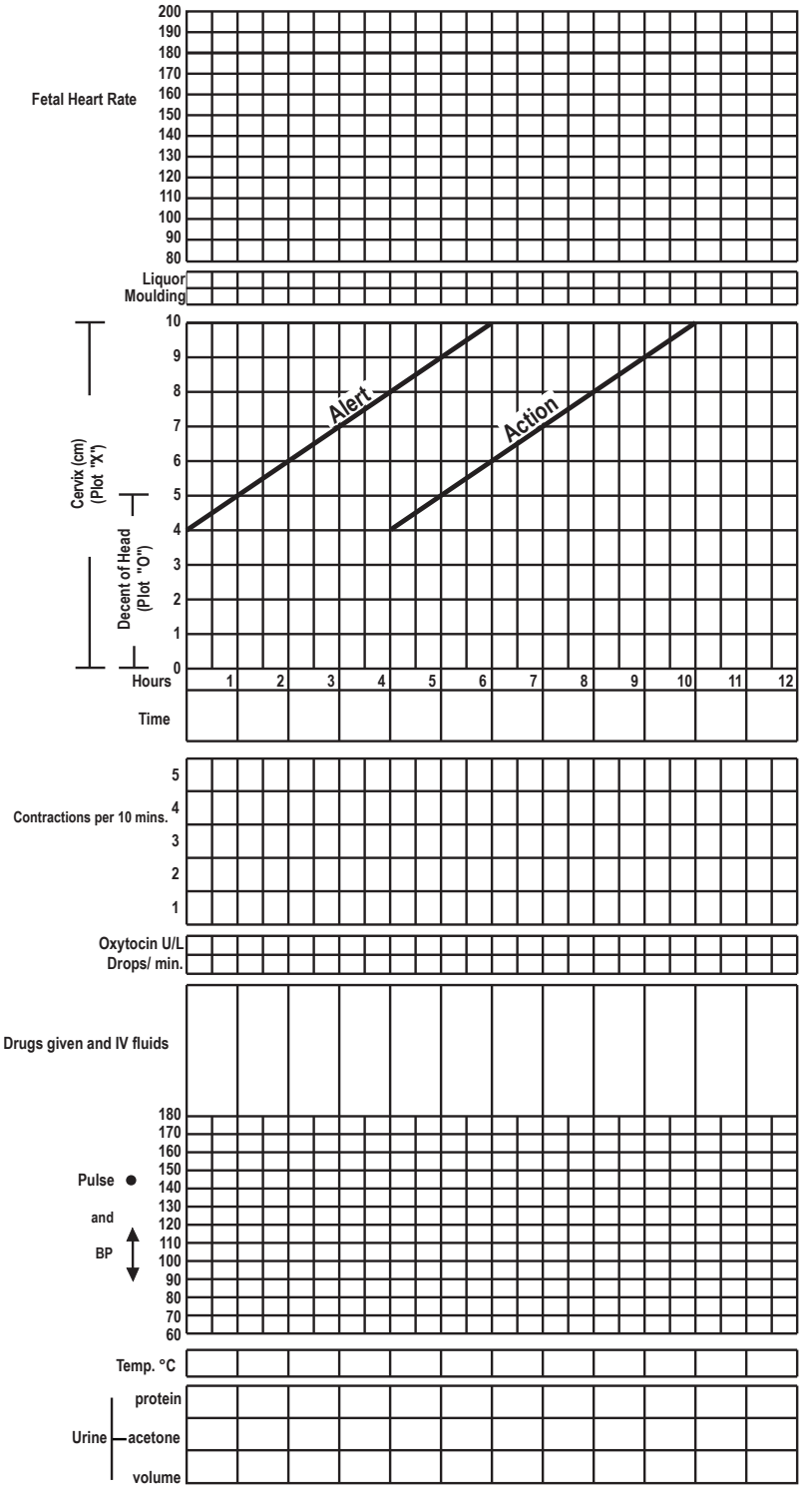


Figure. Partograph— WHO revised version.

The template of partograph referenced here is 'WHO revised partograph'. It excludes latent phase of labour;

- The *previous version of the WHO partograph* also included the **latent phase of labour** (see Figure);

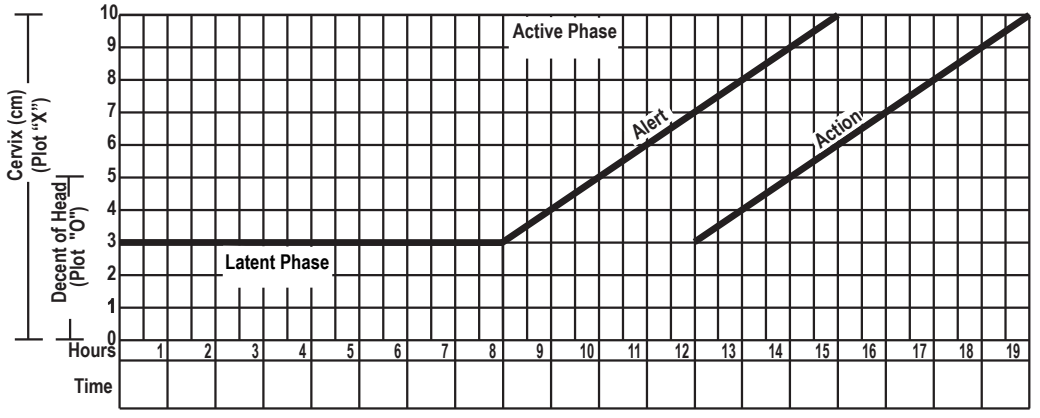


Figure. Central part of *previous WHO partogram* (includes latent phase of labour).

- A line is drawn on the partogram at the end of latent phase demonstrating *progress of 1 cm dilatation/hour*— referred to as the '**alert line'**. *This is the expected progress of labour*;
- Another line (the '**action line**') can be drawn parallel and 4 hours to the right of alert line (see Figure);
- If the *plot of actual cervical dilatation* reaches upto the action line, this indicates slow progress.

iv) Management during first stage of labour

- Maternal and fetal assessments for wellbeing;
- Appropriate pain relief;
- Light diet and oral/parenteral hydration— prevents ketosis;
- Mobilize— during latent phase of labour;
- Vaginal examinations— every 4 hours or as clinically indicated;
- Monitoring progress of labour over a partogram;
- If the membranes are intact, it is not necessary to rupture them if the progress of labour is satisfactory;
- Interventions during 1st stage of labour are best avoided, unless there are identified risk factors.

v) Management during second stage of labour

- Women are advised to assume the left lateral position, squating or on 'all fours'-position— aids in progress of labour;
- Continuation of maternal and fetal surveillance;
- Regional analgesia (epidural, spinal or infiltration with local anaesthetic) may be considered for pain-control. But this may affect the duration of 2nd stage of labour;
    - Pushing can be delayed for up to 2 hours with epidural analgesia;
    - However, in all cases the baby should be delivered *within 4 hours* of reaching full dilatation.
- Vaginal and perineal tears are common with first-time vaginal births;
    - A '**hands-on approach**' may be considered to minimize this. The obstetricians' hands guard the perineum by controlling the speed of delivery of the fetal head;
    - The woman should also be discouraged from bearing down by telling her to take rapid, shallow breaths ('panting');
    - Alternatively, episiotomy may be performed— a surgical cut extending through the perineum and lower vaginal wall.

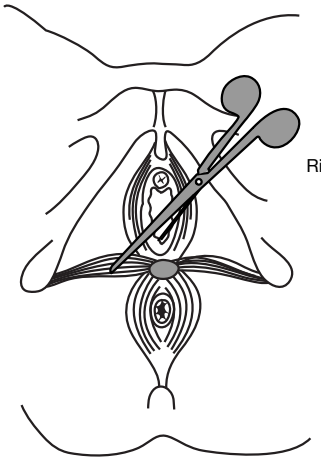


Figure. Illustration of episiotomy incision.

- With delivery of the fetal head, ensure the cord is not wound around the neck.
- The obstetrician may provide gentle traction to deliver shoulders;
    - Gentle traction aimed downwards until the anterior shoulder appears beneath the pubis;
    - Thereafter, traction aimed upwards until the posterior shoulder appears over the perineum.
- If traction is needed to deliver **the body**, it should be applied to fetal shoulders only (not to the head).

vi) Management during the third stage of labour

One of two approaches may be undertaken for management during the 3rd stage of labour (see Table);

- Expectant (or physiological)— delaying cord clamping and delivering placenta by maternal effort without administration of oxytocic drugs;
- Active— placenta is delivered with the aid of certain interventions.

Table. Approaches to management during the third stage.

Active management	**Expectant (or physiological) management**
• Maternal administration of an oxytocic drug as the anterior shoulder of the baby is delivered, or immediately after delivery of the baby; • Clamping of cord after 1-3 minutes; • Controlled cord traction to expedite delivery of placenta once the '**signs of placental separation**' are observed.	• Oxytocic drugs are not used; • Clamping of cord after 1-3 minutes.
Placenta should be delivered within 30 minutes; A 2nd attempt at controlled cord traction should be made after 10 minutes if placenta does not deliver; Use manual removal under general or regional anaesthesia in the operating theatre if placenta still '*retained*'.	If this approach is undertaken, it is safe to extend the time limit of 3rd stage of labour from 30 to 60 minutes. But if the placenta remains undelivered within 60 minutes, active management should be commenced.
↓ incidence of postpartum haemorrhage (PPH).	Associated with heavier bleeding.

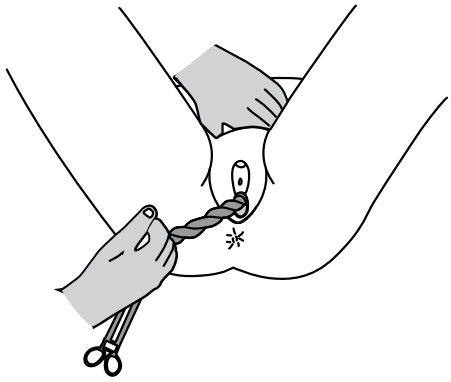


Figure. Illustration of controlled cord traction.

vii) Immediate care of the neonate

- After the baby is born, breathing begins within seconds;
- A pulsating cord can transfer upto 80 ml of blood from placenta to the baby. Delayed clamping of cord (1-2 mins) is recommended to ↓ neonatal anaemia and iron deficiency;
- The baby's head should be kept dependent to allow mucus in the respiratory tract to drain;
- After clamping and cutting the cord, the baby should have an Apgar scores should be calculated at 1 minute, 5 minutes and 10 minutes of age.
- Immediate skin-to-skin contact between mother and baby helps with;
    - Bonding;
    - Keeping the neonate warm;
    - Further release of oxytocin, which aids uterine contractions.
- Initiation of breastfeeding should be encouraged within the first hour of life;
- Before being taken out of delivery room, the first dose of vitamin K should be given.

CHAPTER 29 ABNORMAL LABOUR

In labour, there is a complex interplay of the '**three Ps**'. These are;

- The '**p**owers'— uterine contractions;
- The '**p**assages' of the birth canal— maternal pelvis, perineum and pelvic floor;
- The '**p**assenger'— the fetal presentation, dimensions of presenting part and position.

When any of the 3Ps are unfavourarble, labour is likely to need intervention.

The term '**dystocia**' referes to is an abnormal labour. Labour becomes abnormal when there is poor progress and/or the fetus shows signs of compromise.

Also, if there is a *fetal malpresentation, a multiple pregnancy, a uterine scar or if labour has been induced*, labour cannot be considered normal.

Abnormalities in progress of labour can be categorized into two general types;

- Protraction disorders— labor is slow to progress;
- Arrest disorders— labor ceases to progress.

(I) Poor progress in 1st stage

This can occur in latent phase, active phase or both, and manifests with protraction or arrest disorders;

Protraction can occur during both the latent and active phases of labor, while arrest is recognized only in the active phase.

i) Charactistic patterns of partogram abnormalities

The partogram plays a pivotal role in detection of these abnormalities. Three distinct patterns of abnormal labour progress can be detected;

- Prolonged latent phase (or protracted latent phase);
- Primary dysfunctional labour (or protracted active phase);
- Secondary arrest (of cervical dilation).

a) Prolonged latent phase

This is a protraction disorder of the first stage of labour. Although in most cases, *latent phase does not span* ***> 8 hours***, but a prolonged latent phase is **by definition**;

- Latent phase > 20 hours in primiparas;
- Latent phase > 14 hours in multiparas;

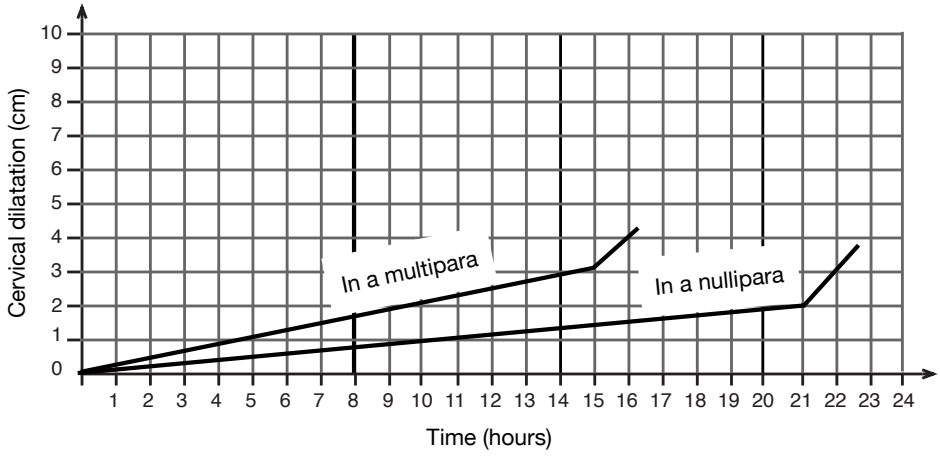


Figure. Illustration of an *ideally diagnostic partogram* demonstrating **prolonged latent phase**.

b) Primary dysfunctional labour (PDL)

PDL (or protracted active phase) refers to poor progress in the active phase of labour.

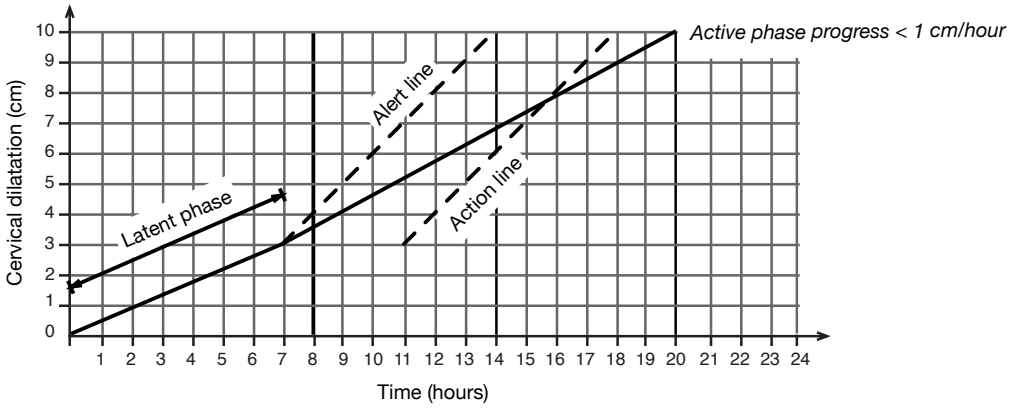


Figure. Illustration of PDL and its diagnostic features on a partogram.

c) Secondary arrest (of cervical dilation)

Secondary arrest also refers to poor progress in the active phase of 1st stage of labour;

By definition, secondary arrest is diagnosed when;

- Progress of cervical dilation is good initially after 3-4 cm of cervical dilation;
- Cervical dilation arrests before completion of active phase (usually seen after 7 cm dilation).

In contrast, **primary arrest** refers to poor progress in the active phase of 1st stage of labour.

By definition, primary arrest is diagnosed when;

- Progress of cervical dilation is arrested after 3-4 cm (in active phase);
- Cervical dilation is < 2 cm in 4 hours of active phase.

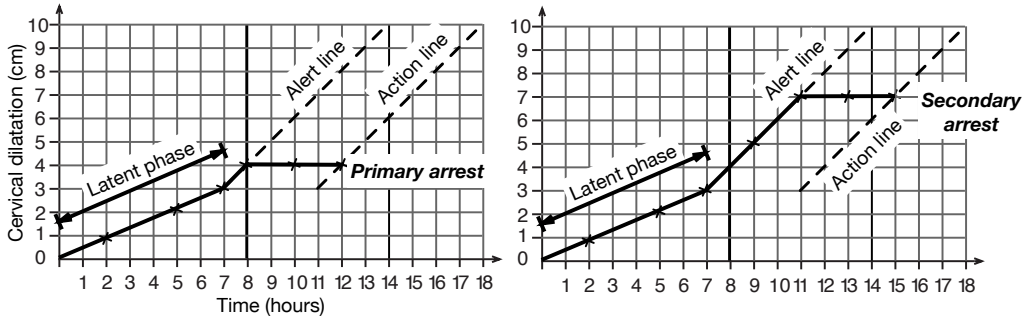


Figure. Illustration of primary and secondary arrest on partograms.

ii) Causes of poor progress in 1st stage

A prolonged 1st stage of labour may occur due to abnormalities of the **3 'P's**;

- Powers— dysfunctional uterine activity;
- Passages— abnormalities of the birth canal;
- Passenger— malpresentation;
- Passages *and passenger*— cephalopelvic disproportion.

a) Dysfunctional uterine activity

This is the *most common cause* of poor progress in labour. It is characterized by infrequent or weak contractions;

- Frequency of contractions can be assessed with *palpation* or with *external uterine tocography*— 4-5 contractions/10 minutes are considered ideal;
- Pressure generated by contractions can only be assessed with **invasive** *intrauterine pressure catheters*;
    - Montevideo units objectively measure uterine contractile activity. This is a measure of average frequency and amplitude of uterine contractions *above the basal tone of uterus*;
    - Montevideo units are calculated as (see Figure)— $pressure_{average}$ *of contractions* x *no. of contractions/10 minutes duration*;
    - Montevideo units of *atleast* 200–250 are associated with adequate contractions.

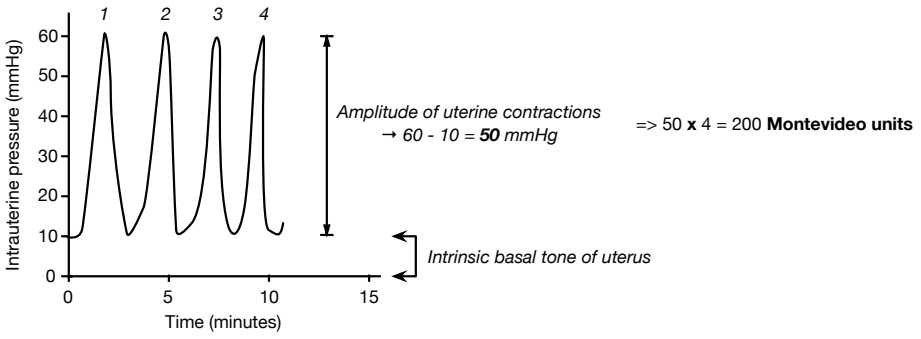


Figure. Montevideo units— calculation using intrauterine pressure catheters.

b) Abnormalities of the birth canal

Uterine fibroids in the lower uterine segment can prevent descent of the fetal head.

Delay can also be caused by '**cervical dystocia**'— a noncompliant cervix that effaces but fails to dilate. This may be due to scarring or rigidity secondary to previous cervical surgery (e.g *cone biopsy*).

c) Malpresentations

Malpresentation is a presentation that is not cephalic;

- A face presentation may apply poorly to the cervix;
    - The resulting progress in labour may be poor;
    - But a face presentation can deliver vaginally if chin is anterior (mentoanterior position).
- Brow presentation is associated with the mentovertical diameter presenting;
    - This diameter is too large to fit through the maternal bony pelvis;
    - Brow presentation often manifests as poor progress in the first stage.
- Shoulder presentation cannot deliver vaginally. It is associated with risks of;
    - Cord prolapse;
    - Uterine rupture.

A breech presentation is often associated with difficulties in delivery of shoulders and/or after-coming head, but a delay in 1st stage of labour is not characteristic.

d) Cephalopelvic disproportion (CPD)

CPD implies anatomical disproportion between fetal head and maternal pelvis. Findings *suggestive* of CPD—

- Fetal head is not engaged;
- Head is poorly applied to the cervix;
- Progress is protracted or arrests despite efficient uterine contractions;
- Vaginal examination shows severe moulding and caput formation;
- Maternal haematuria.

iii) Management of poor progress in 1st stage

- If membranes are intact, artificial rupture of membranes (ARM or amniotomy) may be considered;
- Oxytocin infusion to may be considered to augment contractions;
    - Epidural analgesia provides adequate analgesia for augmented contractions;
    - Dysfunctional uterine activity is ***unlikely in multiparas***. *Decision to augment with oxytocin must be considered very carefully here*;
    - If progress fails to occur despite augmentation with oxytocin, C-section is recommended.
- C-section is needed in cases of;
    - CPD or if labour obstructs;
    - Malpresentations leading to poor progress;
    - Cervical dystocia.
- Monitor fetus with continuous EFM (CTG) as excessive augmented contractions may affect fetus.

(II) Poor progress in 2nd stage

Characterising normal and prolonged second stage of labour aids in determination of poor progress (see Table).

Table. Normal and prolonged second stage of labour.

		With epidural	***Without epidural***
Normal 2nd stage	Primiparas	2 hours	1 hour
	Multiparas	3 hours (2 + 1)	2 hours (1 + 1)
Prolonged 2nd stage	Primiparas	>2 hours	>1 hour
	Multiparas	>3 hours	>2 hours

The causes of delay here can also be classified as abnormalities of the powers, the passages and the passenger;

- The 'powers'— **secondary** dysfunctional uterine activity;
- The 'passages'— e.g. a narrow midpelvis or resistant perineum;
- The 'passenger'— e.g. malpositions.

i) Secondary dysfunctional uterine activity

Secondary dysfunctional uterine activity (also called **secondary uterine inertia**) is the most common cause of second stage delay.

It refers to weak and ineffective uterine contractions after full cervical dilation has occurred— often associated with maternal dehydration and ketosis.

It may be exacerbated with administration of epidural analgesia. In these cases, duration of second stage should not last more than;

- 3 (2 + 1) hours in primiparas;
- 2 (1 + 1) hours in multiparas.

ii) Narrow midpelvis

- A narrow midpelvis (as seen in an android pelvis) prevents internal rotation of the fetal head;
- This may result in arrest of descent of the fetal head at the level of the ischial spines in the transverse position— deep transverse arrest.

iii) Resistant perineum

- The perineum is taut and relatively resistant to strech in a nulliparous woman unlike multiparas;
- A resistant perineum resulting in significant delay in labour is *often an indication for episiotomy*.

iv) Malpositions

Fetal malposition occurs when fetal vertex presents to maternal pelvis in a position other than flexed occipito-anterior (OA).

Malpositions include occipitotransverse (OT) and occipitoposterior (OP, see below) positions and may involve **asynclitism** (sideways tilt of the head).

If the fetus had undergone engagement in the OP position (see Figure);

- A *relatively longer* internal rotation may occur;
    - This corrects an OP position to an OA position;
    - But this longer internal rotation may be associated with ↑ duration of labour.
- The OP position may persist (called persistent OP position);
    - This can deliver with a 'face to pubes' delivery;
    - Depending on degree of flexion of fetal head, persistent OP position is associated with an ↑ diameter presenting to pelvic outlet.
- An incomplete internal rotation stopping at OT position— associated with deep transverse arrest.

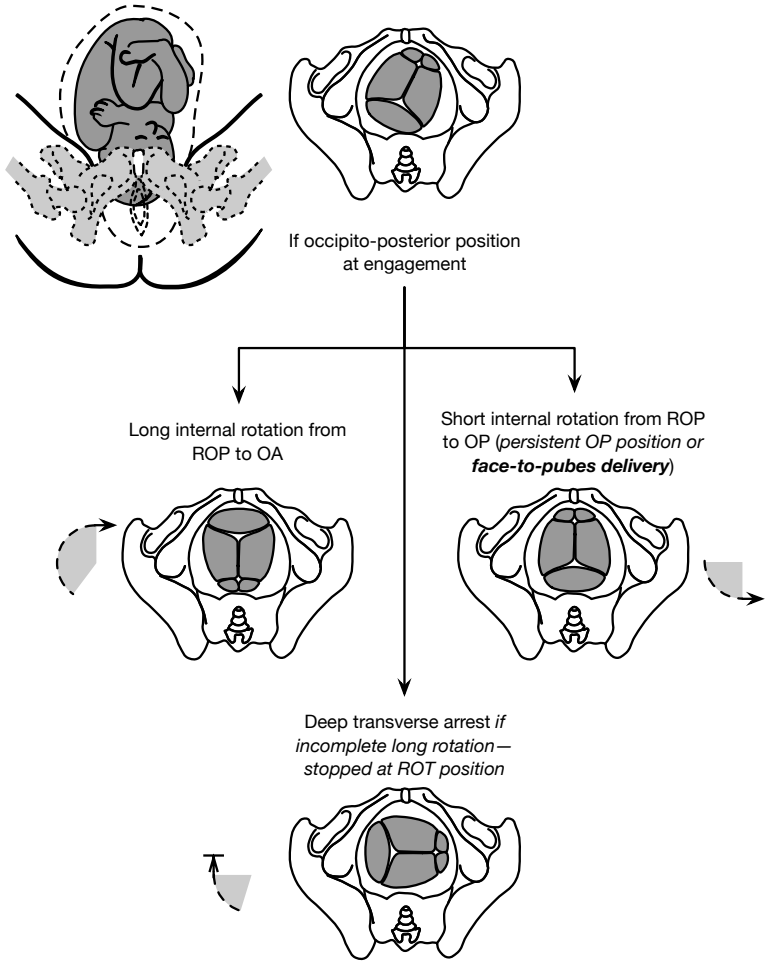


Figure. Illustration of OP malposition and its possible outcomes.

v) Management of poor progress in 2nd stage

If delay is diagnosed **late** in 2nd stage, NICE guidelines recommend that oxytocin should not be started;

- Inefficient uterine activity needs to be corrected proactively at the beginning of the second stage;

- Episiotomy for a resistant perineum leading to delay in labour— especially in nulliparas;
- If labour is obstructed, there may be need for instrumental delivery or C- section;
    - Oxytocin **must never** be used in a multiparous woman where CPD is suspected;
    - Excessive uterine contractions in an obstructed labour may result in uterine rupture in a multiparous woman.
- Monitor fetus with continuous EFM (CTG), especially with meconium stained amniotic fluid.

(III) Breech presentation

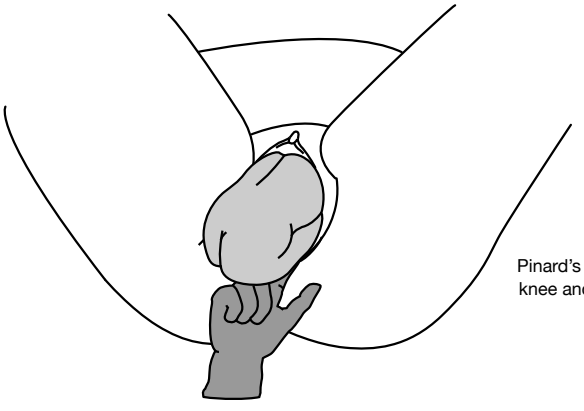
Breech is the most common malpresentation.

In some cases, diagnosis of breech presentation may be made in early labour. In other cases where vaginal delivery is planned for breech, certain pre-requisites need to be considered;

- Presentation should be extended breech or flexed breech— but fetal feet should not be below the fetal buttocks (i.e footling breech);
- There should be no evidence of feto-pelvic disproportion;
- Estimated fetal weight of <3,500 g (ultrasound or clinical measurement);
- No evidence of hyperextension of the fetal head;
- No fetal abnormalities that would preclude safe vaginal delivery (e.g. severe hydrocephalus).

i) Mechanism of breech vaginal labour

- The buttocks are the presenting part and lie in the AP diameter. Once the anterior buttock is delivered and the anus is seen over the fourchette, an episiotomy can be performed (*not earlier*);
- Delivery of the legs and lower body—
    - If the legs are flexed, they deliver spontaneously;
    - If extended, they may need to be delivered using Pinard's manoeuvre (see Figure).



Pinard's manoeuvre— entails using a finger to flex the leg at the knee and then extend at the hip, first anteriorly then posteriorly.

Figure. Illustration of Pinard's manoeuvre.

- Delivery of the shoulders—
    - The baby will be lying with the shoulders in the transverse diameter of the pelvic midcavity;
    - The shoulders rotate into the AP diameter and the anterior shoulder becomes visible— evidenced by appearance of its scapula;
    - The anterior shoulder delivers first;
    - The posterior shoulder also rotates anteriorly (in the opposite direction) and delivers after;
    - The Løveset's manoeuvre essentially copies these natural movements (see Figure).

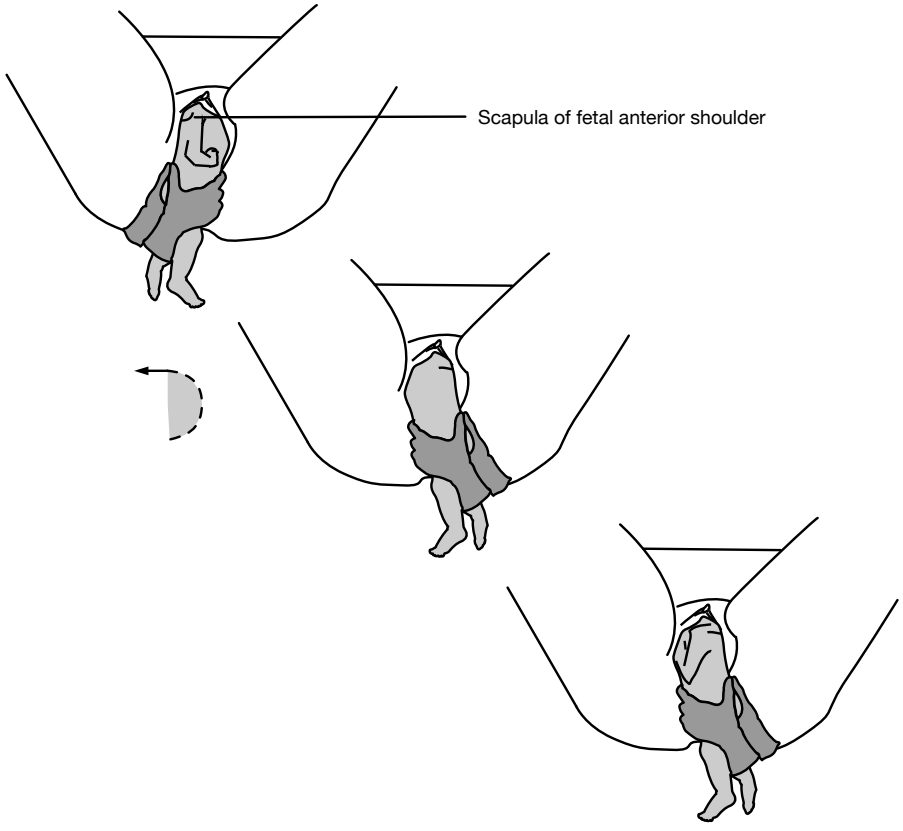


Figure. Illustration of Løveset's manoeuvre.

- Delivery of the head—
    - The head is delivered using the Mauriceau–Smellie–Veit manoeuvre (see Figure);
    - Delivery occurs with first downward and then upward movement (as with instrumental deliveries);
    - If Mauriceau–Smellie–Veit manoeuvre proves difficult, forceps need to be applied.

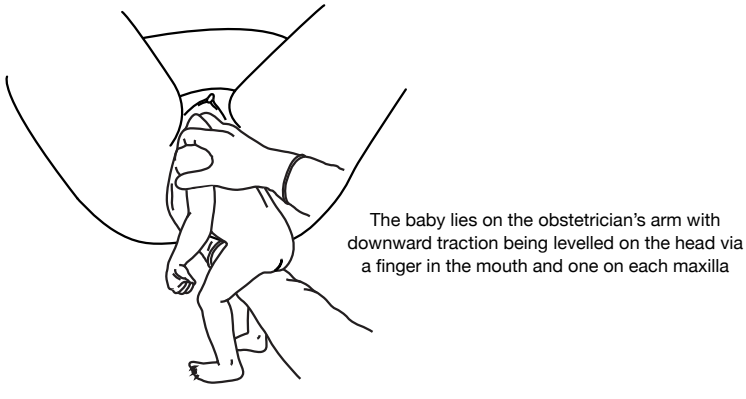


Figure. Illustration of Mauriceau–Smellie–Veit manoeuvre.

ii) Management in labour

- Fetal wellbeing and progress of labour should be carefully monitored;
- An epidural analgesia may be advantageous— prevents pushing before full dilatation;
- Fetal blood sampling from the buttocks provides an accurate assessment of the acid–base status (when the fetal heart rate trace is suspicious).

iii) Complications with breech vaginal delivery

Mechanical difficulties with delivery of shoulders ± after-coming head. This is associated with ↑ risk of;

- Delay in the delivery of the head → prolonged compression of the umbilical cord and asphyxia;
- Damage of fetal brachial plexus;
- Increased risk of cord prolapse— particularly with footling breech;
- Increased risk of CTG abnormalities as cord compression is common;
- Uncontrolled rapid delivery of the head (seen with small fetuses) predisposes to tentorial tears and intracranial bleeding;
- A preterm fetus may deliver through an incompletely dilated cervix and fetal head may stuck.

In order to avoid these potential complications in labour, C-section may be preferred by the patient.

(IV) Induction of labour (IOL)

IOL refers to *planned initiation of labour prior to its spontaneous onset*.

i) Indications and contraindications to IOL

Generally, indications and contraindications to IOL are considered consistently with risks to fetus and/or mother of continuing pregnancy relative to those of ending pregnancy. Such senarios include (see Table);

Table. Indications and contraindications to IOL.

Indications for IOL	**Contraindications to IOL**
• Prolonged pregnancy— most common • PROM • Pre-eclampsia and other maternal HTN disorders • FGR • Maternal diabetes mellitus • Fetal macrosomia • A deteriorating maternal illness • Unexplained antepartum haemorrhage • Twin pregnancy continuing beyond 38 weeks • Intrahepatic cholestasis of pregnancy • Maternal isoimmunization against red cell antigens	**Absolute contraindications—** • Placenta praevia • Severe fetal compromise • Major antepartum haemorrhage • Pre-eclampsia • Matrernal cardiac disease **Relative contraindications—** • Breech presentation • Previous history of C-section— ↑ risk of uterine rupture • IOL at <34 weeks— ↑ risk of failure + subsequent C-section

a) Prolonged pregnancy—

Most common indication for IOL.

It is recommended for 41 and 42 weeks' gestations— because ↑ gestational age is associated with ↑ risk of;

- Stillbirth;
- Fetal compromise in labour;
- Meconium aspiration;
- Mechanical problems at delivery.

b) PROM

The delay between membrane rupture and delivery of the baby is important— ↑ duration is associated with maternal ascending infection (chorioamnionitis) and neonatal infections;

- At term (*beyond 37 weeks*), IOL is recommended **24 hours** following membrane rupture;
- *Before 37 weeks*, indications for IOL need to be thoroughly assessed.

c) Pre-eclampsia and other maternal hypertensive disorders.

- Pre-eclampsia at term is usually managed with IOL.
- C-section is a considerably better option with;
    - Very preterm gestations (<34 weeks);
    - Rapid maternal deterioration or fetal compromise.

d) Fetal macrosomia

- Suspected fetal macrosomia (>90th percentile), **in the absence of maternal diabetes**, is considered an indication for IOL;
- In these cases, fetal weight is estimated by ultrasound. But carries a margin of error in upto 20% cases.

ii) Pre-IOL assessment— the bishop scoring

If labour is induced before the cervix ripens, induction tends to take longer. Bishop scoring system quantifies cervical progress. It is helpful prior to IOL;

- High scores indicate a '**favourable'** cervix. Here IOL is easier, shorter and *less likely to fail*;
- Low scores are associated with a longer IOL session that is more likely to fail and result in C-section.

Table. *Modified* Bishop scoring system.

Score	**0**	**1**	**2**	**3**
Dilatation of cervix (cm)	0	1 or 2 cm	3 or 4 cm	≥ 5
Consistency of cervix	Firm	Medium	Soft	—
Length of cervical canal (cm)	> 2 cm	2 cm to 1 cm	1 cm to 0.5 cm	< 0.5 cm
Position of cervix	Posterior	Central	Anterior	—
Station of presenting part	-3	-2	-1 or 0	Below spines

iii) Methods of IOL

Various methods of IOL have been proposed (see Table).

Table. Methods of IOL.

	Methods	**Comments**
1	Membrane sweep— *an adjunct to IOL*	Insertion and rotational sweep of a gloved finger through the cervix around the inner rim of the cervix— releases physiologic prostaglandins; Only possible if the cervix is beginning to dilate and efface; Offered weekly from 40 weeks— placenta praevia *must be excluded*; Reduces the need for induction.
2	*Prostaglandin **E2***	Can be administered as intravaginal gel, tablet or in pessary form; It ***ripens*** the cervix and initiate contractions; Can be used even when the cervix is **favourable**.
3	ARM	Cervix must be ***favourable***; ARM and oxytocin are often needed ***together*** particularly in primiparas.
4	Oxytocin infusion	Membranes need be ruptured first (spontaneous or artificial); Titrated infusion ↑ every 30 minutes until 3–5 contractions/10 minutes.
5	Mifepristone + misopostol	Is a combination of an antiprogesterone and prostaglandin, *respectively;* Often associated with ↑ complication rates; Preferred in cases of IOL after intrauterine fetal death.

iv) Complications of IOL

Where oxytocics are used, relatively stronger contractions may be observed;

- Epidural analgesia is more commonly needed for analgesia;
- The *rates* of instrumental delivery are ↑ in cases where epidural analgesia is used;
- Long labours augmented with oxytocin predispose to PPH secondary to uterine atony.

Fetal compromise may occur during induced labours;

- This is more likely when;
    - Uerine hyperstimulation as a side-effect of use of prostaglandins and oxytocin;
    - There is ↓ relaxation time between contractions.
- A contraction frequency of >5/10 minutes should be treated— stop oxytocin. Administration of a tocolytic terbutaline can be considered;
- Uterine hyperstimulation may precipitate fetal bradycardia— needs emergency C-section.

If ARM is performed while the fetal head is high, then cord prolapse may occur— needs emergency C-section.

Women with a previous C-section scar are at ↑ risk of uterine rupture if they are induced.

v) Failure of IOL

IOL failure refers to a scenario where;

- An ARM is still impossible after the *maximum number of doses* of prostaglandin have been given, **or**;
- Cervix remains uneffaced and < 3 cm dilated after an ARM has been performed and oxytocin has been infused for 6–8 hours with regular contractions.

If a session of induction fails;

- Rest period followed by attempting induction again at some point in the future, **or**;
- Perform C-section.

Failed induction in the setting of pre-eclampsia or FGR usually necessitates a C-section.

CHAPTER 30 OPERATIVE INTERVENTION IN OBSTETRICS

The most common form of operative intervention is suturing of a perineal tear or episiotomy;

- Women with complications in the first stage of labour are delivered by emergency C-section;
- Complications that occur in the second stage of labour may be addressed with instrumental delivery (with ventouse or forceps) or C-section.

In all cases, operative intervention should only be performed when the benefits outweigh the potential risks.

(I) Perineal trauma

Upto 85% women having vaginal delivery will have some degree of perineal trauma.

It is imperative to examine maternal perineum, vagina and rectum post-delivery of baby and placenta. This is done to classify perineal tears, if any, and manage accordingly.

Iatrogenic episotomy also needs suture-repair.

Factors that ↑ risk of perineal tears include;

- Prolonged labour, especially the active second stage;
- Large infants;
- Instrumental delivery.

Some women perform perineal massage in the antenatal period and this may ↓ risk or extent of tearing.

i) Grading

Perineal trauma is graded into four degrees of severity. Third- and fourth-degree tears are grouped together and termed obstetric anal sphincter injuries (OASIs).

For optimal care, one should classify to a higher grade when in doubt (see Figure and Table).

Table. Grading of perineal trauma.

Degree		**Description**	
1st degree tears		Injury to perineal skin only	
2nd degree tears		Injury to perineum involving muscles but not anal sphincter	
OASI	3rd degree tears	Injury to perineum involving the anal sphincter complex	
		3A	< 50% of external anal sphincter (EAS) torn
		3B	> 50% of external anal sphincter (EAS) torn
		3C	Both EAS and internal anal sphincter (IAS) torn
	4th degree tears	Involvement of perineal muscles, EAS and IAS upto **rectal mucosa**	

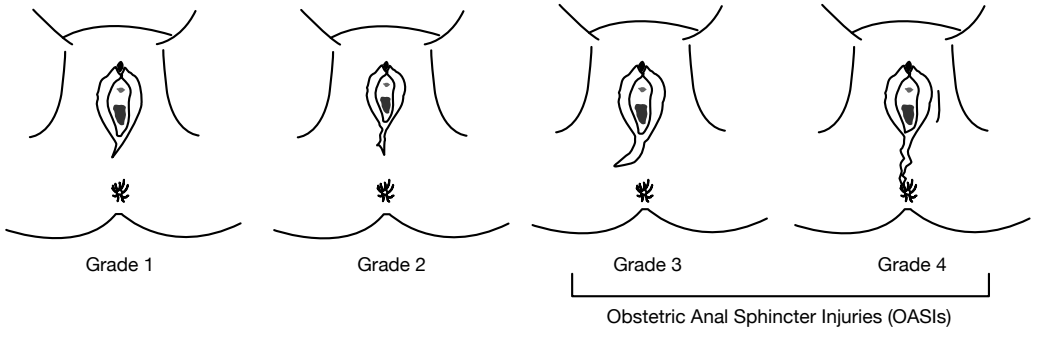


Figure. Grading of perineal trauma associated with vaginal birth.

ii) Complications

- Urinary continence issues;
- Dyspareunia;
- With OASIs, fecal continence issues may be observed;
    - IAS incompetence results in insensible faecal incontinence;
    - EAS incompetence causes faecal urgency.
- Ano-vaginal fistula, rectovaginal fistula may be suspected if the woman complains of passing wind or stool per vaginum.

iii) Management and surgical approach

- It is best to be performed by an experienced operator.
- First-degree tears or minor lacerations with minimal or no bleeding may not require surgical repair.
- Second-degree tears—
    - Adequate analgesia with epidural or local anaesthetic infiltration;
    - It is helpful to place a pad or tampon high in the vagina. This prevents uterine blood from obscuring the view;
    - The vaginal mucosa is repaired first— a continuous stitch should be used here (see Figure);
    - Interrupted sutures are then placed to close the muscle layer (see Figure);
    - Closure of the perineal skin is with interrupted sutures or a continuous subcuticular stitch;
    - Ensure good apposition and no missed tears;
    - Examine rectum post-procedure— no sutures pass through rectal mucosa;
    - Careful count of swabs and instruments should be documented in the operative notes.
- Post-procedure;
    - Examine rectum— no sutures pass through rectal mucosa;
    - Careful count of swabs, instruments and needles should be completed and documented in the operative notes;
    - Prophylactic antibiotics may be indicated if contamination is suspected.

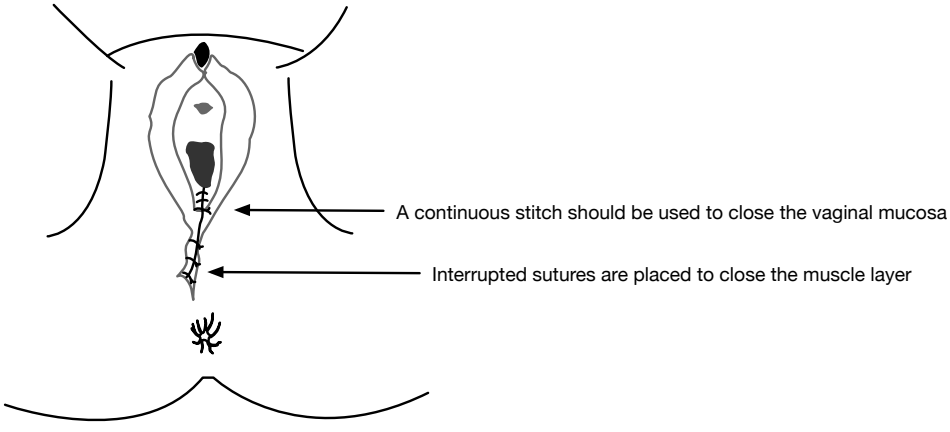


Figure. Illustration of repair of second-degree perineal tears.

a) OASI repair

For third- and fourth-degree perineal tears, OASI repairs are undertaken;

- Here adequate analgesia should be with either a regional or general anaesthetic— only local infiltration does not allow relaxation of the sphincter enough for a satisfactory repair.

- In OASI repairs;
    - Rectal mucosa should be repaired **first**;
    - Then, torn anal sphincter is repaired by *end-to-end repair technique*, or *overlap technique*;
    - The outcome is similar with both techniques (see Figure);
- Ensure muscle approximation with long-acting sutures— provides the muscle adequate time to heal;
- The remainder of the perineal repair is same as for second-degree tears.

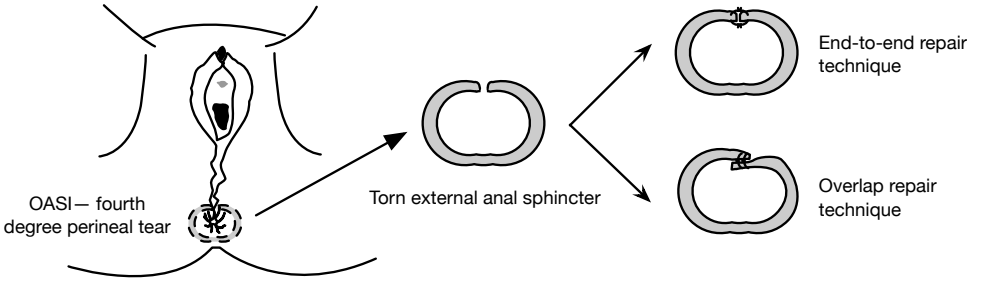


Figure. Illustration of end-to-end repair and overlap techniques of external anal sphincter repair.

b) Care after OASI repairs

- Laxative and a stool softener are recommended for 5–10 days;
- Patient should remain in hospital until she has passed stools;
- An oral broad-spectrum antibiotic should be prescribed for 5–7 days to reduce the risk of infection.
- All women with OASIs should be offered follow-up in the postnatal period. This includes;
    - Physiotherapy with augmented biofeedback— shown to improve continence issues;
    - Evaluation after 6–12 weeks for faecal and urinary symptoms. Helpful investigations include endoanal ultrasound and manometry.

Advice in relation to future pregnancy and delivery;

- Asymptomatic women have low risk of risk of recurrence in later vaginal deliveries;
- Women with fecal symptoms should be investigated;
- Women with ongoing troublesome symptoms should be offered an elective caesarean section in future pregnancies.

(II) Episiotomy

i) Definition

An episiotomy is a surgical incision of the perineum performed during the second stage of labour to enlarge the vulval outlet and assist vaginal birth.

ii) Restrictive versus routine use of episiotomy

Episiotomy may be needed usually when the perineum is being stretched and it is deemed necessary;

- Previously, it was believed that episiotomy was preferable to tearing and thus was used routinely;
- But episiotomy after a case-by-case assessment is often preferred (→ ***restrictive approach***).

Research evidence shows that this restrictive approach is associated with ↓ posterior perineal trauma and ↓ need for suturing with no difference in pain, urinary incontinence or dyspareunia.

A routine episiotomy is not protective of more severe perineal tears (OASI).

iii) Surgical technique of episiotomy

An episiotomy is performed in the second stage;

- If epidural has not been used, the perineum should be infiltrated with local anaesthetic;
- The incision can be midline or at an angle from the posterior end of vulva (a mediolateral episiotomy);
    - A mediolateral episiotomy at a 60° angle to the midline is usually recommended;
    - It starts at the posterior part of the fourchette, moves backwards and then turns laterally before the border of anal sphincter— to prevent extension into the sphincter (OASIs).
- A midline episiotomy is an incision in a relatively avascular area. It is associated with less bleeding, pain and quicker healing but carries an ↑ risk of extension to involve the anal sphincter (OASIs).

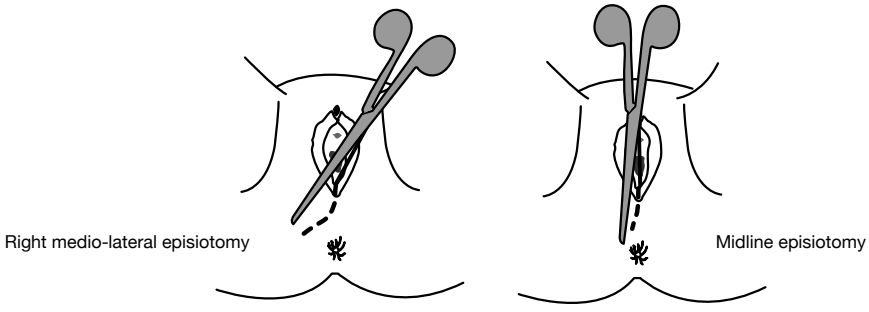


Figure. Illustration of mediolateral and midline episiotomy incisions.

iv) Repair of episiotomy

- Repair of episiotomy is similar to second degree perineal tears;
- If, despite episiotomy, anal sphincter complex becomes involved— OASI repair will be needed.

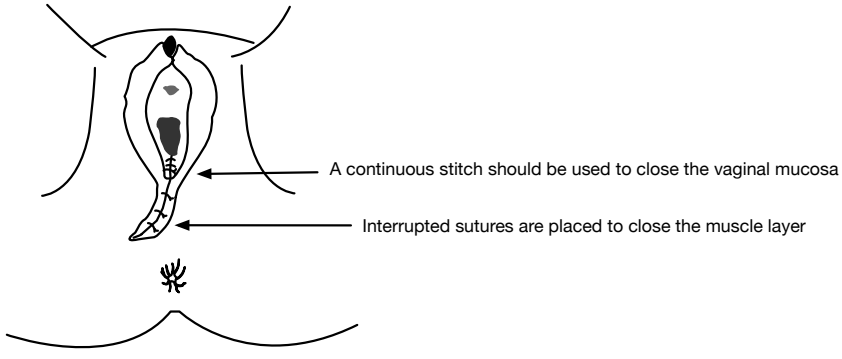


Figure. Illustration of repair of an uncomplicated episiotomy.

v) Complications of repair

The risks of complications are higher with concurrent OASIs;

- Short-term complications of perineal trauma or episiotomy include;
    - Post-procedure pain;
    - Infection— prophylactic antibiotics may be indicated if contamination is suspected;
    - Hemorrhage.
- Long-term effects include;
    - Dyspareunia;
    - Urinary incontinence;
    - Incontinence of flatus or faeces— more likely with OASIs.

(III) Operative vaginal delivery (OVD)

Operative vaginal delivery (OVD, or assisted vaginal delivery) refers to a vaginal birth with the use of forceps or vacuum extractor (ventouse).

C-section in second stage of labour is associated with ↑ risk of complications. Here OVDs are a better option as a trial of OVD can potentially expedite delivery with a minimum maternal and neonatal morbidity.

i) Indications

Indications		**Causes**
Fetal	Suspected fetal compromise— ***Most common fetal indication***	Pathological CTG
		Abnormal pH or lactate on FBS
		Thick meconium
	Prolonged 2nd stage of labour	Malposition
	In a breech delivery, forceps are often applied to the *after-coming head* to control delivery.	
Maternal	Prolonged 2nd stage of labour— ***Most common maternal indication***	Secondary dysfunctional uterine activity Narrow midpelvis Resistant perineum
	Maternal distress	Maternal vomiting
	Maternal exhaustion	
	Prophylactic indication in maternal cardiac disease, or myasthenia gravis.	
Combined fetal and maternal		

ii) Safety criteria and contraindications

OVD should only be performed when the safety criteria have been met (see Table).

Table. Safety criteria and contraindications to OVDs.

Safety criteria	**Contraindications**
Head ≤1/5 palpable per abdomen	High fetal head— 2/5th palpable
Cervix fully dilated and membranes ruptured	Cervix not fully dilated
Station at or below ischial spines	Station above the ischial spines
Exact position of head determined *(for correct placement of instrument)*	
Caput and moulding is no more than moderate	
Pelvis is deemed adequate	
Maternal bladder emptied + foley's catheter *removed or bulb deflated*	

iii) Classification of operative vaginal delivery

The type of delivery in OVDs is determined by the position and descent of the head.

RCOG has recommended a classification system for position and descent, that reflects these management choices (see Table).

Table. Classification of operative vaginal deliveries (OVDs).

<table>
<tr><td colspan="2">Fetal scalp visible without separating the labia
Fetal skull has reached the pelvic floor
Sagittal suture is in the anterio-posterior diameter or right or left occiput anterior or posterior position (rotation does not exceed 45°)
Fetal head is at or on the perineum</td><td>Outlet OVD</td><td rowspan="3">Forceps or ventouse</td></tr>
<tr><td colspan="2">Leading point of the skull (not caput) is at station plus 2 cm or more and not on the pelvic floor
Two subdivisions:</td><td rowspan="2">Low OVD</td></tr>
<tr><td>Rotation of ≤45° from OA position</td><td>Rotation of >45° including OP position</td></tr>
<tr><td colspan="2">Fetal head is no more than 1/5th palpable per abdomen
Leading point of skull is above station plus 2 cm but not above ischial spines
Two subdivisions:</td><td colspan="2" rowspan="2">Mid OVD</td></tr>
<tr><td>Rotation of ≤45° from OA position-
Forceps or ventouse</td><td>Rotation of >45° from OA position—
OT position: ventouse. Non-rotational forceps are contraindicated.
OP position: Kielland's rotational forceps most successful</td></tr>
<tr><td colspan="2">Fetal head is 2/5th or more palpable abdominally and the presenting part is above the level of the ischial spines</td><td colspan="2">OVD not recommended</td></tr>
</table>

iv) Ventouse and Forceps

<table>
<tr><td>Ventouse/vacuum extractors
Vaccum extractors (or ventouse) attach to fetal head using negative pressure and aid in traction.</td><td>Forceps
Forceps are a pair of curved blades— attach to fetal head and aid in traction.</td></tr>
<tr><td colspan="2">The Instruments</td></tr>
<tr><td>These consist of a suction cup.
The suction cup may have inherent vaccum mechanism or is connected to a vacuum pump via tubing</td><td>All basic types of forceps in use today consist of two blades with shanks and handles.</td></tr>
<tr><td colspan="2">Types</td></tr>
<tr><td>Vaccum extractor's type is based on type of cup;
A soft silastic cup, or;
A rigid metal construction.</td><td>Forceps are generally of 3 types;
Non-rotational— grip and allow traction without rotation. E.g. Wrigley's forceps, Simpson forceps, Neville-Barnes forceps.
Rotational— grip, allow rotation and then traction. E.g. Kielland forceps.
Forceps to assist breech deliveries— Piper forceps have long handles and a reverse pelvic curve (see Figure.</td></tr>
</table>

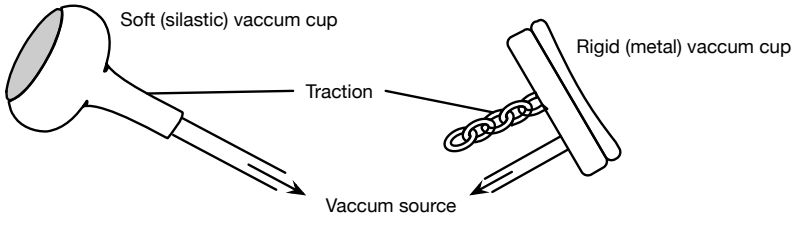


Figure. Illustration of vaccum extractors' types and parts.

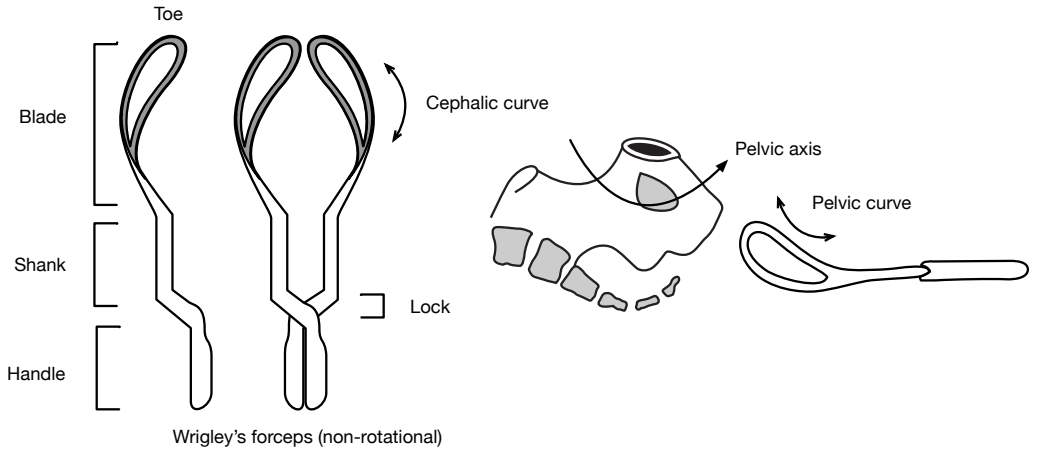


Figure. Illustration of the non-rotational Wrigley's forceps' parts and curves.

v) Choice of instrument

Table. Choice of type of instrument— vaccum extractors and forceps.

Vaccum extractors	**Forceps**
Soft vacuum cups are more likely to fail than rigid; • The soft cups are appropriate for uncomplicated deliveries with an occipito-anterior position (OA); • Metal cups are more suitable for OP, OT and difficult OA positions where the fetus is larger or there is marked caput. The ventouse should not be used in; • Gestations < 34 weeks— ↑ risk of cephalohaematoma and intracranial haemorrhage; • Face or breech presentation; • Significant degree of caput on fetal head.	Choice of forceps depends on fetal occiput position; • Non-rotational forceps **only** suitable when the occiput is anterior with ≤ 45° deviation to left (LOA or ROA). These forceps have a 'cephalic' curve for the head and a 'pelvic curve' which follows the sacral curve. • Rotational forceps have no pelvic curve and enable a malpositioned head to be rotated by the operator to the OA position, **before** traction is applied. *The sliding lock of the Kielland forceps* also facilitates correction of **asynclitism.**

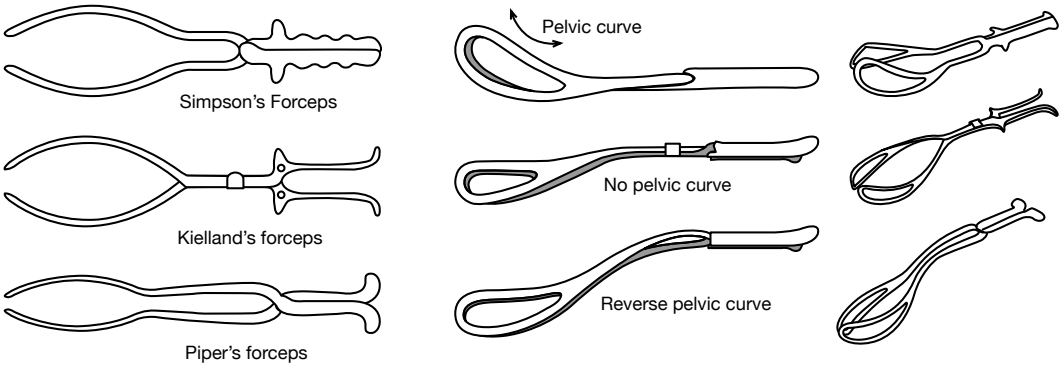


Figure. Illustration of types of forceps.

vi) Procedure

Table. Procedure of ventouse and forceps OVDs.

Ventouse/vaccum extractors	**Forceps**
Technique of use	
Positioning—*the flexion* point on fetal head (*see Fig*). Vaccum pressure— between 0.6 and 0.8 kg/cm^2. Traction— in the plane of least resistance along the axis of the pelvis i.e. the traction plane. Safe and gentle traction is then applied coordinated with uterine contractions and voluntary maternal expulsive efforts. There is a descent phase bringing the head onto the perineum usually achieved in at most three pulls. The crowning phase should occur shortly afterwards, and depending on the resistance of the perineum, may occur with one further pull or *upto three very small pulls* to **minimize perineal trauma**. Rotation— here this is achieved by the natural progression of the head through the pelvis. Episiotomy— in parous women, particularly those requiring ventouse delivery, an episiotomy *may not be necessary*.	Positioning— forceps blades should lie parallel to the axis of the fetal head and between the fetal head and the pelvic wall. Locking— the left blade is inserted before the right and these need to be locked in position before traction. Traction— is applied intermittently coordinated with uterine contractions and maternal expulsive efforts. *The axis of traction changes during the delivery and is guided along the 'J'-shaped curve of the pelvis.* As the head begins to crown, the blades are directed to the vertical and the head is delivered. The majority of forceps deliveries will be completed in no more than three pulls. Rotation— occurs between contractions and may be guided by operator if rotational forceps. Episiotomy— may be considered in nulliparas where anal sphincter damage is more likely.
Complications	
• If incorrect positioning— progressive deflexion of fetal head during traction, and an inability to deliver the baby safely. • Cervical tearing if cervix not fully dilatated; • Fetal cephalohematoma.	• Maternal pelvic floor trauma; • Fetal intracranial haemorrhage.
Failure	
There should not be > 2 episodes of suction 'pop-offs' in a vacuum delivery. Maximum time from application to delivery should ideally be < 15 minutes.	Inability to deliver despite correct placement and use requires re-assessment of the 3 P's.

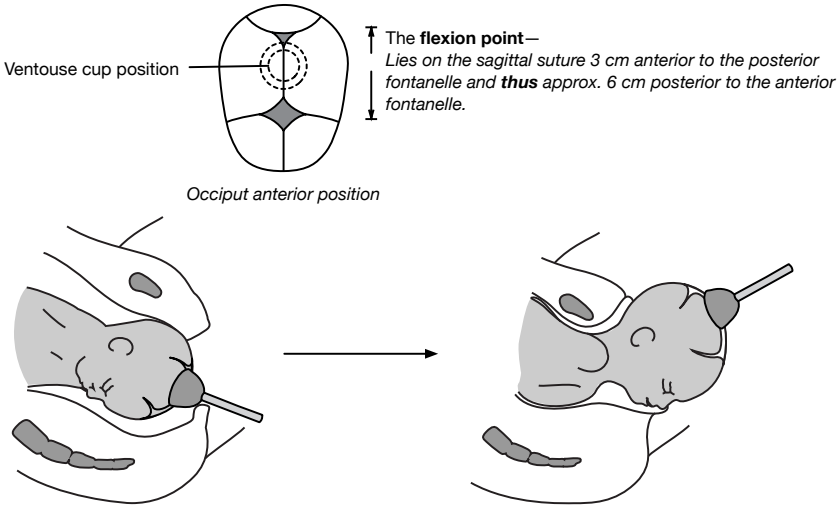


Figure. Illustration of positioning and application of ventouse cup with reference to *flexion point* on fetal head.

vii) Complications of OVDs

OVDs with both vacuum and forceps can be associated with significant maternal and fetal complications;

- Maternal complications;
- Traumatic tears;
- Haemorrhage—
    - PPH is more common in women needing OVD relatively;
    - Measures to limit this include early recognition of abnormal bleeding, use of ocytocics post-delivery, and suture repair of high vaginal wall tears.
- Fetal complications;
    - Cephalohaematoma;
    - Intracranial injuries and haemorrhage.
- Failure of OVD;
    - Anticipate complications and have a back-up contingency plan;
    - It may be possible to complete a failed vacuum delivery with low-pelvic forceps, but a failed forceps delivery needs C-section.

viii) Failure of the chosen instrument

Failure to complete delivery vaginally can occur if;

- The choice of instrument is wrong (e.g. silastic cup ventouse for a rotational delivery);
- Application of the instrument is wrong or difficult;
    - If ventouse fails due to cup detachments, while fetal head is OA and on the perineum— a low-pelvic or outlet OVD with forceps can be safely carried out;
    - Sequential use of forceps in these cases is less traumatic than a second stage C-section.
- Fetal position is incorrectly identified (most commonly OP–OA errors)— a rotational instrumental delivery or C-section may be considered;
- Underlying CPD— manifests as little or no descent with the first pull despite correctly applied instrument and traction in correct axis of maternal pelvis. C-section will be needed;
- Large fetus or poor maternal effort.

Outcomes for babies are worse with multiple or sequential use of instruments relatively. But these need to be considered over **potential maternal complications** associated with a second-stage C-section.

In many cases, delivery by caesarean section is a **safer option for the fetus**.

(IV) Caesarean section

A caesarean section is a surgical procedure in which incisions are made through a woman's abdomen (laparotomy) and uterus (hysterotomy) to deliver one or more babies.

i) Indications

Almost all indications are relative and should be assessed on case-by-case basis for risk to the mother and fetus.

The four major indications accounting for greater than 70% of operations are;

- Previous C-section and its associated complications;
- Malpresentation (mainly breech);
- Failure to progress in labour;
- Suspected fetal compromise in labour.

Other indications, such as multiple pregnancy, placental abruption, placenta praevia, fetal disease and maternal disease, are less common.

ii) Contraindications—

For safe delivery of fetus, there are no contraindications to C-section. However, if there is ↑ risk of complications if there is need for C-section in second stage of labour.

If the fetal head is deep in the pelvis, complications observed with C-section include;

- Major hemorrhage;
- Need for neonatal intensive care;
- Need for repeat C-section in next pregnancy.

OVDs, on the other hand, are not associated with relatively ↑ need of repeat OVDs in subsequent pregnancies. Thus, in these cases a trial of OVD may be considered after thorough assessment.

iii) Classification

Traditionally, caesarean sections have been classified as elective or emergency.

- It is preferrable to label C-sections as "scheduled" for procedures that are planned ahead of time.
- All other caesarean sections can be classified as emergency, irrespective of onset of labour.

Emergency caesarean section can be further categorized on the degree of urgency (see Table).

Table. Classification system for emergency caesarean section

Category 1	Immediate threat to life of woman or fetus
Category 2	No immediate threat to life of woman or fetus
Category 3	Requires early delivery
Category 4	At a time to suit the woman and maternity services

iv) Procedure

a) Preparation

- The bladder should be emptied pre-procedure and a urinary catheter is usually left in situ;
- Anesthesia— spinal (most commonly), epidural or general anaesthesia;
- A left lateral tilt minimizes aorto-caval compression and ↓ incidence of maternal hypotension;
- Prophylactic antibiotics— intravenously prior to the surgical incision.

b) Abdominal incision

The skin and subcutaneous tissues are incised by a transverse or vertical incision (see Figure);

- The transverse suprapubic incision is performed most commonly these days;
    - It is a curvilinear transverse incision made 2 fingerbredths superior to the symphysis pubis;
    - It extends to lateral margins of the abdominal rectus muscles (→ Pfannenstiel incision);
    - Though the skin incision is transver, rectus muscles should be separated vertically in the midline (see Figure);
    - Further dissection deeper is with blunt dissection.
- A vertical skin incision is performed rarely nowadays (see Figure);
    - It is made from the lower border of the umbilicus to the symphysis pubis;
    - It can be easily extended if needed during the procedure;
    - This provides greater ease of access to the pelvic and intra-abdominal organs relatively;
    - Further dissection deeper is with sharp dissection;
    - It use includes cases with (but not limited to) extreme maternal obesity, need for access to uterine fundus and suspected intra-abdominal pathology.

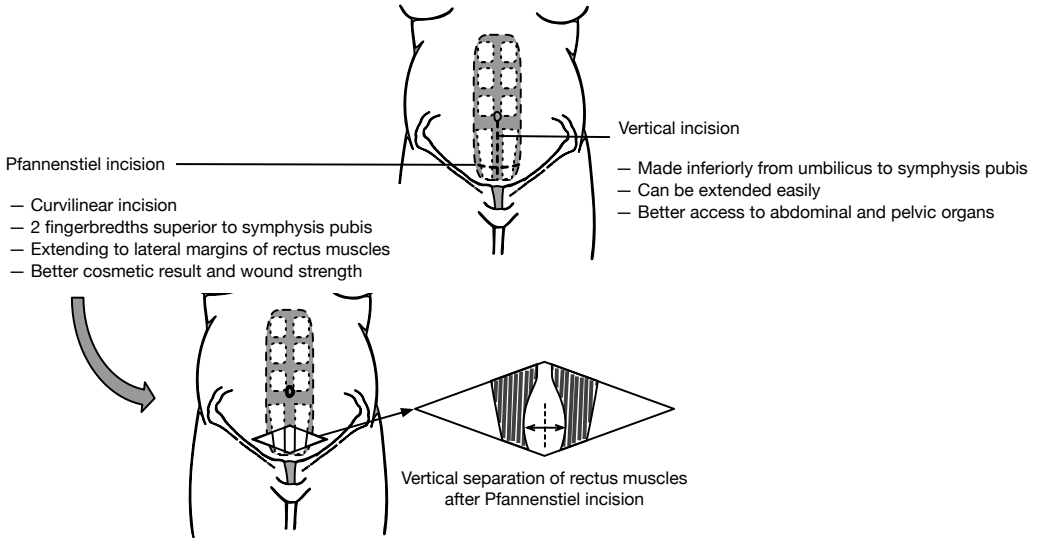


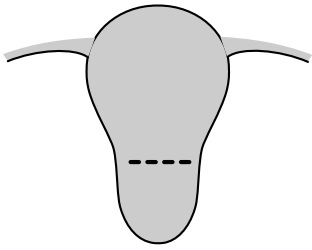
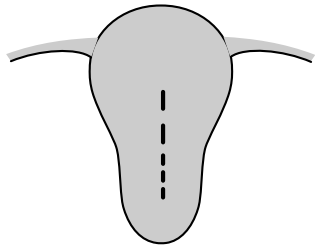
Figure. Illustration of Pfannenstiel and vertical incisions of abdominal wall.

c) Uterine incision

The uterus is incised by;

- A transverse incision in the lower uterine segment (commonly), or;
- Less commonly— a vertical incision often incorporating the upper uterine segment.

Table. Transverse and vertical uterine incisions.

Lower segment transverse uterine incison	**Vertical uterine incision**
	
The lower uterine segment is opened in a transverse plane for a distance of 1–2 cm. The incision is extended laterally to allow delivery of the fetus.	The lower uterine segment is incised vertically— ***low vertical incision***. It can be extended to incorporate upper uterine segment (→ ***classical C-section incision***) .
Advantages— • Ease of repair; • ↓ blood loss; • Low incidence of rupture in later pregnancies.	The vertical uterine incision is used (but not limited to) cases with; • Fibroids or adhesions in lower uterine segment; • Placenta praevia; • Transverse lie with fetal back down; • Certain fetal abnormalities e.g. conjoined twins; • Carcinoma of the cervix.

Once the uterus is incised,

- The membranes are ruptured if still intact;
- The obstetric surgeon's hand is positioned below the presenting part;
- The fetus can be delivered **manually** or ***with forceps*** through the incision;

- After fetus is delivered, administer an oxytocic— to aid uterine contraction and placental separation;
- The placenta is delivered by controlled cord traction.

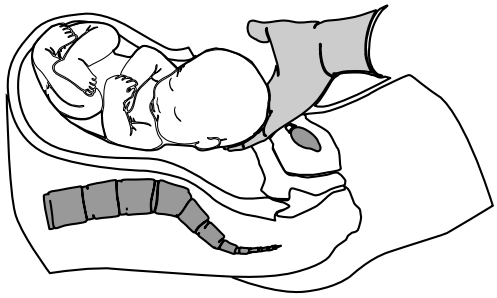


Figure. Illustration of manual delivery during C-section (*rectum not shown*).

v) Complications

Common complications include;

- Haemorrhage;
- Infection of the wound, urinary tract or endometrium;
- For the baby— transient tachypnoea of the newborn (TTN).

a) Intraoperative complications

- Haemorrhage;
- Organ damage— bowel or bladder damage may occur due to adhesions from previous surgery.

b) Postoperative complications

- Infection—
    - This is associated with fever, wound infection, endometritis, bacteraemia and UTI;
    - It is commonly polymicrobial, spread from the genital tract;
    - Other common causes of postop fever include haematoma, atelectasis and DVT.
- Venous thromboembolism.
- Other complications in future pregnancies include;
    - Placenta praevia— ↑ risk with each previous caesarean section procedures;
    - Placenta accreta— if placenta *in future pregnancies* overlies previous C-section scar.

c) Subsequent birth following C-section

This may be carried out by elective (i.e. scheduled) repeat caesarean section (ERCS) or attempted vaginal birth after caesarean section (VBAC);

- Relatively ↑ risk of rupture of scar from previous C-section— excess risk of 0.5-1% (VBAC vs. ERCS);
- After assessment, it may often be appropriate to offer a **T**rial **O**f **L**abour **A**fter **C**-section (TOLAC) to those with a previous uncomplicated lower segment C-section and no other adverse obstetric feature.

From a maternal perspective, ERCS avoids labour with its risk of;

- Pelvic floor trauma (urinary and anal);
- Need for emergency C-section;
- Scar dehiscence or rupture.

However, ERCS carries ↑ maternal risks of;

- Bleeding;
- Febrile morbidity;

- Prolonged recovery;
- Thromboembolism;
- Long-term bladder dysfunction;
- Placenta praevia in subsequent pregnancies.

From fetal perspective, ERCS reduces risk of scar rupture, but ↑ risk of transient tachypnea of newborn (TTN).

vi) Management of complications

- Haemorrhage— blood transfusion;
    - Oxytocin infusion;
    - Prostaglandin administration;
    - Bimanual compression;
    - Conservative surgical procedures, e.g. uterine compression sutures;
    - In severe cases— hysterectomy (i.e. caesarean-hysterectomy);
        - *Most common indication for caesarean hysterectomy is uncontrollable maternal haemorrhage;*
        - Other indications include uterine atony, rupture or fibroids preventing uterine closure and haemostasis.
- Venous thromboembolism;
    - Adequate hydration;
    - Early mobilization;
    - Prophylactic heparin administration.
- Iatrogenic bladder injury;
    - Instilling methylene blue-coloured saline *transurethrally* aids diagnosis in suspected cases;
    - If detected, repair is needed with single or interrupted sutures and Foley's catheter is kept *in-situ* for 7-10 days.

CHAPTER 31 OBSTETRIC EMERGENCIES

An emergency is defined as a serious situation or occurrence that happens unexpectedly and demands immediate action.

Prompt recognition and treatment of these emergencies/complications of pregnancy is essential to limit morbidity and mortality.

Table. Common obstetric emergencies.

<table>
<tr><th colspan="3">Maternal</th><th>Fetal</th></tr>
<tr><td rowspan="6">Haemorrhage</td><td rowspan="2">Antepartum</td><td>Placenta previa</td><td>Fetal bradycardia</td></tr>
<tr><td>Abruptio-placenta</td><td>Umblical cord prolapse</td></tr>
<tr><td rowspan="4">Postpartum</td><td>Uterine atony</td><td>Shoulder dystocia</td></tr>
<tr><td>Trauma</td><td rowspan="13">Vasa previa</td></tr>
<tr><td>Retained placenta</td></tr>
<tr><td>DIC</td></tr>
<tr><td rowspan="2">Hypertensive disorders</td><td colspan="2">Pre-eclampsia</td></tr>
<tr><td colspan="2">Eclampsia</td></tr>
<tr><td rowspan="2">Uterine causes</td><td colspan="2">Inversion</td></tr>
<tr><td colspan="2">Rupture</td></tr>
<tr><td rowspan="7">Sudden maternal collapse</td><td colspan="2">Amniotic fluid embolus</td></tr>
<tr><td colspan="2">Pulmonary embolus</td></tr>
<tr><td colspan="2">Shock (septic, hemorrhagic or anaphylactic)</td></tr>
<tr><td colspan="2">Cardiac causes, e.g. myocardial infarction</td></tr>
<tr><td colspan="2">Intracranial events– bleeds, thrombosis</td></tr>
<tr><td colspan="2">Biochemical causes – e.g. hypoglycaemia</td></tr>
<tr><td colspan="2">Anaesthetic events</td></tr>
</table>

(I) The collapsed/unresponsive patient

This can occur secondary to a variety of causes similar to a non-pregnant adult. Potentially, any of the obstetric emergencies can lead to maternal collapse.

It Is recommended that a structured approach is undertaken (see Figure);

1. Call for help;
2. Evaluation systematically—'ABCDE' approach for mother;
    A. Airway;
    B. Breathing;
    C. Circulation;
    D. Disability;
    E. Exposure.
3. Resuscitation— this may be in the form of;
    A. Cardiopulmonary resuscitation (CPR) if maternal cardiac or pulmonary arrest, or;
    B. Definitive care with focused management of underlying cause.
4. Evaluate fetal wellbeing— using CTG.

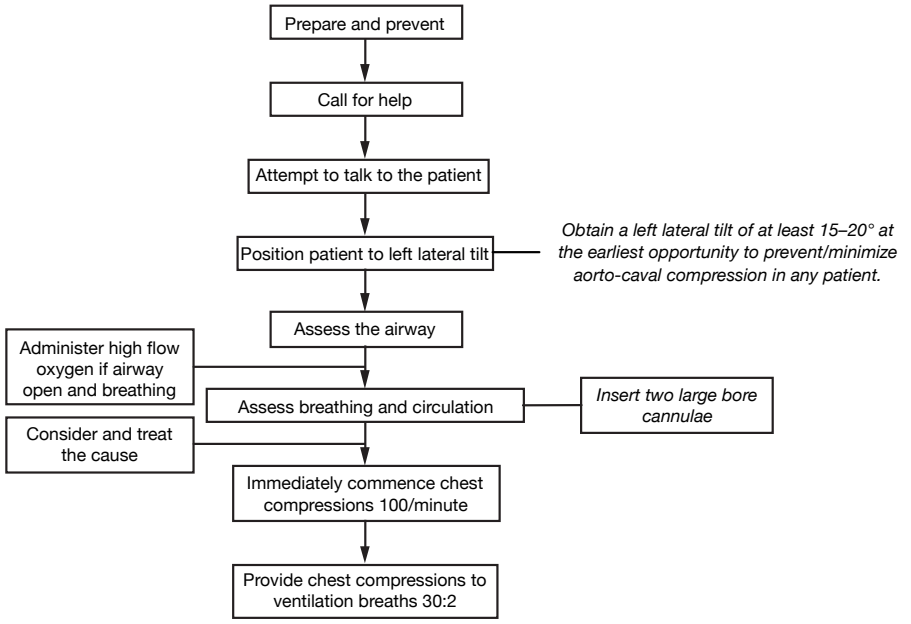


Figure. The structured approach to managing obstetric emergencies.

(II) Maternal obstetric emergencies

i) Obstetric haemorrhage

Maternal obstetric haemorrhage is the most common obstetric emergency.

Table. Definitions and classifying obstetric haemorrhage.

APH	**PPH**	**Severity**
Any vaginal bleeding occurring after 20th weeks till delivery of the baby	Primary PPH Loss of &500 mL blood from the genital tract within 24 hours of delivery	Minor obstetric haemorrhage Blood loss between 500 and 1000 mL
	Secondary PPH Loss of &500 mL blood from the genital tract between 24 hours and 12 weeks post delivery	Major obstetric haemorrhage Blood loss ≥2,500 ml, or requiring a blood transfusion ≥5 units red cells or treatment for coagulopathy

a) Antepartum haemorrhage (APH)

(*Also see Chapter 22: Antenatal obstetric complications and Chapter 24: Placetation and related disorders*);

- Placenta praevia is most dangerous for the mother;
- Placental abruption is more dangerous for fetus than the mother;
- Vasa praevia is not dangerous for the mother but is nearly always fatal for the baby.

b) Postpartum haemorrhage (PPH)

PPH is defined as blood loss ≥500 ml;

- It can be primary or secondary (*for secondary PPH, see Chapter 32: Puerperium*);
- Secondary PPH is usually the result of retained products of conception and/or uterine infection;
- The causes of PPH can be referred to as "the four T's" (see Table).

Table. Causes (*aide-mémoire: four 'Ts'*) and risk factors associated with PPH.

<table>
<tr><th colspan="2">Causes</th><th colspan="2">Risk factors</th></tr>
<tr><td>Tone</td><td>Uterine atony— MCC of PPH</td><td colspan="2">Maternal</td></tr>
<tr><td rowspan="3">Tissue</td><td>Retained placenta and/or membranes</td><td>Pre-existing</td><td>Intrapartum</td></tr>
<tr><td>Uterine inversion</td><td rowspan="4">↑ maternal age
Placenta previa
Placenta accreta
Primiparity
Grand multiparity
Uterine fibroids
Previous C-sections
Bleeding disorders
Obesity
Previous PPH</td><td rowspan="4">Prolonged labour
C-section
Instrumental delivery
Pyrexia in labour
Episiotomy/perineal trauma
DIC</td></tr>
<tr><td>Uterine rupture</td></tr>
<tr><td rowspan="2">Trauma</td><td>Vaginal or perineal tears</td></tr>
<tr><td>Uterine tears at C-section</td></tr>
<tr><td rowspan="2">Thrombin</td><td>Underlying clotting disorders, e.g. Von Willebrand's disease.</td><td colspan="2">Fetal</td></tr>
<tr><td>Consumptive coagulopathy</td><td colspan="2">Large baby
Multiple pregnancy
Polyhydramnios
Shoulder dystocia</td></tr>
</table>

c) Uterine atony

Uterine atony is most common cause of primary PPH and can potentially lead to major obstetric haemorrhage.

It refers to failure of uterus to contract after the delivery of the placenta;

This may occur idiopathically or associated with certain risk factors. These include;

- A retained placenta or membranes (most commonly associated);
- Macrosomia;
- Multiple pregnancy;
- Prolonged labour;
- Induction of labour;
- Grand multiparity;
- Polyhydramnios;
- Antepartum haemorrhage;
- Placental abruption.

Active management of the third stage of labour significantly reduces incidence of uterine atony.

Management includes administration of oxytocics and application of manual manoeuvres to aid uterine contraction. This is carried out as part of the algorithmic approach to PPH.

d) Clinical features of PPH

Anxiety, thirst, lethargy, slow capillary refill (> 2 seconds) ± hemodynamic changes (↑ HR, ↓ BP) in association with high estimated blood loss are commonly observed;

- The earliest symptom encountered is maternal tachycardia.
- BP changes often may not manifest *immediately* with upto 1000 mL of blood lost.

e) Investigations and management of PPH

Management of PPH should not be delayed. Thus, an algorithmic priority-based approach to investigations and management is undertaken (see Figure);

- Emptying uterus of clots and urinary bladder of urine aids uterine contractions;
- Secondary PPH is usually the result of retained products of conception and/or uterine infection;

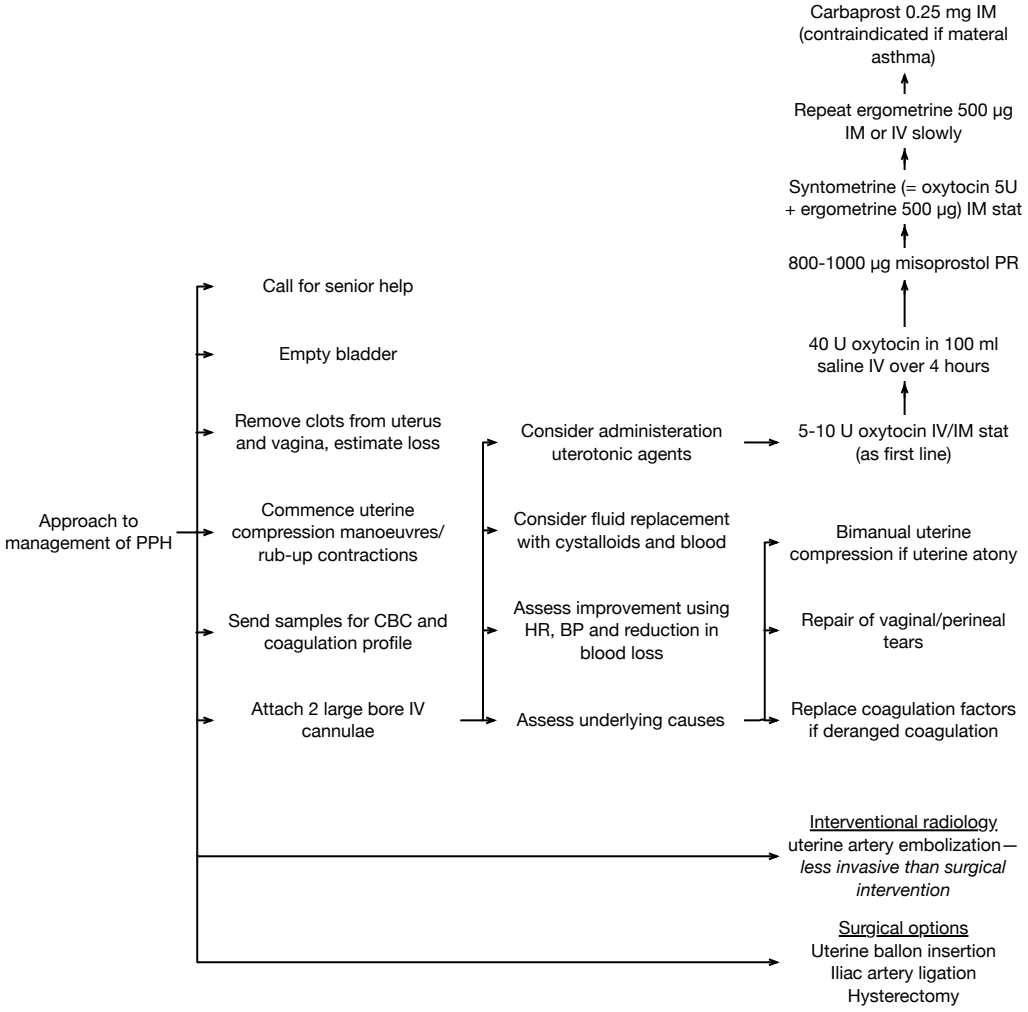


Figure. An exemplary algorithmic priority-based approach to management of PPH.

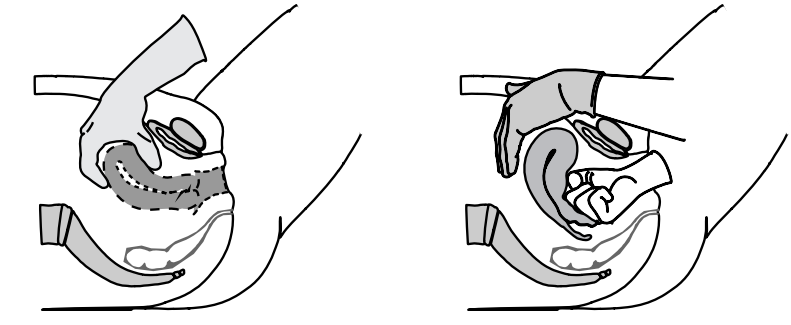


Figure. Illustration of rubbing-up a uterine contraction in comparison with bimanual uterine compression.

f) Prevention of PPH

- Iron supplementation pre-partum as indicated to optimize haemoglobin levels prior to delivery.
- Prophylactic use of oxytocin agents for high-risk patients.

ii) VTE and pulmonary embolism

Thrombosis is the most common cause of maternal death in developed countries unlike developing countries where maternal hemorrhage is more commonly cited for maternal death.

a) Aetiology and risk factors

(*See Chapter 22: Antenatal obstetric complications*).

b) Clinical features

VTE manifests variably. It may be asymptomatic or present with;

- If DVT— unilateral calf or groin pain ± swelling;
- If pulmonary embolism (PE)— haemoptysis, SOB ± cyanosis and maternal collapse. O_2 sats on pulse oximetry may be ↓.

It is important to recognize that PE is more common in the puerperium;

- O_2 sats on pulse oximetry may be ↓;
- ABGs are often needed to confirm hypoxia;
- Pulmonary auscultation may reveal a friction rub.

c) Diagnosis and management

For maternal collapse, urgent resuscitation should be instituted using the ABCDE approach. In these cases, management takes precedence over diagnosis.

If PE is suspected, anticoagulation should be instituted— low-molecular weight heparin (LMW-heparin) according to body weight subcutaneously.

Investigative options include;

- Chest X-ray— to rule out other causes;
- Lower limbs Doppler ultrasound— to rule out lower limb VTE;
- Ventilation perfusion (V/Q scan) or computed tomography pulmonary angiography (CT-PA);
- D-dimer level are of low value in *ruling-in diagnosis* due to its physiologic elevation in pregnancy.

In the case of a collapsed patient with pulmonary embolus, management options include;

- IV unfractionated heparin for anticoagulation;
- Thrombolytic therapy;
- Thoracotomy and surgical embolectomy.

When deep vein thrombosis (DVT) is suspected clinically, compression duplex ultrasound is helpful;

- If this is negative and there is a low level of clinical suspicion, anticoagulants can be discontinued;
- If clinical suspicion remains high or symptoms fail to resolve, ultrasound may be repeated or magnetic resonance venography (MR-venography) may be performed.

d) Prevention

Assessment for risk of thrombosis should be performed on all patients in early pregnancy using RCOG guidelines (see *Chapter 22: Antenatal obstetric complications*).

iii) Maternal sepsis

Sepsis is an important cause of morbidity and mortality in the obstetric population.

Sepsis and severe sepsis is defined based on certain clinical features (see Table).

Table. Features of sepsis and severe sepsis.

Sepsis	**Severe sepsis**
New-onset altered mental state	↓ score on glasgow comma scale (GCS)
Temperature >38°C or <36°C	SBP <90 mmHg (or >40 mmHg ↓ from baseline)
Heart rate >100 bpm	Heart rate >130 bpm
Respiratory rate >20/minute	Respiratory rate >25/minute
Blood glucose >7.7 mmol/L (in absence of diabetes)	Oxygen saturation <91%
WBC >12 × 10^9 /L or <4 × 10^9 /L with >10% immature band forms	Lactate > 2 mmol/L

a) Aetiology and risk factors

In the obstetric population, most commonly encountered organisms are group A β-hemolytic streptocci (e.g. *Streptococcus pyogenes*) and *E. coli*.

Complex interplay of certain risk factors may predispose to sepsis (see Table).

Table. Risk factors associated with sepsis.

Prolonged rupture of membranes
Immunocompromised patients or immunosuppressants use
Obesity
Diabetes
Anaemia
UTI
Vaginal discharge
Previous pelvic infection
Group A streptococcal infection in close contacts
Amniocentesis and other invasive procedures
Cervical cerclage

b) Management

Management guidelines for sepsis may vary in different hospitals based on antibiotic susceptibility and presence of septic shock. However, it is recommended to;

- Obtain blood cultures before administration of antibiotics;
- Administer broad-spectrum antibiotics early;
    - A combination of either piperacillin/tazobactam or a carbapenem + clindamycin— provides broad spectrum coverage for treatment of severe sepsis;
    - Consult an infectious disease specialist if no response to first-line antibiotics.
- Measure serum lactate— prognostic value;
- In cases of hypotension ± serum lactate ≥4 mmol/L, administer 20 ml/kg of crystalloid or an equivalent;
- Administer vasopressors to ↑ BP if no response— maintain mean arterial pressure (MAP) ≥65 mmHg.

Measure lactate and WBC counts to help assess the response to initial treatment;

- Administer high-flow oxygen to control O_2 sats;
- Measure accurate hourly urine output;
- For persistent hypotension, insertion of central venous line may be considered for septic shock.

iv) Pre-eclampsia, eclampsia and HELLP syndrome

(*See Chapter 24: Placentation and related disorders*).

v) Uterine inversion

Uterine inversion is a rare complication occurring during the third stage of labour. Uterine inversion occurs when the uterus is partially or wholly inverted.

a) Aetiology

This can occur after vaginal delivery or **C-section** and thought to occur as a result of traction on umbilical cord before the placenta has separated.

Associated factors are a fundal or morbidly adherent placenta and C-sections performed associated with full cervical dilation.

b) Diagnosis

The inverted uterus may be obvious at the introitus. Other signs include;

- Lack of a palpable uterus in the abdomen;
- Feeling of a 'dimple' in the uterine fundus on abdominal examination.

The inverted uterus stretching the cervix causes vagal stimulation;

- There may be signs of cardiovascular collapse and shock;
- Haemorrhage is commonly seen, but symptoms are often out of proportion to estimated blood loss.

c) Classification

The uterine fundus descends either the uterine cavity, through the cervix. This can be classified into four degrees of severity (see Figure).

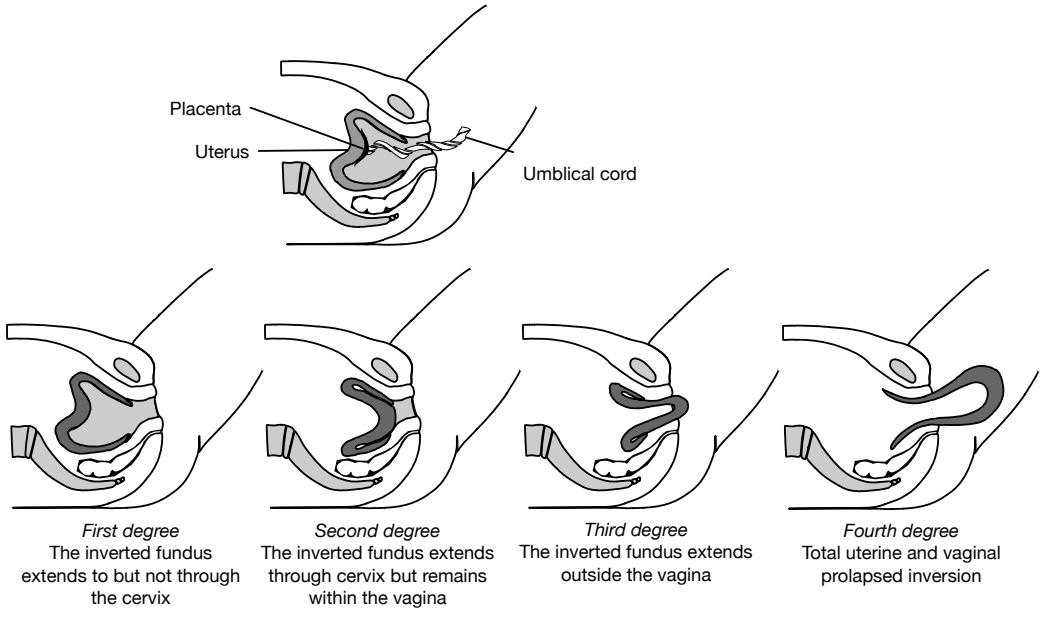


Figure. Illustration of the four degrees of uterine inversion.

d) Management and complications

It is very important not to remove the placenta if it is still attached as this will ↑ the bleeding.

The longer uterine inversion stays inverted the more difficult it is to replace it back— a retraction ring forms between upper and lower uterine segments, preventing eversion.

Attempt manual replacement as soon as the diagnosis is made. This is done by by ***manual compression*** *through*

the cervix (see Figure);

- If manual replacement is unsuccessful, transfer to the operating theatre for replacement of the uterus under anaesthetic.
- If this is also unsuccessful, attempt hydrostatic replacement by running 2–3 litres of warm saline via tubing into the vagina or via a silastic cup ventouse (see Figure);
    - This causes vaginal vault- and cervical- ballooning— enables uterus and placenta to gradually reduce, thus correcting the inversion;
    - After confirming reduction, administer an oxytocic agent to maintain uterine contraction.
- If this is unsuccessful, surgical procedures may be considered to reposition the uterus *from above*.

Rarely, *hysterectomy* may be needed.

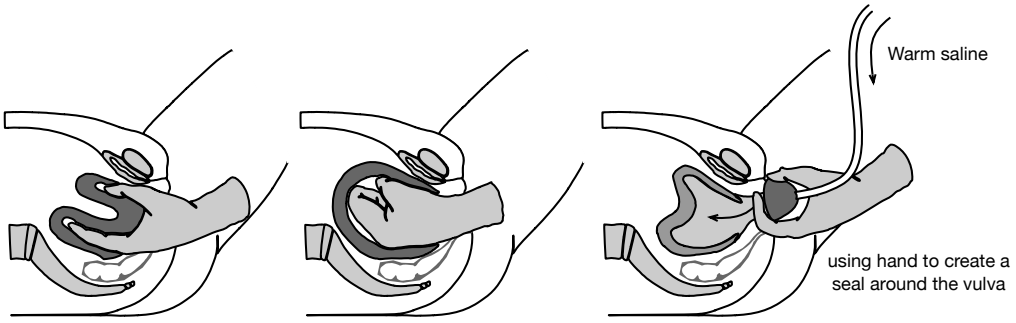


Figure. Illustration of manual replacement of uterus and hydrostatic replacement via a ventouse cup.

vi) Uterine rupture

Uterine rupture refers to a tear of the uterus.

It is rare obstetric complication associated with significant maternal and fetal morbidity and mortality. This is in contrast to **uterine scar dehiscence** (see Figure);

- Uterine scar dehiscence refers to occult scar separation without disruption of serosa of uterus as observed on laparotomy;
- Here, haemorrhage and risk of maternal and fetal complications is low.

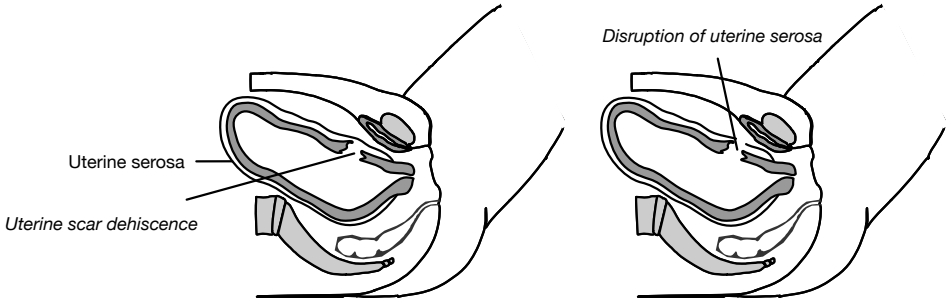


Figure. Illustration of uterine scar dehiscence and uterine rupture.

a) Aetiology

Uterine rupture occurs mainly in association with a previous C-section or uterine injury (e.g. a previous surgical uterine evacuation of retained products of conception with inadvertent uterine perforation)— this is because scar tissue does not have the same inherent strength as myometrium.

Table. Risk factors for uterine rupture.

Previous Caesarean section— *most common risk factor*, especially if < 12 months since last C-section
Previous uterine surgery e.g. myomectomy that inadvertently breached endometrial cavity
Induction and augmentation of labour with oxytocin
High parity
Macrosomic fetus
Placenta percreta
Fetal version, e.g. breech extraction
Congenital uterine anomaly, e.g. unicornuate uterus

b) Clinical features

The vast majority of cases occur during labour, usually during late first stage or the active second stage;

- The patient may initially complain of abdominal pain (referred to as "scar tenderness"). This may be masked if there is epidural analgesia;
- Other maternal symptoms include severe sudden abdominal pain and shock;
- Typically, uterine contractions stop + *FHR decelerations and later fetal bradycardia* may be seen on CTG.

To an unsuspecting obstetrician, uterine rupture may not be recognized immediately;

- The obstetrician may have chosen to deliver fetus with ventouse or forceps based on suspicious CTG;
- But mother bleeds internally, shows signs of circulatory collapse and uterine rupture is recognized later.

Haematuria may be present if the uterus has ruptured into the bladder.

c) Management

From maternal perspective, an urgent laparotomy is required for control of hemorrhage and repair;

The fetus should be delivered by the quickest route possible;

- If the cervix is fully dilated, vaginal delivery may be considered by an experienced obstetrician;
- However, an urgent laparotomy will still be needed for repair of uterine lesion.

Hysterectomy may be considered in cases of difficult to manage uterine rupture.

vii) Amniotic fluid embolism

Amniotic fluid embolism is a rare cause of maternal collapse and death. It is specific to pregnancy and believed to be caused by amniotic fluid entering the maternal circulation;

- This causes acute cardiorespiratory compromise and disseminated intravascular coagulation (DIC);
- In some cases, there may be an abnormal maternal reaction to amniotic fluid as the primary event.

a) Clinical features and diagnosis

It is difficult to diagnose and is typically diagnosed at postmortem— the presence of fetal cells (squames or hair) in the maternal pulmonary capillaries is observed.

Symptoms associated with amniotic fluid embolism include;

- Shortness of breath ± chest pain;
- Light-headedness;
- Restlessness and distress;
- Pins and needles in the fingers;
- Nausea and vomiting;
- Maternal collapse.

b) Management

- Management is supportive, requiring intensive care, and there are no specific therapies available;
- Perimortem caesarean section should be carried out within 5 minutes or as soon as possible after cardiac arrest— for the benefit to improve effect of resuscitation techniques;
- In the case of sudden collapse, management should be with the structured ABCDE approach.

The prognosis is poor—approximately 30% of patients die in the first hour.

(III) Fetal obstetric emergencies

i) Umblical cord prolapse

Umbilical cord prolapse may be defined as the descent of the umbilical cord through the cervix alongside or past the presenting part in the presence of ruptured membranes. It carries significant risk of morbidity and mortality for the **fetus**.

a) Aetiology

Umblical cord prolapse can occur if the presenting part does not fit well into the maternal pelvis, giving 'space' for the cord to prolapse when the membranes rupture. Certain risk factors are also associated with this.

Table. Risk factors for umblical cord prolapse.

Maternal risk factors	**Fetal risk factors**
Pelvic tumours (e.g. fibroids in the lower segment) Narrow pelvis Multiparity	Prematurity or low birthweight (<2.5 kg) Malpresentation, e.g. breech (↑ ***risk with footling***) Transverse and oblique lie Fetal congenital abnormalities Multiple pregnancy Polyhydramnios Placenta praevia

b) Diagnosis

Most commonly, it is diagnosed by seeing the cord at the introitus or feeling it during vaginal examination with rupture of membranes.

Signs of fetal distress on CTG following artificial or spontaneous rupture of membranes can occur— as compression of the umbilical vein reduces the flow of oxygenated blood to the fetus;

- Variable decelerations;
- Persistent bradycardia, if compression is not relieved.

When suspected, perform vaginal examination immediately as early detection is crucial for timely delivery.

c) Management

Call for senior help and prepare operating theatre for emergency delivery.

- Meanwhile, attempt to prevent further cord compression by;
    - Elevating the presenting part or filling the bladder with 500mL of saline;
    - Avoid handling the cord— causes cord spasm;
    - Place mother in knee to chest or left lateral position.
- Confirm fetal viability by auscultation of the fetal heart using CTG.

Delivery is generally performed by;

- Category 1 emergency C-section (here → immediate threat to fetus) if pathological fetal heart pattern;
- Category 2 emergency C-section if normal fetal heart pattern.

d) Complications and prognosis

- Total cord compression for longer than 10 minutes will cause cerebral damage without intervention;
- If the cord prolapse occurs outside hospital, the fetus is likely to be dead by the time of admission.

With a healthy term baby and prompt diagnosis in hospital, the prognosis is usually excellent.

ii) Shoulder dystocia

Shoulder dystocia is defined as a vaginal cephalic delivery that requires additional obstetric manoeuvres to deliver the fetus after (see Figure);

- The fetal head has delivered;
- Gentle traction is unsuccessful in delivering the shoulders.

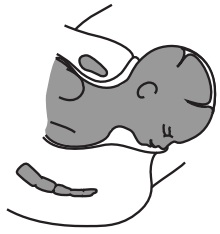


Figure. Illustration of shoulder dystocia.

a) Aetiology

During vaginal delivery, the shoulders rotate to make use of the widest pelvic diameters;

- If the shoulders have not entered the pelvic inlet through AP diameter, the anterior shoulder may become caught above the symphysis pubis;
- This usually manifests around the restitution phase of the cardinal movements of labour (i.e. after delivery of fetal head).

Occasionally, both shoulders (or rarely, the posterior shoulder) may remain above the pelvic brim.

Shoulder dystocia is associated with certain risk factors. But but these are not useful clinically as reliable predictors (see Table).

Table. Risk factors associated with shoulder dystocia

Maternal *risk factors*	**Fetal *risk factors***	**Intrapartum *risk factors***
Diabetes	Macrosomia	Long first stage of labour
Short stature	Postmaturity	Long second stage of labour
Previous shoulder dystocia		Instrumental delivery
Obesity		Induction of labour
		Use of oxytocin

b) Diagnosis

Diagnosis is clear when the shoulders fail to deliver during the next contraction after delivery of the head.

Often, it is preceded by the '**turtle sign**' as a warning sign— retraction of the fetal head towards the perineum following delivery of the fetal head (similar to a turtle attempting to withdraw into its shell).

c) Management

Shoulder dystocia is managed by a sequence of manoeuvres designed to facilitate delivery while minimizing the risk of fetal damage (see Figure).

The basic principle of all these manoeuvres is to reduce the AP diameter of the shoulders and gain the maximum space in the maternal pelvis.

After delivery of the baby, the risks of maternal morbidity should be remembered: prevent the PPH and check for vaginal trauma.

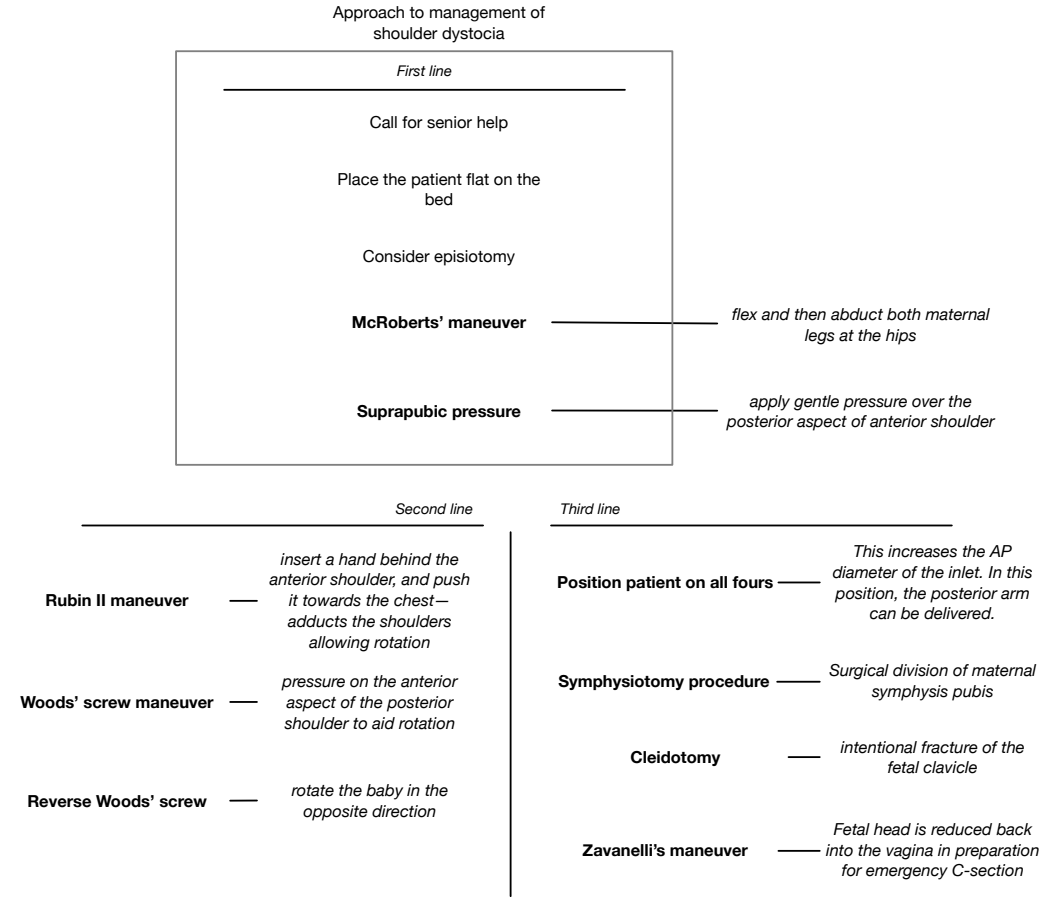


Figure. Algorithmic approach to management of shoulder dystocia.

d) Complications

It is associated with significant morbidity for both— the mother and fetus.

Maternal complications include;

- ↑ perineal trauma (third- and fourth-degree tears);
- Postpartum haemorrhage;
- Psychological trauma.

Fetal complications arise primarily due to occlusion of neck vessels in the fetal neck;

- Without intervention, there is the risk of cerebral damage— hypoxic brain injury;
- Inappropriate downward traction on fetal head causing lateral flexion of the head on the neck, will cause stretching of the brachial plexus and nerve damage— Erb's palsy can occur;
- Fractured clavicle or humerus.

Shoulder dystocia is associated with recurrence, a scheduled C-section may be suggested for next pregnancy.

CHAPTER 32 PUERPERIUM

The puerperium refers to the 6-week period following completion of the third stage of labour. It is characterized by various maternal changes.

(I) Physiological changes

i) Uterine involution

Involution is the process by which the postpartum uterus, weighing about 1 kg, returns to its prepregnancy state of less than 100 g;

Immediately after delivery, the uterine fundus lies about 12 cm above the symphysis pubis (or 4 cm below the umbilicus). However, by 2 weeks, the uterus becomes no longer palpable.

Involution occurs by a process of autolysis, whereby muscle cells diminish in size as a result of enzymatic digestion of cytoplasm;

- Autolysis does **not** affect the number of muscle cells;
- By-products of autolysis are absorbed into bloodstream and excreted in urine.

Involution appears to be accelerated by the release of oxytocin in women who are breastfeeding;

- A delay in involution **without** *any other signs or symptoms* (e.g. bleeding) is of no clinical significance;
- Uterus is observed to be relatively larger following a C-section.

ii) Genital tract changes

Following delivery there may be small cervical lacerations;

- The internal os closes by the end of 1st week postpartum;
- The external os may remain open permanently— characteristic funnel shape of a parous cervix.
- Assessment of the postnatal cervix is important in diagnosing retained products of conception (RPOCs, *see secondary postpartum haemorrhage below*).

iii) Lochia

Lochia is the blood-stained uterine discharge. It is comprised of blood and necrotic superficial layer of decidua;

- **Lochia rubra**— red lochia during the first few days after delivery. This may gradually change to;
- **Lochia serosa**— pink and serous lochia by the 2nd week;
- Thereafter, the basal layer of endometrium completes regneration of endometrium by the 3rd week and lochia reduces to a scanty yellow-white discharge (**lochia alba**)— lasts for about 1 month.

Persistent red lochia suggests delayed involution that is usually associated with infection or a retained piece of placental tissue (*see secondary postpartum haemorrhage and puerpural sepsis below*).

(II) Recovery after childbirth

i) Postnatal assessment

The postnatal visits schedule may vary depending on the type of delivery and outcome. However, it is crucial to provide women information about danger signs (see Table).

Table. Signs and symptoms of potentially life-threatening postnatal conditions.

Signs and symptoms	**Condition**
Sudden and profuse blood loss or persistent increased blood loss	Postpartum haemorrhage
Faintness, shivering, abdominal pain and/or offensive vaginal discharge	
Fever, shivering, abdominal pain and/or offensive vaginal loss	Infection

Headaches accompanied by one or more of the following symptoms within the first 72 hours after birth: visual disturbances, nausea/vomiting	Preeclampsia/eclampsia
Unilateral calf pain, redness or swelling Shortness of breath or chest pain	Thromboembolism

ii) Recovery after normal birth

Maternal changes are commonly observed postpartum. These are mainly on the perineum, bladder, bowel and maternal psychology.

a) Perineal pain

Perineal discomfort is a common complaint.

For analgesia, a step-by-step approach may be taken. This includes;

- Local application of crushed ice or 5% lignocaine gel for short-term relief;
- Paracetamol is often an effective analgesic. NSAIDs, e.g. diclofenac (PO or PR), may also be added);
- Codeine derivatives should be avoided— associated with maternal constipation and neonatal drowsiness in breastfed babies.

Perineum shoulde be kept clean— daily cleaning or showering using tap water is adequate. Wounds, if any, should be irrigated twice daily and healing allowed to occur by secondary intention.

Spontaneous opening of repaired perineal tears and episiotomies usually results from secondary infection;

- Infection may manifest with redness, warmth, pain and swelling ± ↑ maternal temperature;
- Swabs for culture/sensitivity studies should be taken if infection is suspected and broad-spectrum antibiotics should be commenced;
- If there is a collection of pus, drainage needs removal of any skin sutures;
- Surgical repair should never be attempted in the presence of infection.

b) Bladder distention and urinary incontinence

Voiding difficulty and overdistension of the bladder are common after childbirth. Contributing factors include;

- Use of regional anaesthesia for delivery (epidural/spinal)— normal bladder sensation may take upto 8 hours to recover;
- Traumatic delivery— vulvovaginal haematoma;
- Stool impaction in the rectum.
- Periurethral swelling and edema;

Overstretching of bladder secondary to urinary retention should be prevented— tears can occur and can lead to hypocontractility and hypoaesthesia of bladder.

An assessment of bladder function can be made at 6-8 hours postpartum. A distended bladder would either be palpable as a suprapubic cystic mass or it may displace the uterus— ↑ height of uterine fundus.

- In women without use of epidural/spinal anesthesia, intermittent Foley's catheterization may be needed if the mother;
    - Does not void;
    - Voids < 300 ml (such small amount may can be due to overflow incontinence);
    - An intermittent Foley's catheter drains >150 mL of urine abruptly with inability to void.
- A Foley's catheter should be left *in situ* for upto 48 hours if a transiently inserted catheter drains > 1 liter of urine— till periurethral swelling settles.
- A Foley's catheter should be left *in situ* for 12-24 hours until the woman is mobile **after regional anesthesia for C-section**— this ↓ risk of overdistension of bladder.

Pressure necrosis of the bladder or urethra may occur with prolonged obstructed labour. Incontinence may be observed in these cases in the 2nd week postpartum— *when the slough separates.*

Vaginal delivery is strongly associated with development of urinary stress incontinence in the long-term;

- Acutely developed incontinence should be investigated to exclude a vesicovaginal, urethrovaginal or, rarely, ureterovaginal fistula as a more likely cause;
- A clean-catch specimen of urine may be sent for microscopy and C/S to rule out infection.

Small fistulae may close spontaneously after a few weeks but large fistulae require surgical repair.

c) Constipation and anal continence issues

Constipation is a common observed in early puerperium;

- It usually occurs in association with preceeding diet interruption, dehydration, and opiate analgesia;
- It should be avoided in cases with OASI-repairs;
- Prophylactic interventions should be instituted in these cases. These include lactulose PO, isphaghula husk PO, or other laxatives for atleast 2 weeks.

Anal sphincter trauma ± OASIs can occur with vaginal delivery despite episiotomy;

- With OASIs, fecal continence issues may be observed;
    - IAS incompetence results in insensible faecal incontinence;
    - EAS incompetence causes faecal urgency.
- Ano-vaginal fistula or rectovaginal fistula are rare complications;
    - These may be suspected if the woman complains of passing wind or stool per vaginum;
    - Approximately 50% of small anovaginal fistulae will close spontaneously over a period of 6 months, but larger fistulae will require formal repair.
- Thus, all women with OASIs should be offered follow-up postpartum. This includes;
    - Physiotherapy with augmented biofeedback— shown to improve continence issues;
    - Evaluation after 6–12 weeks for faecal and urinary symptoms. Investigations helpful in assessment include endoanal ultrasound and manometry.

iii) Recovery after C-section

Although C-section ↓ the risk of pelvic floor problems, it is associated with ↑ risk of infection (wound, urine and **chest**), anaemia and thromboembolism.

a) Wound care

Acceptable wound care includes;

- Covering operative wound by a sterile dressing in theatre;
- Remove operative wound dressing after 24 hours;
- Remove sutures or staples by the 5th day;
- Gently cleaning and drying the wound daily with tap water.

b) Anemia

Anaemia is common postoperatively. It is common practice to check Hb levels after C-section;

- Asymptomatic women with haemoglobin >7 g/dl can be treated with iron PO;
- Blood transfusion aids recovery if severe anemia.

c) VTE

Generally, early mobilization and good hydration are important for all women, with 1–6 weeks of lowmolecular-weight heparin given to those with multiple risk factors.

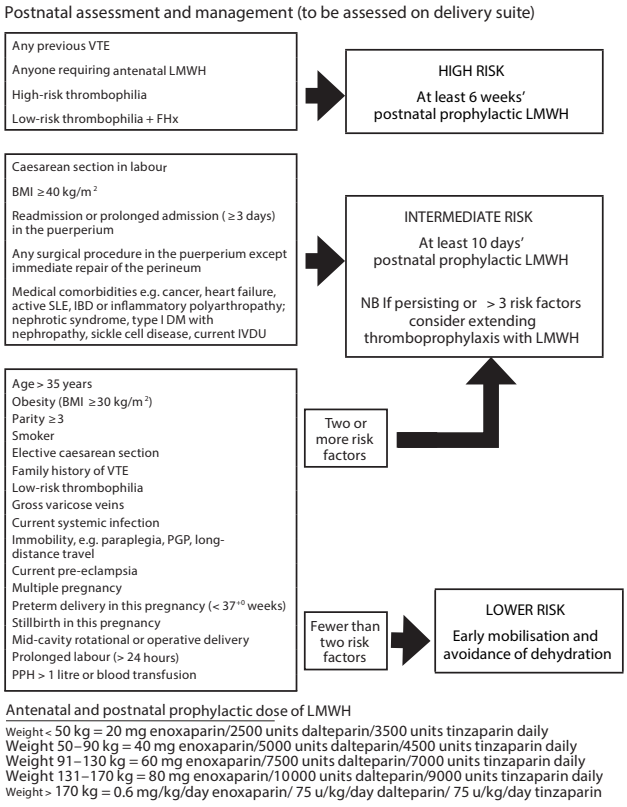


Figure. Illustration of post-natal thromboprophylaxis (RCOG Green Top Guidelines No. 37).

(III) Puerperal disorders

i) Hypertension

This is more likely in individuals affected with pre-eclampsia;

- Almost half of all eclamptic fits occur postnatally;
- Blood pressure should be kept under 150/100 mmHg;
- Labetolol or slow-release nifedipine are preferred antihypertensives;
- Antihypertensives may be continued for 1–2 weeks postnatally.

Those who are still on antihypertensives at 6 weeks postnatally should be referred for further assessment.

ii) Puerperal pyrexia and pelvic genital tract infection

Puerperal pyrexia (of significance) is defined as a temperature of 38°C or higher on any 2 of the first 10 days postpartum, **exclusive of the first 24 hours**.

a) Aetiology and risk factors

A mildly elevated temperature is not uncommon in the first 24 hours, but any pyrexia associated with tachycardia should be investigated.

- As a rule of thumb, atelectasis is the most common cause of fever in the *first 24 hours*;
- Aspiration pneumonia (Mendelson's syndrome) may be suspected if there is a spiking temperature associated with wheezing, dyspnoea or evidence of hypoxia following general anaesthetia;

Pelvic genital tract infection following delivery (also called **puerperal sepsis**) is the most significant cause of puerperal pyrexia;

- Puerperal sepsis is usually polymicrobial originating from bowel that colonize lower genital tract;

- Genital tract lacerations can also harbour pathogenic organisms;
- Debris and blood clots also provide an excellent culture medium for organisms.

Other sites associated with puerperal pyrexia include chest, throat, breasts, urinary tract, C-section wound or perineal wounds and legs.

Table. Organisms and risk factors associated with puerperal **genital tract** infection.

Organisms
Aerobes
Gram-positive • beta-haemolytic streptococcus, groups A, B, D • *Staphylococcus epidermidis* and *S. aureus* • Enterococci – *Streptococcus faecalis* Gram-negative • *Escherichia coli* • *Haemophilus influenzae* • *Klebsiella pneumoniae* • *Pseudomonas aeruginosa* • *Proteus mirabilis* Gram-variable— *Gardenella vaginalis*
Anaerobes
Peptococcus species Peptostreptococcus species Bacteroides – *B. fragilis, B. bivius, B. disiens* Fusobacterium species
Miscellaneous
Chlamydia trachomatis *Mycoplasma hominis* *Ureaplasma urealyticum*

Risk factors for puerperal infection
Underlying risk factors
Obesity Diabetes Human immunodeficiency virus (HIV) infection
Antenatal risk factors
Antenatal intrauterine infection. E.g. chorioamnionitis Prolonged rupture of membranes Cervical cerclage for cervical incompetence
Intrapartum risk factors
Prolonged labour Multiple vaginal examinations OVDs C- section Manual removal of the placenta Retained products of conception (RPOC)

b) Clinical features

Affected individuals commonly present with;

- Malaise and fever ± rigors;
- If the focus is genital tract, abdominal discomfort, vomiting and diarrhoea are observed;
    - Discharge of offensive lochia;
    - Secondary PPH.

Examination findings may vary with spread of infection. With puerperal genital tract infection, there may be;

- Uterine ± adnexal tenderness;
- Peritoneal signs— rigidity and guarding;
- Bogginess in pelvis— pelvic abscess. This may be observed with spread of infection to;
    - Myometrium— endometritis;
    - Fallopian tubes and ovaries— salpingo-oophoritis;
    - Connective tissue of pelvic organs— parametritis (also called **pelvic cellulitis**);
- Infected surgical site or genital tract tears.

c) Investigations

Table. Investigations for puerperal genital tract infections.

Investigations	**Abnormalities**
CBC	Anaemia, leukocytosis, thrombocytopenia
Urea and electrolytes	Fluid and electrolyte imbalance
High vaginal swabs Infected wound swabs Blood C/S	Infection screen
Pelvic ultrasound	Retained products, pelvic abscess
Clotting screen (with haemorrhage or shock)	Disseminated intravascular coagulation
Lactate	Acidosis and prognostic value
Arterial blood gas	Acidosis and hypoxia

d) Management

Mild-to-moderate infections can be treated with a broad-spectrum antibiotic (e.g. co-amoxiclav or a cephalosporin, such as cefalexin, plus metronidazole) till culture/sensitivity results are available.

Infectious diseases specialist consult may be taken in severe cases.

e) Complications

- Pelvic peritonitis— can ead to pelvic abscesses;
- Perisalpingitis (relatively less likely to lead to tubal occlusion and subfertility over long-term—*than **PID***);
- Tubo-ovarian abscess— rare;
- Septic thrombophlebitis— by spread to large vessels of pelvis;
- Severe sepsis (see Table);
- Necrotizing fasciitis— a rare fatal infection of skin, fascia and muscle.

Table. Features of sepsis and severe sepsis.

Sepsis	**Severe sepsis**
New-onset altered mental state	↓ score on glasgow comma scale (GCS)
Temperature >38°C or <36°C	SBP <90 mmHg (or >40 mmHg ↓ from baseline)
Heart rate >100 bpm	Heart rate >130 bpm
Respiratory rate >20/minute	Respiratory rate >25/minute
Blood glucose >7.7 mmol/L (in absence of diabetes)	Oxygen saturation <91%
WBC >12 × 10^9 /L or <4 × 10^9 /L with >10% immature band forms	Lactate > 2 mmol/L

iii) Secondary postpartum haemorrhage (secondary PPH)

Secondary PPH is defined as fresh bleeding from the genital tract between 24 hours and 6 weeks after delivery.

a) Clinical features and aetiology

It commonly occurs between days 7- 14 with *low-grade fever, pungent lochia and uterine tenderness*. The cause is usually attributed to either endometritis or retained products of conception (RPOC, see Table).

Secondary PPH in other cases may be associated with;

- Hormonal contraception;

- Bleeding disorders (e.g. von Willebrand's disease);
- Choriocarcinoma.

Table. Classical distinguishing features of endometritis in comparison with RPOC.

	RPOC	**Endometritis**
Abdominal symptoms	Crampy low abdominal pain	Constant low abdominal pain
Uterine examination	Uterus larger than appropriate	Closed internal os
	Open internal os	

b) Investigations

Pelvic ultrasound may rule out retained products *if uterus is empty*— findings may be inconclusive as debris, clots and fluid can be seen in a normal postpartum uterus.

c) Management

- Conservative management with antibiotics if diagnosis is not clear;
- Heavy beeding may require;
    - Volume resuscitation with IV fluids or blood transfusion;
    - Oxytocic agent administration;
    - Uterine evacuation.

Further intervention may be considered after establishment of a cause.

iv) Symphysis pubis diastasis

This refers to spontaneous separation of the symphysis pubis (compared to symphysiotomy). It occurs in 1 in 800 vaginal deliveries and is predominantly associated with forceps delivery, rapid second stage of labour or severe abduction of the thighs during delivery.

It is usually noticed after delivery. Affected mothers present with symphyseal pain aggravated by weight-bearing and walking. On examination, pubic tenderness, waddling gait or a palpable interpubic gap may be observed.

Treatment includes bed rest, anti-inflammatory agents, physiotherapy and a pelvic corset to provide support and stability.

v) Psychiatric disorders

(*see Chapter 34: Psychology and pregnancy*).

(IV) Contraception in puerperium

Though breastfeeding in the puerperium provides contraceptive effect, but can be unreliable;

- Oxytocin release with breastfeeding inhibits normal pulsatile release of LH— lactational amenorrhea;
- In order to gain the maximal contraceptive effect, mother needs to *exclusively* breastfeed on-demand.

Ovulation can occur by 4–6 weeks postpartum. For those desiring more effective contraception;

- Barrier method contraceptives are least invasive;
- POPs may be preferred over COCs—
    - POPs, if considered, should be commenced around day 21 after delivery;
    - If POPs are commenced before day 21, there may be ***puerperal breakthrough bleeding***;
    - COCs enhance risk of thrombosis in the puerperium and can have an adverse effect on the quality of breast milk.
- Injectable contraception (e.g. Depo-Provera) is also very effective;
- Injectable contraception should preferably be given 5–6 weeks postpartum— *this is also due to* risks of

puerperal breakthrough bleeding with earlier administrations.

An intrauterine contraceptive device is also an option;

- But, this carries a risk of uterine perforation in breastfeeding mothers;
- Thus, it is best to wait for 4–8 weeks to allow for normal uterine involution before insertion.

Female sterilization can also be offered;

- Laparoscopic tubal ligation is less invasive but performed after 6 weeks postpartum;
- Tubal ligation by a mini-laparotomy, however, can be performed in the first few postpartum days.

(V) Stillbirth

Stillbirth refers to a baby born with no signs of life.

Perinatal death— stillbirth after 24 weeks gestation or death within 7 days of birth.

In these unfortunate cases;

- Bereavement counselling should be provisioned for the couple;
- Certain investigations may lead to diagnosis— to institute preventative measures in later pregnancies;

Table. Investigation into perinatal death.

Investigations	**Reason**
CBC	Anaemia, leukocytosis
Clotting profile	DIC
LFTs (+ bile acids)	Obstetric cholestasis
Kleihauer test	Fetomaternal transfusion
Antibodies to Rh antigen	Haemolytic disease
Virology screen	Cytomegalovirus, parvovirus infections
Autoantibody screen (anti-cardiolipin and lupus anticoagulant)	APLA, SLE
Blood and placental swab for culture	*Listeria monocytogenes* infection
Toxoplasma antibodies	Toxoplasmosis
HBA_1C	Diabetes (undiagnosed)
Placental examination	Evidence of infection or vasculopathy
Cytology of placenta	Fetal chromosomal abnormalities
Skin biopsy/cardiac blood/placental biopsy	
Fetal full-body X-ray or MRI	To identify congenital defects

Autopsy may yield insight into the causative factors in other cases.

CHAPTER 33 BREAST AND BREASTFEEDING

(I) Anatomy of the breast

The breasts in females are modified sweat glands that consist of lobules and ducts in a fibrofatty stroma.

They lie superficial to the pectoralis major, external oblique and serratus anterior muscles, extending between the second and sixth rib from the sternum to the axilla.

The breast is comprised of 15–25 functional units arranged radially from the nipple. Ea unit is made up of a lactiferous duct, a mammary gland lobule and alveoli.

The lactiferous ducts dilate to form a lactiferous sinus before converging to open in the nipple. Contractile myoepithelial cells surround the ducts as well as the alveoli.

A pigmented area called the areola, which contains sebaceous glands, surrounds the nipple.

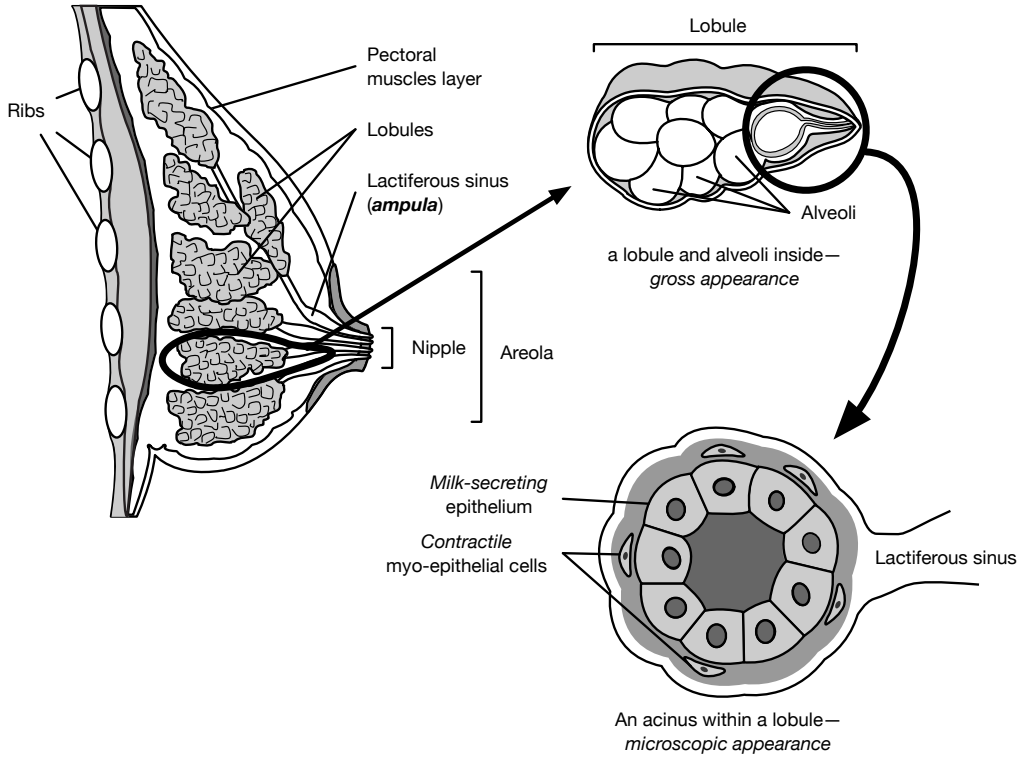


Figure. Illustration of breast anatomy and histology.

(II) Histology

The epithelium is cuboidal-to-columnar lining the ductules and ducts (see Figure).

A characterisitic cell type is a myoepithelial cell seen in breast, which functions to contract under hormonal control to propel milk out through the breast.

(III) Physiology

A female adult breast can produce milk with approximately 2 weeks of hormonal stimulation.

Various hormones contribute to the physiology of breast and breastfeeding;

- Estrogens are observed to stimulate proliferation of the lactiferous ducts;
- Progesterone stimulates development of the mammary lobules;

- Human placental lactogen (hPL) is released during pregnancy and modulates breast development;
- Prolactin has a direct action on the secretory cells in lobules to synthesize milk proteins;
- Oxytocin stimulates contraction of myoepithelial cells around alveoli and lactiferous ducts— aids expulsion of milk.

During pregnancy, the areola becomes darker and the sebaceous glands also become prominent (referred to as 'Montgomery's tubercles' here).

(IV) Compositions

i) Colostrum

Colostrum is a yellowish fluid secreted by the breast;

- It is commonly observed at the first few breastfeeding sessions, but can be observed earlier;
- It is replaced by 'milk' by the 2nd day postpartum;
- Colostrum has a high concentration of proteins— particularly IgA.

For its role in protecting newborn against infection, its feeding to newborns is strongly recommended.

ii) Milk

The major constituents of breast milk are lactose, protein, fat and water.

The composition of breast milk is not constant, but compared to cow's milk, breast milk provides slightly more energy, fat, lactose and less protein (see Table);

- Lactalbumin is the major protein in breast milk, unlike cow's milk which consists of 90% caseinogen;
- Breast milk contains all vitamins except Vitamin K; although vitamin D supplementation is recommended
- Absorption of iron from breast milk is better than from cow's milk despite a lower concentration;
- Breast milk contains IgA antibodies, which provides immunogenic cover to infections in the newborn.

Table. Comparison between human and cow's milk.

	Human breast milk	**Cow's milk**
Energy (kcal/mL)	75	66
Lactose (g/100 mL)	6.8	4.9
Protein (g/100 mL)	1.1	3.5
Fat (g/100 mL)	4.5	3.7
Sodium (mmol/L)	7	22
Water (mL/100 mL)	87.1	87.3

(V) Advantages of breastfeeding

Breastfeeding the newborn has many advantages. These include;

- Readily available at the right temperature and ideal nutritional value;
- Cheaper than formula milk;
- Breast feeding is associated with a ↓ risk of;
    - Necrotizing enterocolitis in preterm babies;
    - Childhood infective illnesses, especially gastroenteritis;
    - Atopic illnesses, e.g. eczema and asthma;
    - Juvenile diabetes;

  - Childhood cancer, especially lymphoma;
  - Pre-menopausal breast cancer.
- Contraceptive effect for the mother— manifests as amenorrhoea.

(VI) Positioning and practices

Correct positioning is important for effective breastfeeding;

- The baby's mouth should be placed over the nipple and areola such that breast tissue as a '**teat**' extends far back up to the junction of hard palate with soft-palate;
- The tongue applies peristaltic force to the underside of the teat against the support of the hard palate;
- There should be minimal friction.

When the baby is properly attached, breastfeeding is pain-free. Babies should be fed on demand until feeding finishes spontaneously on each breast.

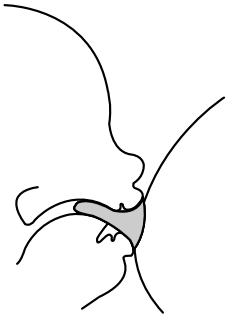


Figure. Illustration of proper positioning for breastfeeding.

(VII) Medications and breastfeeding

Certain medications use in breastfeeding mothers can be transferred to the baby (see Table).

For psychotropic drugs effects with breastfeeding, *see Chapter 34: Psychology and pregnancy*.

Table. The use of common drugs in breastfeeding mothers.

Breastfeeding contraindicated		
Aspirin (at doses of ≥ 300mg) Amiodarone Lithium Chemotherapy medications		
Breastfeeding not contraindicated		
Possible neonatal side-effects (monitor baby closely)	Benzodiazipines Certain psychiatric medications Certain anti-seizure medications Certain antithyroid medications (e.g. carbimazole)	
Use alternatives if possible	*Chloramphenicol* *Tetracyclines*	*Metronidazole* *Quinolones*
Monitor baby for jaundice	*Sulphonamides* *Dapsone*	*Trimethoprim/sulfamethoxazole* *Sulfadoxine/pyrimethamine*
Use alternative drug (may inhibit lactation)	Estrogens— e.g. COCs Thiazide diuretics Ergometrine	

Safe in usual doses	Paracetamol, low-dose aspirin, ibuprofen Penicillin antibiotics Erythromycin Antituberculous medications Antimalarials, **except** mefloquine Antihelminthics Antifungals	*Most bronchodilators* Corticosteroids Antihistamines Antacids Drugs for diabetes *Most antihypertensives* Digoxin

(VIII) Breast disorders

i) Blood-stained nipple discharge

Blood-stained nipple discharge of pregnancy is often referred to as 'rusty pipe syndrome';

- It is believed to be due to epithelial proliferation;
- It is typically bilateral and usually occurs in late pregnancy or early breastfeeding and lasts up to 1 week.

The condition is self-limiting, and the woman should be reassured.

ii) Painful nipples

Nipples become very sensitive during late pregnancy and in the first week of breastfeeding. Sensitive nipples can cause marked discomfort during the first minute of breastfeeding but improves thereafter.

If the covering epithelium of nipple is denuded, there is considerable pain— cracked nipples;

- The most common cause of cracked nipples is poor positioning during breastfeeding, but thrush (fungal infection) may be contributory;
- It occurs *after the first week of feeding* and worsen during feeds;
- It is associated with an ↑ risk of development of breast abscess.

Treatment includes provision of proper breastfeeding techniques, and may include local antibiotic ointment, analgesics, or resting the affected nipple.

In the painful period, expression of milk via a breast-pump on the affected may be considered. In these cases, breastfeeding should be resumed once the nipple has healed.

iii) Galactocele

A galactocele (or lactocele) is a sterile, milk-filled retention cyst of the mammary ducts;

- It occurs secondary to blockage by thickened secretions;
- Examination shows a fluctuant swelling without signs of inflammation;
- It usually resolves spontaneously— this can be assisted by massaging the breast towards nipple;
- In resistant cases, surgical aspiration or excision may be considered.

iv) Breast engorgement

Engorgement of the breasts usually begins by the 2nd or 3rd postpartum day and if breastfeeding has not been effectively established;

- Affected individuals present with painfully engorged breasts (can be bilateral);
- Breast engorgement can lead to fever (upto 102°F) in puerperium but this does not last >24 hours.

The diagnosis is mainly clinical and more likely in the absence of systemic symptoms. However, infective causes should be excluded.

Management options include;

- Provision of proper breastfeeding techniques— most effective treatment and provision;

- Expression of milk— manually or via a breast pump;
- Wearing underclothes that provide firm support.

v) Mastitis

Mastitis refers to inflammation of the breast.

a) Aetiology

It is most commonly associated with a blocked duct that obstructs flow of milk;

- Infection may occur in which case, it is referred to as infective mastitis;
- Source of infection is most commonly the baby's nose or throat;
- Staphylococcus aureus is the most common organism;
- Other organisms include coagulase-negative staphylococci (CoNS) and Streptococcus viridans;
- Suppurative mastitis (an abscess in development) is characterized by purulent fluid collection in the breast.

b) Clinical features

- The affected segment of the breast is painful and appears red and oedematous;
- Flulike symptoms with tachycardia and pyrexia may develop;
- Suppurative mastitis presents with rigors, fever, pain and reddened, swollen breast (usually unilateral);
- In contrast to breast engorgement, infective mastitis develops later (typically third to fourth postpartum week) and persists for longer.

c) Investigations

Though the diagnosis is mainly clinical, a sample of the milk should be taken for culture/sensitivity studies before starting antibiotics.

Ultrasound may aid in the diagnosis of a breast abscess.

d) Management and treatment

- Early localized mastitis can be managed with massage of the breast (towards the nipple) and analgesia;
- Flucloxacillin provides cover against the common organisms while awaiting microbiology;
- Breastfeeding can be continued during this process.

e) Complications

Complicated cases with breast abscess may be treated by incision and drainage under general anaesthesia.

CHAPTER 34 PSYCHOLOGY AND PREGNANCY

Pregnancy significantly impacts maternal psychosocial health.

Various emotional and psychological changes are observed commonly in a pregnant woman— both antenatal and post-partum;

- The incidence of new-onset psychiatric disorder during pregrnancy (antepartum) is low. In contrast, the risk of incidence is higher in puerperium;
- Pregnant women with pre-existing mental illness are at risk of an antenatal or post-natal recurrence or exacerbation. But post-partum remains higher-risk period for such events.

Thus, the post-natal period represents perhaps the highest risk period in a woman's life for the development of a psychiatric disorder.

(I) Normal emotional and behavioral changes of pregnancy

A wide variety of 'normal' emotional and behavioural changes can occur during pregnancy (see Figure);

- These are common and can be observed during pregnancy or post-partum;
- Postpartum, it is common for mothers to develop post-partum pinks and/or blues. These are mild symptoms and resolve spontaneously.

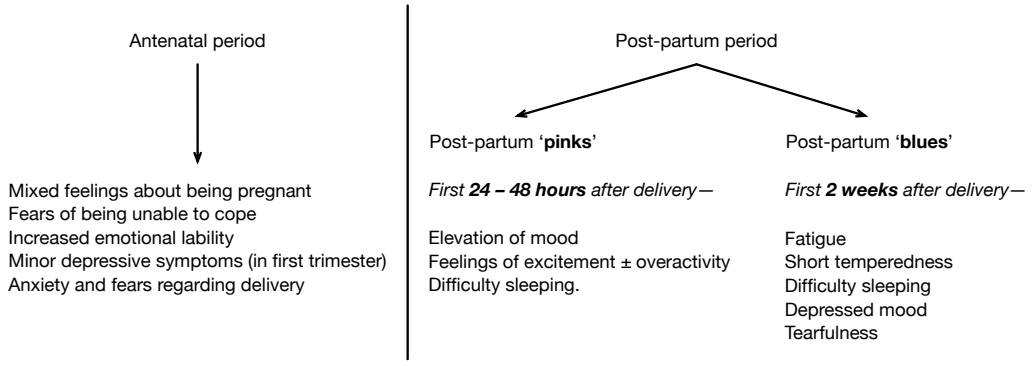


Figure. The commonly occurring 'normal' emotional symptoms— antenatal and postpartum.

However, certain symptoms may be unusual and further assessment needed. These include;

- Panic attacks;
- Episodes of low mood of prolonged duration (>2 weeks);
- Low self-esteem;
- Guilt or hopelessness;
- Thoughts of self-harm or suicide;
- Mood changes that disrupt normal social functioning;
- Somatic symptoms (e.g. poor appetite, early wakening);
- Change in 'affect'.

It may be challenging in many cases distinguish these from their overlap with normal symptoms.

(II) Screening mental health problems for pregnancy

The National Institute for Health and Clinical Excellence (NICE) Clinical Guideline No. 45 '*Antenatal and postnatal mental health*' recommends screening all pregnant women with a set of questions (see Table).

If the woman is found to have a pre-existing psychiatric illness, she should be referred;

- For pre-pregnancy counselling;
- For assessment and planning of treatment regimen during pregnancy.

If the answers to these questions raise concerns for a new-onset disorder, specialist referral may be needed.

Table. Screening questions for mental health during and after pregnancy

At 'booking'
Is there a past history of severe mental illness (including schizophrenia, bipolar disorder, postpartum psychosis and severe depression)? Have you ever received treatment from a psychiatrist or specialist mental health team? Have you ever been admitted as an inpatient for psychiatric care? Do you have a family history of mental health problems, particularly perinatal or bipolar illness?
At booking, and in the post-natal period (at least twice)
During the past month, have you often felt down, depressed or hopeless? During the past month, have you often been bothered by having little interest or pleasure in doing things? Are these feelings something you need or want help with?

(III) Pregnancy and pre-existing psychiatric disease

Here, assessment should be made to the safety of treatment medications over the risk of relapse if they are withdrawn.

A specialist consult is often needed.

i) Depression

Depression can affect pregnancy and its outcome (see Table).

Table. Effects of pregnancy on depression and *vice-versa*.

Effect of pregnancy on depression	**Effect of depression on pregnancy**	**Illness postpartum**
Does **not** improve or worsen active depression.	Psychosocial factors of depression adversely affect pregnancy and antenatal care. Biological factors of depression may impact placental function— FGR and preterm labour.	↑ risk of recurrence or exacerbation.

Psychological treatments, including self-help approaches, **cognitive–behavioural therapy (CBT)**, counselling and interpersonal psychotherapy may replace or supplement drug treatment.

It may be considered to reduce dosages under supervision— in the late third trimester to limit anticholinergic, serotonergic and extrapyramidal side effects in the neonate.

Electroconvulsive therapy (ECT) is not absolutely contraindicated in pregnancy— may be indicated if catatonia.

ii) Schizophrenia

Women with schizophrenia may be at greater risk of unplanned pregnancies as a result of their illness.

Older 1st generation 'typical' antipsychotics e.g. fluphenazine, trifluoperazine, haloperidol, chlorpromazine and flupenthixol do not have teratogenic effects.

Here, risks of fetal teratogenesis is lesser than risk of relapse or exacerbation by discontinuation of medications.

It may be considered to replace medications or reduce dosages under supervision— in the third trimester to minimize levels in the newborn and prevent symptoms of withdrawal or toxicity.

Schizophrenia demonstrates multifactorial inheritance— children of affected parents are at ↑ risk of inheritance.

Neuroleptic drugs (in moderate dosages) are not a contraindication to breastfeeding.

iii) Bipolar disease

Also known as 'manic depression', it is controlled with a combination of mood-stabilizing drugs (lithium, carbamazepine and sodium valproate), antidepressants and neuroleptics.

Mood-stabilizing drugs are notoriously teratogenic, but stopping these medications risks relapse. Here, maternal risks take precedence over potential fetal teratogenic risk.

It may be considered to replace medications or reduce dosages under supervision— if the illness is stable.

Postpartum relapse occurs in approximately 50% of women with bipolar disease. It is important to institute preventive therapy immediately after delivery;

- Lithium is contraindicated in breastfeeding— bottle-feeding may be considered;
- Alternatively, a neuroleptic or antidepressant can be used for prophylaxis.

iv) Anxiety disorders

- Anticipation of labour and the arrival of a new baby may all exacerbate an existing anxiety disorder;
- Benzodiazipines have teratogenic potential (see below). CBT may ↓ the need for drug treatment;
- Neonatal withdrawal effects are commonly observed in infants born to women who have used regular higher doses during pregnancy (neonatal abstinence syndrome);
- Breastfeeding aids to ↓ the severity of the neonatal withdrawal, as small amounts reach breast milk.

(IV) Psychotropic medications during pregnancy and breastfeeding

Table. Psychotropic medications during pregnancy, their risks and breastfeeding suggestions.

	Teratogenesis	**Neonatal risk**	**Breastfeeding risk**
TCAs	Amitriptyline, imipramine— safe.	***Neonatal abstinence syndrome*** *(with TCAs & SSRIs)*	Safe
SSRIs	Risk of congenital abnormalities—***Fluoxetine significantly safer than paroxetine;*** ↑ risk of preterm labour and LBW.	*Persistent pulmonary hypertension (SSRIs)*	Relatively safe by SSRIs with shorter half-lives, e.g. sertraline
MAO inhibitors	Rarely used nowadays. Contraindicated in pregnancy— *impairs placental function.*	—	—
Antipsychotics	Older 1st generation 'typical' antipsychotics **do not have teratogenic effects**. *(E.g. fluphenazine, trifluoperazine, haloperidol, chlorpromazine and flupenthixol)*		Typical antipsychotics— safe
Mood-stabilizers	Lithium— • *In 1st trimester—cardiac defects (e.g.* ***Ebstein's anomaly****)* • *In 3rd trimester— fetal hypothyroidism, polyhydramnios and diabetes insipidus* Carbamazepine— 'fetal anticonvulsant syndrome' Valproate— **neural tube defects** and 'fetal anticonvulsant syndrome'	Lithium— neonatal hypothyroidism	Breastfeeding contraindicated with lithium— neonatal toxicity Carbamazepine and valproate— safe

	Teratogenesis	Neonatal risk	Breastfeeding risk
Anti-anxiety	Benzodiazipines— ↑ risk of facial clefts, cleft lip and/or palate *if used in 1st trimester*	Neonatal abstinence syndrome Floppy baby syndrome	

(V) New-onset psychiatric disease in pregnancy

Complex interplay of biological, environmental and social factors with emotional changes in pregnancy may lead to development of a new-onset psychiatric disease in pregnancy, but this is rare.

Anxiety (± panic attacks), specific phobias relating to labour (*tocophobia*) or needles may be observed.

Anxiety, phobias, depression or other illnesses require specialist referral where non-pharmacologic therapy may be trialed initially.

Depression with its onset during the pregnancy is a strong risk factor for postpartum depression. Here, both pharmacological and non-drug treatment may be necessary.

(VI) New-onset psychiatric disease in puerperium/postpartum

Here is the highest risk time for new-onset disease;

- Affective (mood) disorders account for the majority. These may manifest as depression or bipolarity (± psychosis) in severe cases;
- NICE recommendations are to screen all women with a set of questions *at least* twice in the postpartum (see Table).

Table. Screening questions recommended for mental health during and after pregnancy.

At booking, and in the post-natal period (at least twice)
During the past month, have you often felt down, depressed or hopeless?
During the past month, have you often been bothered by having little interest or pleasure in doing things?
Are these feelings something you need or want help with?

i) Postpartum non-psychotic depressive illness

This refers to depression that develops postpartum. It shoulde be characterized in contrast to the 'normal' postpartum blues.

a) Aetiology and risk factors

Certain risk factors may contribute to the aetiology of this postpartum illness (see Table).

Table. Risk factors for postnatal depressive illness.

Past history of psychiatric illness.
Depression during pregnancy.
Obstetric factors (e.g. caesarean section/fetal or neonatal loss).
Social isolation and deprivation.
Poor relationships.
Recent adverse life events (bereavement/illness).
Severe postnatal 'blues'.

b) Clinical features

Symptoms of severe postnatal depressive disorder may vary and often overlap with normal emotional changes.

Table. Symtoms associated with postpartum non-psychotic depressive illness.

Early-morning wakening	Impaired concentration
Poor appetite	Tearfulness
Diurnal mood variation (worse in the mornings)	Feelings of guilt and failure
Low energy and libido	Anxiety
Loss of enjoyment	Thoughts of self-harm/suicide
Lack of interest	Thoughts of harm to the baby

c) Management and treatment

Most women recover spontaneously within 3–6 months but treatment may be needed for severe symptoms.

Management options include;

- Remedy of social factors;
- Non-directive counselling— significantly beneficial for milder disorders;
- Interpersonal psychotherapy;
- Cognitive–behavioural therapy (CBT);
- Drug therapy— TCAs or SSRIs are safe.

ii) Puerperal psychosis

It is a severe psychiatric illness affecting women after delivery. It presents most commonly on the 5th postpartum day, but usually before 4 weeks.

a) Aetiology and risk factors

Table. Risk factors for postpartum psychosis.

Previous history of puerperal psychosis
Previous history of severe non-postpartum depressive illness
Family history (first/second-degree relative) of bipolar disorder/affective psychosis

b) Clinical features

The onset is characteristically abrupt, with a rapidly changing clinical picture.

Symptoms of puerperal psychosis include;

- Restless agitation;
- Insomnia;
- Perplexity/confusion;
- Fear/suspicion;
- Delusions/hallucinations;
- Failure to eat and drink;
- Thoughts of self-harm;
- Depressive symptoms (guilt, self-worthlessness, hopelessness);
- Loss of insight.

c) Management and treatment

Urgent referral is necessary. These individuals usually need admission to a psychiatry unit for acute symptoms.

Treatments options include;

- Acute pharmacotherapy with neuroleptics, such as chlorpromazine or haloperidol;
- Antidepressants (which will take 10–14 days to be effective) as a second-line treatment;
- Treatment of mania with lithium;
- Electroconvulsive therapy (ECT)— particularly for severe depressive psychoses.

Recovery usually occurs over 4–6 weeks, but treatment with antidepressants will be needed for ≥ 6 months.

Women with a previous history of puerperal psychosis should be considered for starting prophylactic lithium from the 1st postpartum day.

iii) Complications

Table. Complications associated with postpartum depressive illness (± psychosis).

Immediate	**Later**
Physical morbidity	Social/cognitive effects on the child
Prolonged psychiatric morbidity	Psychiatric morbidity in the child
Disrupted social attachment to infant	Marital issues
Disrupted emotional development of infant	↑ risk of recurrence in future pregnancies
Suicide/infanticide— rare	

-x-

CHAPTER 35 NEONATOLOGY

A systems approach is necessary for good neonatal care. Here, the review of topics is limited to the spectrum of obstetric management.

Good neonatal care includes;

- Appropriate care in the delivery room;
- Care in the postnatal ward;
- Diagnosis and management of birth injuries, congenital anomalies and problems in neonates.

(I) Care in the delivery room

Majority of babies achieve smooth transition from intrauterine to extrauterine life.

i) Asphyxia neonatorum

This refers to failure of neonate to cry or start adequate respiration within one minute of birth;

- Asphyxia livida— It is said to occur if neonate is cyanosed with gasping or apnea. The mucle tone is normal or ↑ and HR is > 100/minute with good pulsations. *Apgar score is about 4-7*;
- Asphyxia pallida— the neonate is pale, hypotonic and apneic. HR is <100, pulsations in umblical cord are weak and no response to stimulation. *Apgar score is about 0-3— indicates intrauterine hypoxia.*

Asphyxia neonatorum can be prevented and managed with the "4 A's";

- Anticipation;
- Assessment by APGAR scoring;
- Action— ventilation correction steps performed along with neonatal resuscitation algorithm;
- Aftercare.

a) Anticipation

Fetuses at high risk of developing asphyxia should be anticipated. Such scenarios include;

- Preterm deliveries;
- Vaginal breech deliveries;
- Thick meconium staining of the amniotic fluid;
- Significant fetal distress;
- Significant antepartum haemorrhage;
- Serious fetal abnormality (e.g. hydrops, diaphragmatic hernia);
- Rotational forceps or vacuum deliveries;
- Caesarean section— unless elective and under regional anaesthesia;
- Multiple deliveries.

b) APGAR scoring

This aids in assessment of the newborn's adjustment to extrauterine life;

- The Apgar score is usually recorded at 1 and 5 minutes of birth (see Table);
- Apgar score ≥ 8 is generally considered good;
- Low scores, if they do not improve, predict impending need for resuscitation manuevres.

c) Action— neonatal resuscitation and ventilation correction steps

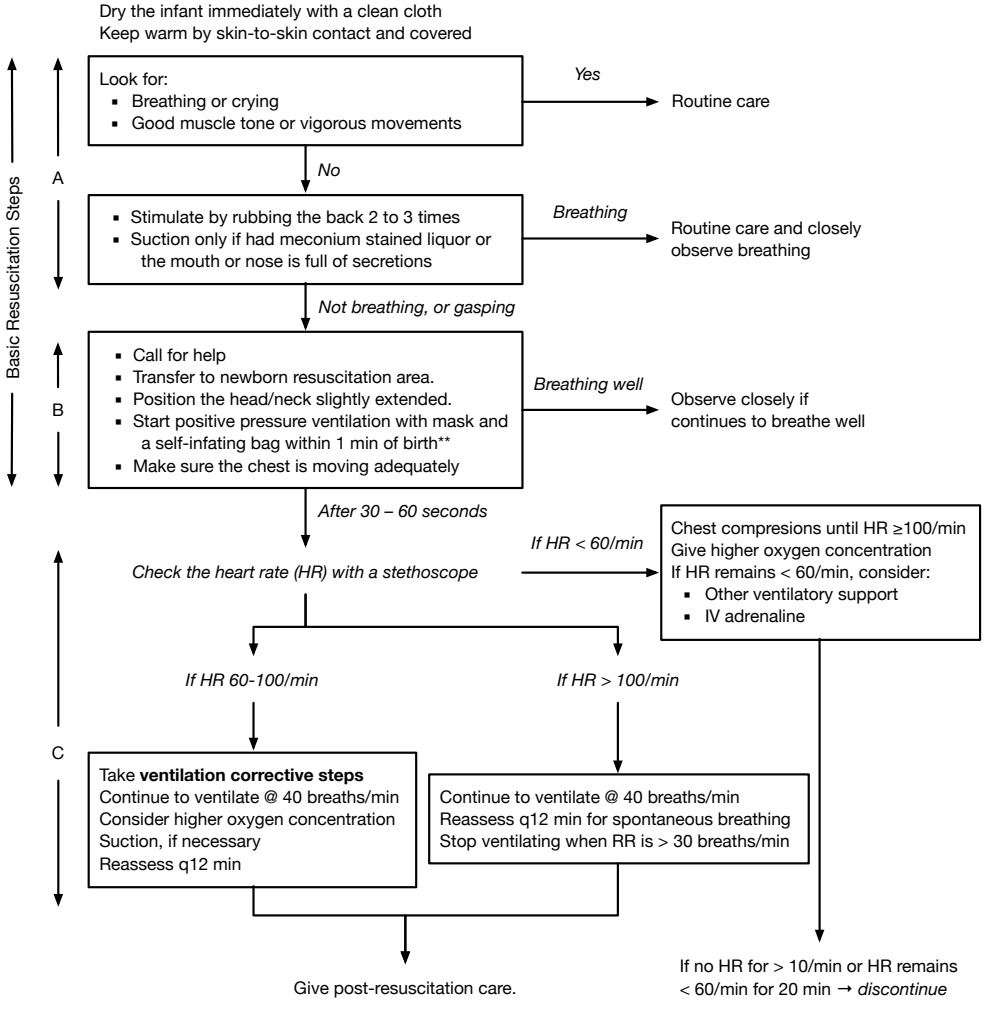
Neonatal resuscitation is performed by an algorithmic approach (see Figure).

Ventilation correction steps can be remembered with *aide mémoire* '***MR. SOPA***';

- M— adjust Mask in the face;
- R— Reposition the head to open airway;
- S— Suction mouth then nose;
- O— Open mouth and lift jaw forward;
- P— gradually increase Pressure every few breaths until visible chest rise is noted;
- A— consider artificial Airway (ETT or LMA).

Table. The APGAR score.

	Score	0	1	2
A	Appearance	White or blue	Pink + blue extremities	Pink all over
P	Pulse rate	Absent	< 100 bpm	> 100 bpm
G	Grimace (response to stimulation)	None	Grimace	Cry or cough
A	Activity (muscle tone)	Limp	Some flexion	Well flexed, active
R	Respiratory effort	Absent	Gasping or irregular	Regular/ strong cry



***Positive pressure ventilation should be initiated with air for infants with gestation > 32 weeks. For very preterm infants, it is preferable to start with 30% oxygen if possible.*

Figure. Algorithmic approach to neonatal resuscitation.

ii) Aftercare

Successful resuscitation should be followed by close observation, and early discharge is not recommended.

Review of the case aids in planning further management.

It is common practice to administer the single-dose vitamin K before baby is shifted from delivery room.

(II) Care in postnatal wards

For the baby, care in the postnatal wards comprises of neonatal examination and blood tests;

A thorough neonatal examination should be performed within 72 hours of birth. Its aims include;

- Diagnosis of congenital malformations;
- Diagnosis of common minor problems;
- Continuing of care— e.g. vaccinations and advice.

i) Neonatal examination

A neonatal examination is performed from head-to-toe. An abnormality detected on examination can be a part of a syndrome. Thus, abnormalities should be assessed thoroughly on a case-by-case basis;

- Feel the anterior fontanelle for tension (*may feel tense if baby is crying*);
- Palpate cranial sutures and check the scalp for swellings (e.g. cephalohematoma);
- Measure the head circumference;
- Look at the face for colour (cyanosis/pallor/ jaundice);
- Palpate the abdomen, feeling for masses, including large bladder or kidneys;
- Examine the eyes;
- Examine the ears, nose and mouth (cleft palate);
- Examine the neck, including the clavicles;
- Examine the arms, hands, legs and feet;
- Feel for the femoral pulses;
- Examine hips to exclude *developmental dysplasia of hip (DDH)*;
- Examine the genitalia and anus;
- Examine baby's back and spine;
- Assess tone;
- Measure heart rate and respiratory rate;
- Auscultate for heart murmurs— pulse oximetry can aid in detection of postductal hypoxia;

ii) Screening for genetic diseases

Screening for genetic diseases is usually carried out 5 days after birth. These include;

- Sickle cell disease;
- Cystic fibrosis;
- Congenital hypothyroidism;
- The '6 metabolic conditions'—
    - Phenylketonuria (PKU);
    - Medium-chain acyl-CoA dehydrogenase deficiency (MCADD);
    - Maple syrup urine disease (MSUD);
    - Isovaleric acidaemia (IVA);

- Glutaric aciduria type 1 (GA1);
- Homocystinuria (HCU, pyridoxine unresponsive subtype).

(III) Minor problems encountered in neonates

i) Erythema toxicum

Erythema toxicum refers to a rash characterized by multiple white pinpoint 'heads' on oval erythematous base.

It usually appears on the second or third day and resolves resolves spontaneously. Histopathology is rarely needed— shows eosinophil infiltration.

ii) Transient neonatal pustular melanosis

This is an eruption characterized by small pustule-like spots which progress to a hyperpigmented macules but remain without erythema.

Hyperpigmented macules may resembling a freckle but fades in a few weeks.

It is more commonly observed in Afro-carribean population.

iii) Milia

Milia are small yellowish-white spots, especially common on the nose, which represent retention cysts of the pilosebaceous follicles.

They disappear spontaneously in a few months.

iv) Mongolian blue spots

Mongolian blue spots have a characteristic blue-black macular appearance often seen over the sacrum or lower spine.

They fade slowly over the first few years.

v) Port wine stains

Port wine stains are angiomatas due to a malformation of the capillaries within the dermis.

Laser therapy can be considered for cosmetic improvement in facial lesions.

Port wine stains in the region of the trigeminal nerve are sometimes associated with intracranial vascular abnormalities as part of Sturge–Weber syndrome.

vi) Dimple marks

Simple midline dimples on the back are common.

In rare cases, they may be associated with spinal abnormalities. Such may be the case if;

- Dimples that are large > 5 mm diameter, or;
- High on the back (> 2.5 cm from the anus), or;
- Other lesions nearby e.g. haemangiomas, skin tags, hairy patches or subcutaneous masses.

Ultrasound and/or magnetic resonance imaging (MRI) of the spinal cord aids in ruling out spinal abnormalities.

vii) Genital findings

- In female babies, hymenal tags and small amounts of vaginal bleeding are common;
- In male babies— retractile testis, unilateral undescended testis or scrotal hydrocele may be observed.

(IV) Birth injuries

i) Head swellings

Head swellings are often observed in neonates. These can be (see Figure);

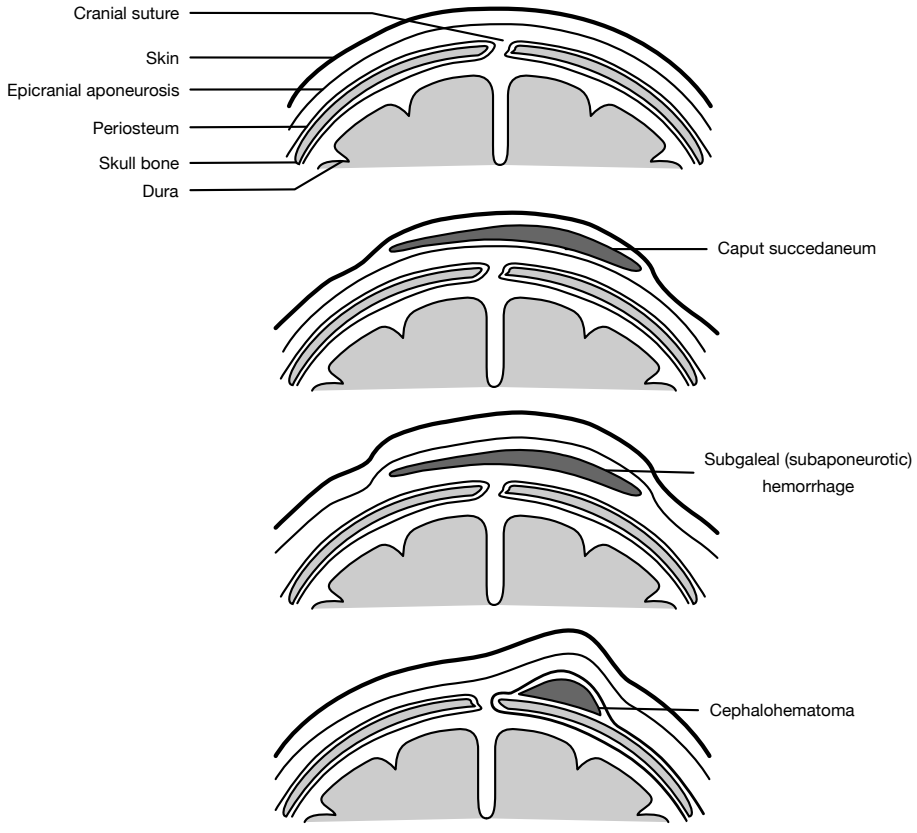


Figure. Illustration of neonatal head swellings.

- Caput succedaneum— edematous skin swelling that *crosses suture lines*. No treatment is required.
- Subgaleal (subaponeurotic) haemorrhage— boggy swelling of the scalp that *crosses suture lines*;
    - It is often associated with ventuouse delivery;
    - The blood collects in the subaponeurotic space— hypovolemic shock may be observed in severe cases.
- Cephalohematoma— hemorrhage under the periosteum of cranial bones which are adherent to the cranial sutures. Hence, the hematoma *does **not** cross the suture lines*;
    - It appears a few days after birth and resolves over 3-4 weeks;
    - Hyperbilirubinemia may develop with breakdown of hemoglobin in the extravasated fluid.

ii) Nerve palsies

Nerve palsies may be observed in a neonate.

a) Brachial plexus injuries

Brachial plexus injuries are often associated with difficult births, particular shoulder dystocia.

Erb's palsy affects the C5 and C6 nerve roots of brachial plexus— the baby's arm is held at the baby's side, internally rotated and pronated;

- Examination may reveal the affected arm to be flaccid initially;

- After 48 hours, Erb's palsy can be distinguished from other injuries— the arm is internally rotated and pronated being held to the side (*waiter's tip position*, see Figure);
- Total recovery occurs in 75% of babies over a few weeks to months;
- Physiotherapy aids in minimizing risk of contracture.

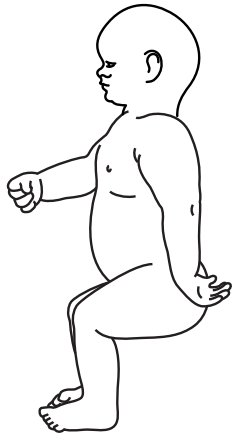


Figure. Illustration of Erb's palsy— waiter's tip position of the arm.

Other brachial plexus injuries e.g. Klumpke's palsy (affects lower roots— C8 and T1) are rare.

In a complete palsy of upper and lower roots of brachial plexus;

- The arm remains flail;
- There may be a ptosis and a Horner's syndrome due to damage to the stellate ganglion;
- In these cases, phrenic nerve (innervates the diaphragm) palsy should also be considered in these cases.

b) Facial nerve palsy

Facial nerve palsy is often associated with use of forceps in labour. However, prognosis is good, and recovery is seen within 3 weeks.

iii) Neonatal fractures

The most common sites of neonatal fracture are clavicle, humeral shaft and femoral shaft;

- Almost all neonatal fractures heal without sequelae.
- Immobilization of the fracture is difficult in neonates but may help.

(V) Congenital abnormalities

i) Cleft lip/palate

Cleft lip and/or palate are often associated breastfeeding problems. Such cases are managed with feeding with special techniques, preferably with expressed breast milk.

Repair is not urgent and done several months after birth by plastic surgeon.

ii) Ankyloglossia

It is not uncommon for babies to be born with a short, thick or tight lingual frenulum (see Figure).

This may restrict the mobility of tongue (upward lift and forward protrusion) and is referred to as ankyloglossia or tongue-tie;

- Ankyloglossia without difficult breastfeeding is managed conservatively;
- Appropriate breastfeeding techniques can aid in better breastfeeding if needed;
- If unsuccessful, then surgical division of tongue-tie can be performed.

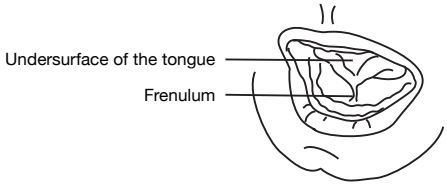


Figure. Illustration of ankyloglossia.

iii) Congenital diaphragmatic hernia (CDH)

It is thought to be caused by failure of closure of pleuroperitoneal canal;

- It occurs most commonly on the left side and detected antenatally from the 18-20 week anomaly scan;
- With reversal of physiologic bowel herniation during 12th week of embryological development, the bowel may herniate into the chest cavity;
- The dominant features of CDH include pulmonary hypoplasia and pulmonary hypertension.

Neonates are managed with;

- Titrated ventilation (often using high-frequency oscillation)— for pulmonary hypoplasia;
- Inhaled nitric oxide— for pulmonary hypertension.

Definitive treatment is surgical repair once the baby is stable. An operation to repair the defect is undertaken when the baby is stable. This may take days or weeks.

Survival post-surgery is dependent on the degree of lung hypoplasia.

iv) Exomphalos and gastroschisis

These are abdominal wall defects;

- Exomphalos— herniation of bowel ± viscera through umbilicus. The herniated tissues are covered with a membranous sac. Exomphalos is more likely to be associated with other congenital abnormalities or rarely Beckwith-Wiedemann syndrome;
- Gastroschisis— bowel herniation through abdominal wall defect lateral to umbilicus. The herniated tissues is not covered with membrane.

Presence of uncomplicated gastroschisis does not affect management of labour;

- Immediately after birth the baby's abdomen is wrapped to prevent fluid loss and trauma to the bowel;
- The wrapping is clear plastic so that the bowel can be visualized;
- Omphalocele associated with Beckwith-Wiedemann syndrome can present with hypoglycemia resulting in brain injury if not corrected.

The treatment depends on whether the neonatal abdominal can accomodate the bowel loops;

If the bowel loops can fit into the abdominal cavity— primary repair of abdominal wall is performed;

Abdominal cavity may need to be expanded before the bowel can fit. In these cases, the abdominal cavity is expanded using gravity using a 'silo' (see Figure);

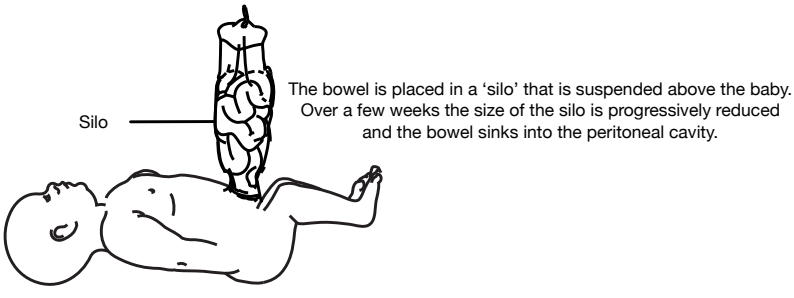


Figure. Illustration of a 'silo'— used in management and treatment of abdominal wall defects.

v) Developmental dysplasia of hips (DDH)

Many babies have stable joints but are found to have a 'clicky hip'. This is not abnormal but may be due to an unstable joint— i.e. developmental dysplasia of hip (DDH);

This often occurs in association with certain factors;

- Breech presentation (whether delivered by Caesarean section or vaginally)
- Family history of dysplastic hip
- Any deformity suggesting intrauterine compression, or oligohydramnios
- Clicky hip on clinical examination, or one with restricted abduction

Focused examination of hips is a part of neonatal examination and screening;

- It involves Ortolani–Barlow manoeuvres (see Figure);
- Hip joint ultrasound is the first line *investigation* and is more reliable than examination manoeuvres.

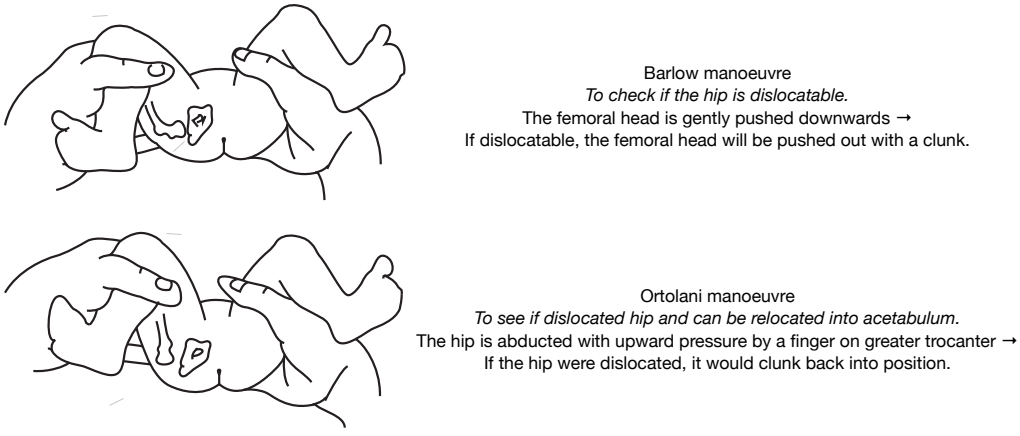


Figure. Illustration of Ortolani and Barlow manoeuvres.

Management is best under orthopedics and involves use of Pavlik's harness— maintains hip flexion and limits adduction. Untreated DDH leads to abnormal gait, limp and early onset hip osteoarthrosis.

vi) Spina bifida

Spina bifida is a neural tube defect.

It is can be detected at 18-20 week anomaly scan.

It can be further subtyped as;

- Meningocoele— normal spinal cord, defect covered with skin;
- Myelomeningocoele— abnormal spinal cord and exposed defect;
- Spina bifida occulta— cord covered with bone and skin with overlying skin lipoma or hair.

Presence of spina bifida does not affect the management of labour but infection of high concern;

- The baby should be wrapped in clear film to protect the back from trauma and infection;
- Neuro-surgical repair is performed within 48 hours to close the lesion.

vii) Hypopspadias

Hypospadias refers to an abnormally located urinary meatus.

Repair is not urgent and circumsicion should not be performed— foreskin is used during repair of hypospadias.

Surgical correction takes place between 6 months and 1 year after birth.

viii) Ambiguous genitalia

Ambiguous genitalia refer to any condition in which the male or female genitalia appear abnormal.

Ambiguous genitalia may be more likely if testes can not be palpated bilaterally.

If no gonads can be felt in the inguinal region, and the phallus is small (the usual neonatal penis is 3 cm stretched length), the baby may be a female baby with **congenital adrenal hyperplasia** (CAH). *This is important to recognize with urgent investigations to avoid neonatal collapse secondary to salt loss*.

ix) Talipes

The most common skeletal disorder is talipes. It can be detected antenatally using ultrasound.

It can be further classified as (see Figure);

- Talipes equinovarus— the forefoot is supinated and ankle plantarflexed.
- Talipes calcaneovalgus— the forefoot is everted and ankle dorsiflexed.

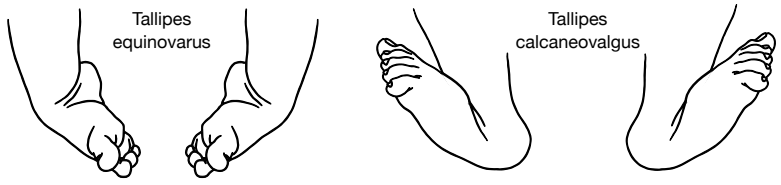


Figure. Illustration of talipes equinovarus and calcaneovalgus.

In cases of **talipes equinovarus**, it is important to distinguish between postural talipes from fixed talipes. In fixed talipes, the foot can not be repositioned by gentle manipulation;

- Positional talipes is temporary and often associated with oligohydramnios;
- Fixed talipes requires orthopaedic management via splints or plasters.

x) Congenital heart disease

Antenatal screening for cardiac anomalies is performed at 18-20 weeks' anomaly ultrasound scan. Thus, cardiac anomalies are already detected before birth in most cases.

Cyanotic congenital heart diseases are particularly significant in neonates. These anomalies are dependant on a patent ductus for oxygenation of blood and include (*aide mémoire: 5 'Ts'*);

- Truncus arteriosus;
- Transposition of great vessels (TGV);
- Tricuspid atresia;
- Tetralogy of fallot (ToF);
- Total anomalous pulmonary venous return (TAPVR).

These babies may present with cyanosis ± breathlessness. If the ductus is not kept open (e.g. using prostaglandin E2), heart failure and cardiovascular collapse can occur.

Auscultation may reveal a murmur over the precordium without known congenital heart anomalies— these shoulde be distinguished from common innocent murmurs. Features of innocent murmurs include;

- The murmur is mid-systolic, grade 1–2/6 and best heard at the left sternal edge;
- There are no audible clicks;
- The pulses are normal;
- The baby is otherwise well.

The '**100% oxygen test**' helps distinguish between cyanotic heart disease and pulmonary disease;

1. *Determine PaO_2 while the infant is on room air;*
2. *Give 100% oxygen for 10-20 min by mask or endotracheal tube;*

3. *Obtain **ABGs** while the infant is breathing **100% oxygen**.*

Because of intracardiac right-to-left shunting, the newborn with cyanotic congenital heart disease (in contrast to the infant with pulmonary disease) is unable to raise the arterial saturation, even in the presence of increased ambient oxygen.

Appropriate care should be taken to avoid air or clots in the IV lines as these can lead to embolism via R→L shunting.

(VI) Diagnoses more common in term babies

i) Respiratory disorders

a) Meconium aspiration syndrome (MAS)

MAS is a chemical pneumonitis secondary to aspiration of meconium by the neonate.

It is generally seen in post-term pregnancies;

- Amniotic fluid and cellular debris swallowed by fetus *in utero* is converted by enzymes and bacteria in the bowel to meconium;
- Fetal asphyxia *peripartum* is associated with meconium passage and staining of the amniotic fluid;
- The fetus/neonate can aspirate meconium before or after birth;
- As the fetus also makes breathing efforts with asphyxia, meconium aspiration can be potentiated;
- Aspiration before birth is often observed to manifest more severely;
- This results in respiratory tract obstructive features and chemical irritation to airways.

The neonate presents with tachypnoea, worsens over 24–48 hours and then gradually improves.

The management is centered around;

- Early detection of meconium staining of amniotic fluid— thick fresh meconium;
- Prevent further aspiration of meconium— Suction of neonate's oropharynx at birth;
- Prompt airway resuscitation if needed (as part of neonatal resuscitation);
- Antibiotic therapy;
- In severe cases— mechanical ventilation (with high frequency oscillation) ± supplementary surfactant;
- Extracorporeal membrane oxygenation— for resistant cases.

Even with early detection of meconium staining of amniotic fluid, MAS takes its course. Suctioning the oropharynx as soon as the fetal head delivers can be attempted.

MAS is associated with development of persistent pulmonary hypertention of newborn (PPHN) in addition to pneumonitis.

b) Persistent pulmonary hypertension of the newborn (PPHN)

Usually there is a rapid postnatal fall in pulmonary vascular resistance after birth. PPHN, in contrast, is characterized by an elevated pulmonary vascular resistance (PVR).

PPHN can occur as a primary disorder (structurally abnormal pulmonary arteries→ idiopathic PPHN) or as a complication of asphyxia, infection or pulmonary hypoplasia.

Affected neonates show respiratory distress with cyanosis— due to *resultant* R→L shunting of blood across the foramen ovale and the PDA.

PPHN is essentially a diagnosis of exclusion;

- The diagnosis is suspected in a baby who remains hypoxic in 100 per cent oxygen (→ 100% oxygen test) and a normal chest radiograph.
- Echocardiography confirms the R→L shunt at atrial and/or ductal level and aids in excluding congenital heart disease.

Nitric oxide is an effective treatment for PPHN. Other therapeutic options include;

- Warmth;
- Artificial ventilation;
- Supplementary oxygen.

c) Transient tachypnoea of the newborn (TTN)

As the name implies, TTN is characterized by a high respiratory rate in the neonate. It is the most common respiratory disease of term infants.

Fetal lungs are filled with 'lung liquid' in utero— for normal lung development and growth. During labour, however, the production of lung liquid ceases and reabsorption begins.

It is thought to be caused by the persistence of fetal lung fluid. This is more likely after C-section in the absence of labour— as vaginal delivery aids squeezing of lung fluid out from thorax;

TTN is often a diagnosis of exclusion, and other causes of tachypnea should be excluded first. These include (but not limited to);

- Infection;
- Heart disease;
- RDS.

ABGs show hypoxia ± hypocarbia. Hypercarbia is unusual and should be investigated.

The chest X-ray classically shows hyperexpansion of lungs. Perihilar shadowing and fluid in the lateral fissure can also be observed.

TTN is self-limiting and gradually resolves over 1–3 days. There are no long-term complications.

In the acute phase, however, management includes;

- Supplementary oxygen to maintain oxygen saturation;
- Oral feeding may need to be suspended if significant tachypnoea (BR > 60/min);
- Prophylactic antibiotics till infection can be ruled out.

ii) Vitamin K deficiency bleeding (VKDB)

Vitamin K deficiency is a preventable cause of bleeding (→ vitamin K deficiency bleeding (VKDB)) and consequent neonatal morbidity.

VKDB is secondary to deficiency of vitamin K dependant factors II, VII, IX and X. It can occur in three forms;

- Very early VKDB— bleeding manifesting within 1st day of birth. This is morely to manifest in babies whose mothers have taken drugs that interfere with the manufacture of vitamin K-dependent clotting factors, e.g. antituberculous or anticonvulsant drugs.
- Classical VKDB— bleeding manifesting on days 2–7 of life. There may be bleeding from the umbilical stump, bruising or melaena.
- Late VKDB— bleeding manifesting from week 2 to 6 months of age. Small warning bleeds from the gum are common. Here, there is high risk of intracranial haemorrhage.
- Late VKDB is rare but particular observed in exclusively breast-fed babies. Other contributing factors include;
    - Vitamin K prophylactic dose *missed at birth*;
    - Intestinal malabsorption;
    - Liver disease.

Diagnosis of VKDB is with coagulation tests— normal platelet count, ↑ thrombin time and ↑ prothrombin time.

Treatment of VKDB is with IV vitamin K and fresh frozen plasma (FFP) transfusion.

Prophylactic vitamin K administration is recommended at birth;

- A single intramuscular dose of 1mg vitamin K is effective alone;
- If oral dosage is chosen over intramuscular route, atleast 3 doses of 2mg will be needed— at birth, at 3-4 days and at 6 weeks of age.

Prophylactic vitamin K administration prevents all forms of VKDB unless there is an undetected underlying cause.

iii) Neonatal jaundice and kernicterus

Upto 2/3^{rds} of all neonates develop visible jaundice in the first week of life.

a) Physiological jaundice

This refers to neonatal hyperbilirubinemia that develops over a period of days.

Immature UDP-glucuronosyltransferase enzyme activity in liver is cited as a cause. Contributing factors include;

- High neonatal hematocrit;
- Short live of neonatal red cells;
- Breast-feeding;
- Relatively low amount of intestinal bacteria in neonates;
- Use of albumin-bound medications— displace albumin.

Here, a gradual rise in serum unconjugated bilirubin concentration is observed.

Generally, unconjugated bilirubin levels reach 6-8 mg/dL by 72-96 hours of age, followed by a fall to 1 mg/dL by 10th day in an otherwise healthy child.

The liver enzymes are induced over the first 3–4 days after birth normally. In physiological jaundice, however;

- Total bilirubin rise **remains less than** 5 mg/dL/day;
- Total bilirubin is **not higher than** 12.9 mg/dL in term or 15 mg/dL in preterm.

b) Hyperbilirubinemia and breastfeeding

There are two clinical entities associating breast-feeding with hyperbilirubinemia (see Table).

Table. Breastfeeding associated jaundice and breast-milk jaundice.

	Breastfeeding associated jaundice	**Breast-milk jaundice**
Onset	Relatively early-onset— 2-4 days of age	Relatively late-onset— 5-10 days of age
Aetiology	Poor feeding or delay in initiation of breast feeding— due to exaggerated enterohepatic circulation of bilirubin.	Certain factors in breast milk e.g. *β-glucuronidase, fatty acids and pregnanediol* enhance intestinal absorption of bilirubin.
Diagnosis	Diagnoses of exclusion— feeding frequency in first 3 days of life *inversely related* to bilirubin levels.	Diagnoses of exclusion— baby is otherwise healthy.
Management	Provision more frequent feedings to stimulate meconium passage and excretion of bilirubin in the stool. Additional feeds of water supplements are of no value here.	Higher levels of bilirubin may need treatment with the algorithmic approach to treatment of jaundice.
Recurrence	—	All children of the mother develop this late onset form of jaundice— ↑ recurrence risk in subsequent babies.

c) Pathological jaundice

Neonates manifesting jaundice on the first day of life should be investigated— most common causes in these cases are associated with hemolysis.

Jaundice may be secondary to unconjugated or conjugated hyperbilirubinemia (see Figure).

High concentrations of unconjugated bilirubin are neurotoxic, unlike conjugated bilirubin which is not toxic.

Hypothyroidism should always be ruled out in all neonates with jaundice.

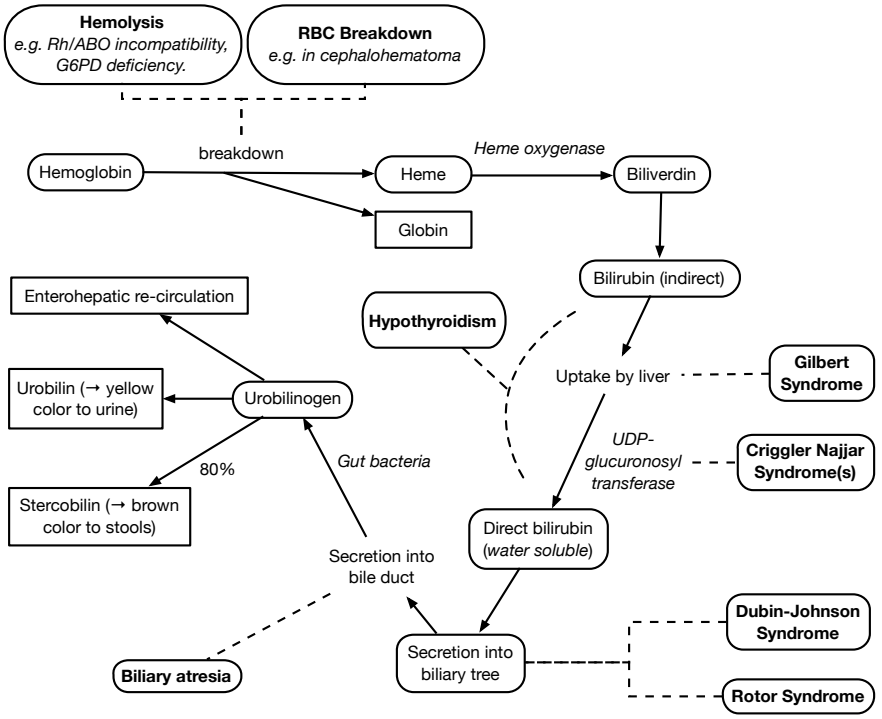


Figure. Illustration of haemoglobin degradation pathway and associated pathologies. Defects/disorders lead to ↑ levels of preceding markers except hemolysis which lead to ↑ levels of downstream markers.

d) Kernicterus

Jaundice with high levels of unconjugated bilirubin can lead to kernicterus;

- Classically, kernicterus refers to yellow staining of the basal ganglia by bilirubin;
- Clinically, kernicterus manifests as bilirubin encephalopathy. Affected neonates show signs of athetoid cerebral palsy, sensorineural deafness, paralysis of up-gaze and dental enamel dysplasia.

The level of unconjugated bilirubin at which kernicterus can occur in well term infants is not known with certainty, but levels ≥ 25 mg/dL carry higher risk.

e) Management

Bilirubin levels in neonates should be referenced with the percentile normogram. Often serial bilirubin level measurements are needed to predict and prevent dangerous levels of unconjugated bilirubin.

An algorithmic approach to management of neonatal jaundice is taken;

- Breastfeeding associated jaundice is benign and dietary changes aid in resolution;
- Phototherapy converts toxic unconjugated bilirubin to nontoxic isomers which are excreted in the urine. Light in the visible spectrum (wavelength 425 - 475 nm) is effective;
- If phototherapy fails to prevent a rising trend of bilirubin levels, exchange transfusion is performed.

Exchange transfusion involves withdrawing a small aliquot of blood from the baby and replacing it with a small aliquot of cross-matched blood. This is repeated every 5 minutes over 4 hours. The aim is to replace twice the baby's circulating volume (130 ml/kg). *If there is evidence of active alloimmune disease (e.g. rhesus or ABO incompatibility) on direct antiglobulin testing (DAT), then immunoglobulin (Ig) during phototherapy can reduce the need for exchange transfusion.*

Exchange transfusion is a very effective treatment.

iv) Hypoglycemia

Healthy term babies of appropriate weight who are breastfed may have lower blood glucose concentrations than formula-fed babies in the first 2–3 days of life.

Table. Infants at risk of developing symptomatic hypoglycaemia

Infants with fetal growth restriction
Infants of diabetic mothers
Preterm infants
Infants who have experienced significant hypoxia in labour
Infants who are 'large for dates' – possibility of undiagnosed maternal gestational diabetes

Very rarely, hypoglycaemia can occur from breast milk insufficiency. Although neonates have high amounts of ketone bodies as an alternate fuel, prolonged symptomatic hypoglycaemia can lead to brain damage.

An apparently healthy term baby may have underlying metabolic disease predisposing to hypoglycemia in early life. These include;

- Idiopathic hyperinsulinaemic hypoglycaemia of infancy (previously called neisidioblastosis);
- Medium chain acyl coenzyme A dehydrogenase (MCADD) deficiency.

Detection of hypoglycemia is with heel-prick blood on glucometer strips or blood glucose sampling (more accurate). Pre-feed testing and monitoring may be considered in neonates with risk factors.

v) Neonatal encephalopathy and HIE

Neonatal encephalopathy is a clinical condition suggesting that brain injury has occurred altering brain function.

Aetiology and clinical presentations vary. Hypoxic-ischemic encephalopathy (HIE) refers to perinatal hypoxic-ischemic insult as a cause of neonatal encephalopathy.

HIE should be suspected in cases complicated with;

- Perinatal fetal distress;
- Low APGAR scores at birth requiring resuscitation;
- Metabolic acidosis on cord blood sample or early neonatal sample;
- Seizures;
- Renal impairment (blood in the urine and a low urine output);
- Altered CNS state e.g. hypotonia.

Neonatal encephalopathy leads to changes in the conscious level and muscular tone— there may be hypotonia or hypertonia. A structured approach to assessment of encephalopathy should be undertaken. Sarnat grading is an example of such a structured approach (see Table).

Table. Sarnat grading for neonatal encephalopathy.

	Grade I (mild)	**Grade II (moderate)**	**Grade III (severe)**
Alertness	Hyperalert	Lethargy	Coma
Muscle tone	Normal or ↑	Hypotonic	Flaccid
Seizures	None	Frequent	Uncommon
Pupils	Dilated, reactive	Small, reactive	Variable, fixed
Respiration	Regular	Periodic	Apnoea
Duration	<24 hours	2-14 days	Weeks

The first seizure in hypoxic–ischaemic encephalopathy often occurs after 12 hours, which makes early discharge risky after resuscitation has been required.

The threshold for diagnosis of HIE should be high and differential diagnoses should be ruled out. These include;

- Infection— lumbar puncture with bacterial and viral (e.g. HSV) detection tests;
- Abnormal brain findings— Brain MRI;
- Hypoglycemia;
- Metabolic disorders— Lactate, blood pH, serum ammonia levels.

Diagnosis of HIE may be supported by certain investigatiory findings;

- Cranial ultrasound scan— cerebral edema;
- Renal function tests— renal impairment secondary to the aetiological hypoxic-ischemic insult.

Diagnois of HIE is confirmed by MRI brain scans. Moreover, severity of changes on MRI can serve in diagnostic assessment;

- Altered signals in the basal ganglia suggest a rapid onset but short-lived (<20–30 minutes) hypoxia. This is because basal ganglia are most metabolically active part of neonatal brain;
- Altered signals in the cerebral cortex suggest a relatively longer hypoxic insult. This is because cortex is comparatively less metabolically active.

Additionally, MRI brain findings are associated with prognostic outcomes (see Figure);

- Basal ganglia injury is associated with dyskinetic cerebral palsy;
- Internal capsule injury is associated with upper motor lesions (e.g. spastic hemiplegia);
- Cerebral cortex injury is associated with learning difficulties.

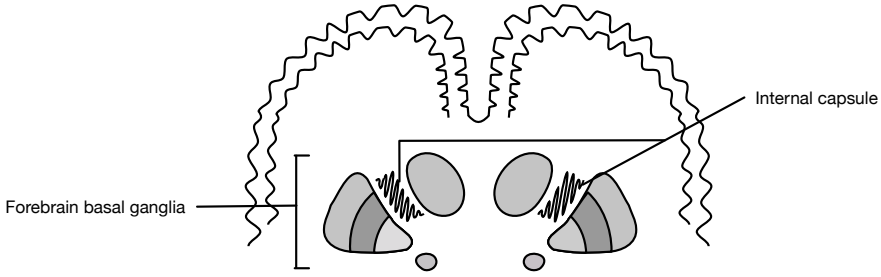


Figure. Illustration of cerebral cortex, forebrain basal ganglia and internal capsule on frontal view.

The baby is treated aggressively initially. **For HIE**;

- Artificial ventilation is usually needed to maintain respiratory drive;
- Poor myocardial function may occur after severe hypoxic-ischaemic insult— consider inotropic support;
- Renal impairment— secondary to a severe hypoxic-ischaemic insult. Initially poor urine output followed by high urine output is often observed in these cases;
- Prophylactic antibiotic cover— acyclovir may also be considered for HSV infection;
- Therapeutic hypothermia improves outcome in HIE. In developed countries, it is standard-of-care in HIE.

Assessment of progress in neonatal encephalopathy involves both clinical assement (e.g. using Sarnat grading) and investigations.

The use of electroencephalogram (EEG) helps to evalulate seizure activity in neonates— **In HIE**, amplitude integrated electroencephalography (aEEG; also referred to as *cerebral function monitoring*, **CFM**) aids in highlighting background electrical activity to determine prognosis. e.g. normal background, despite frequent seizures, can be considered *reassuring*.

In most cases, however, determining prognosis and outcome is difficult and senior input is recommended.

(VII) Diagnoses more common in preterm babies

Main problems of prematurity include, among others;

- Respiratory distress syndrome;
- Chronic lung disease;

- Preterm brain injury;
- Hypoglycaemia;
- Necrotizing enterocolitis;
- Infection;
- Patent ductus arteriosus;
- Jaundice.

i) Respiratory distress syndrome (RDS) and chronic lung disease

Respiratory distress syndrome (RDS) is also named hyaline membrane disease (HMD) or surfactant deficient lung disease (SDLD).

- It is the most common respiratory disorder affecting preterm infants but rare in term neonates;
- Almost all neonates born at 26 weeks or before develop RDS and the aetiology is cited as insufficient pulmonary surfactant.

Affected neonates develop progressive respiratory distress over a course of several days after which progressive resolution of symptoms is observed by 4^{th} day.

Addition clinical features include;

- Cyanosis;
- Tachypnoea;
- Respiratory grunting;
- Intercostal recession ± sternal recession.

ABGs show respiratory failure while diagnosis is confirmed by CXR which shows evidence of alveolar fluid with a *ground-glass appearance* or *air bronchograms* but these radiological findings are not always specific to RDS.

RDS is managed with supplementary oxygen, continuous positive airway pressure (CPAP) ventilation or mechanical ventilatory support and administration of surfactant via endotracheal tube.

The course of RDS can be complicated with the development of **chronic lung disease of prematurity**— this refers to neonates' persistent dependance on oxygen after 28 days of age. This chronic lung disease of prematurity is thought to be a milder form of bronchopulmonary dysplasia.

Prophylactic antenatal administration of steroids to mother lowers incidence of neonatal RDS.

ii) Preterm brain injury

The pattern of brain injury in preterm babies is different from that seen in term babies.

This is because premature neonates can often withstand lower oxygen levels as they have lower metabolic requirements.

The major patterns of brain injury in preterm babies can be categorized;

- Germinal matrix hemorrhage (GMH)— hemorrhage within ependyma of germinal matrix (see Figure);
    - In many cases, blood can rupture through the ependyma into lateral ventricles leading to intraventricular hemorrhage (GMH-IVH) with or without acute ventricular dilation;
    - Bleeding into the substance of the brain is usually followed by breakdown of tissue into a **porencephalic cyst**.
- Parenchymal injury (also referred to as periventricular leucomalacia, PVL)— loss of white matter secondary to ischemia. These lesions often cavitate over time.

Ventricular enlargement is often a sign of periventricular myelin loss and brain shrinkage, rather than raised intracranial pressure hydrocephalus.

Although hemorrhagic parenchymal infarctions can usually be seen by cerebral ultrasonography, PVL is difficult to visualize by ultrasonography.

The prognosis of preterm brain injuries varies, and senior senior consult is recommended. Cerebral palsy is almost universal in cases with bilateral occipital PVL.

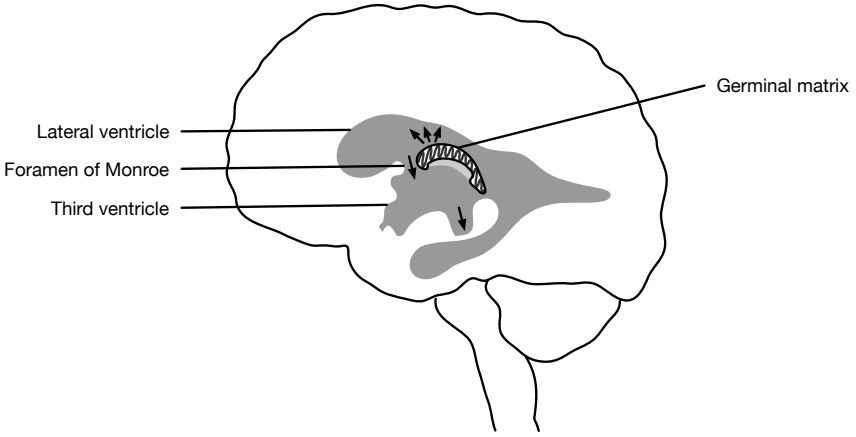


Figure. Illustration of GMH and continuing spread to the third ventricle (GMH + IVH).

iii) Necrotizing enterocolitis (NEC)

NEC is more commonly a disease of pre-term babies or LBW babies weighing < 1500g at bith.

It is characterized by intestinal necrosis in watershed distributions.

In addition to prematurity, it is associated with;

- FGR;
- Congenital heart disease.

Though it is of unknown aetiology, ↑ osmotic load with parenteral feeds (which may be used if baby is unable to take oral feeds), infection and hypoxia are often cited as contributing factors in pathogenesis.

It starts as food intolerance as the stomach does not empty between feeds— increased gastric aspirate ± (bile- or blood-stained) after feeds, after enteral formula feeding is started.

Affected infants present with a triad of abdominal distention, hematochezia and pneumatosis intestinalis (radiographic finding).

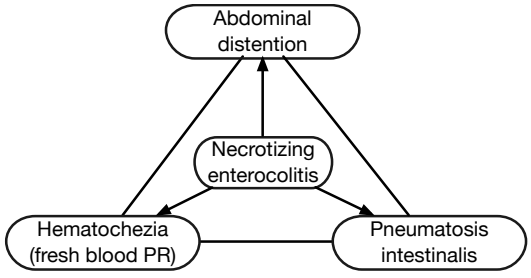


Figure. Classic triad of necrotizing enterocolitis.

In addition there is;

- Fever;
- Vomiting;
- Shock, jaundice and intestinal perforation— in severe cases.

On examination, tender abdomen may be indicative of peritonitis.

Abdominal Xray in these cases may yield;

- Distended bowel loops;
- Air in the portal/hepatobiliary tract— better appreciable on ultrasound scan;
- Pneumatosis intestinalis is pathognomonic— air in the bowel wall/intramural air;
- Air under the diaphragm— if intestinal perforation.

Management involves;

- Discontinuation of enteral feeds/NPO;
- Orogastric tube for gastric decompression;
- Total parenteral nutrition (TPN);
- Antibiotics for 'triple coverage' against gram-positive, gram-negative and anaerobic bacteria;
- Peritoneal drainage via paracentesis may be considered;
- Surgery— **definitive treatmnent** but often delayed till infant stabilizes. Surgical options include;
    - Resection of non-viable necrotic segments with anastomosis;
    - Ileostomy or colostomy and later reanastomosis;

Complications associated with NEC include;

- Strictures with healing;
- Long-term need for stoma;
- Short bowel syndrome— with surgical resections. This may be countered with bowel-lengthening procedure later.

Long-term need for TPN can be complicated by cholestatic jaundice.

iv) Retinopathy of prematurity (ROP)

ROP is an acquired retinal diease. Administration of high concentration of oxygen in preterm babies (<32 weeks) is notoriously established as a cause. Other contributing factors include;

- Low birthweight (<1,500g);
- Poor postnatal weight gain;
- Low levels of insulin-like growth factor;
- Excessive activity of intraocular vascular endothelial growth factor (VEGF).

ROP reflects arrest of neuronal development and pathological vascularization in retina. As retinal development is incomplete in preterm babies (see Figure);

- Immature retinal blood vessels constrict when exposed to high O_2 concentrations— leading to *cessation of vascular growth*;
- In severe cases of ROP, *pathological neurovascularization* may occur instead of normal vascularization under the effects of VEGF;
- Retinal detachment can result from concurrent over-proliferation of endothelial cells in retina.

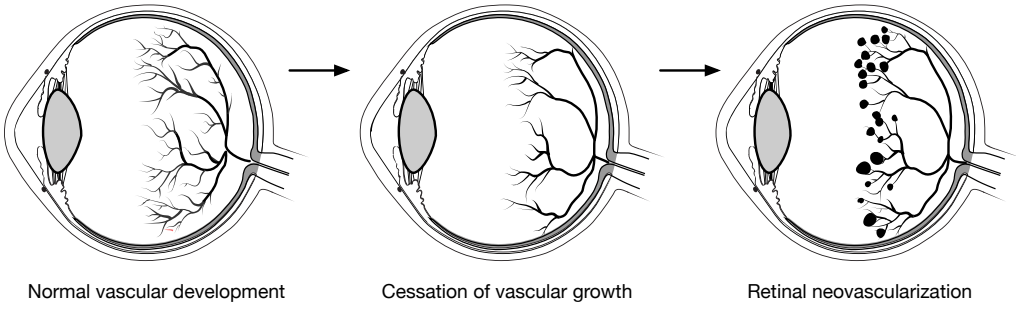


Figure. Illustration of pathogenesis in ROP.

A preterm infant under oxygen therapy must have blood PO2 levels monitored— risk if higher with pO_2 levels >100mmHg.

All low-birth-weight babies who received oxygen therapy should be screened for ROP— once before discharge post-birth and later at age 4-6 weeks;

- Indirect ophthalmoscopy is preferred over direct ophthalmoscopy;

- Fundus fluorescein angiography (FFA) documents retinal vascular anatomy better, as the fluorescein dye *lights-up* the retinal vasculature.

Treatment is effective especially with early detection;

- Laser treatment or cryotherapy— standard of care best determined by ophthalmology;
- Other treatments such as intraocular injection of anti-vascular endothelial growth factor (anti-VEGF) can also be considered.

If untreated, ROP can lead to vascular proliferation in the retina, retinal detachment and partial or complete blindness.

Treatment, however, does not affect visual problems due to cortical blindness or squints.

(VIII) Infections

In neonates, certain infections may be characteristically seen in the first few days of life. These include;

- Pyoderma— localized skin infection by staphylococci;
- Umblical infection— a purulent discharge or inflamed periumblical area raises suspicion. This can be treated with topic antisepsis with spirit/alcohol or parenteral therapy may be indicated.
- Conjunctivitis—
    - Silver nitrate is commonly used for irrigation of neonate's eyes at birth for prophylaxis against infections.
    - Conjunctivitis can still occur despite prophylaxis and these manifest variably.
    - However, the day after birth when conjunctivitis manifests can aid in narrowing-down probable causes and guide empiric treatment (see Figure).

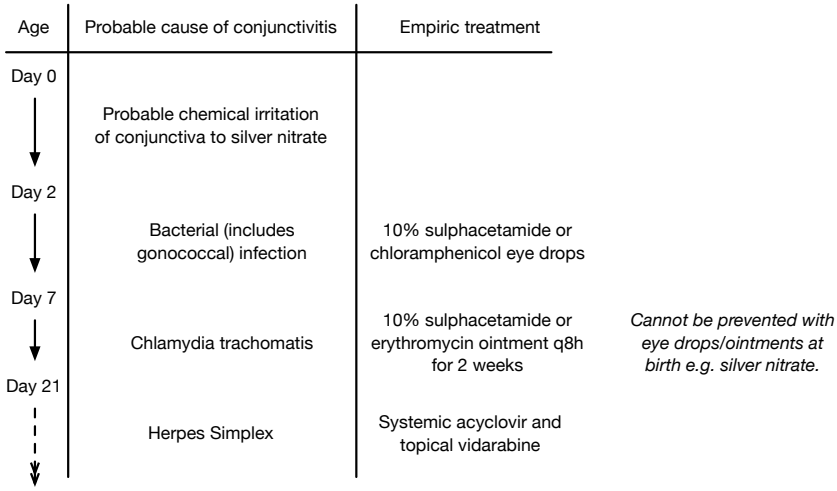


Figure. Illustration of probable causes of conjunctivitis and periods of manifestation.

- Oral thrust— presenting as white patches on tongue or buccal mucose. Topical nystatin drops or 1% gentian violet is adequate for treatment.

For other infections, *see Chapter 27: Infections in pregnancy*.

INDEX OF CONTENTS

---xxx---