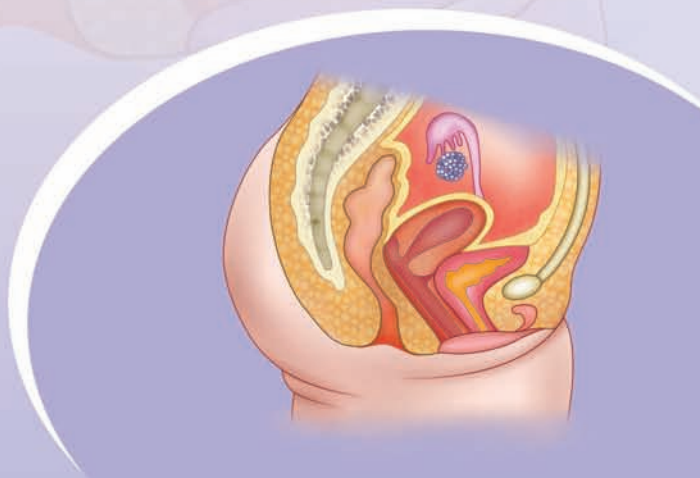
Section 7

Reproductive System



Chapter 74

Male Reproductive System

INTRODUCTION

Reproductive system ensures the continuation of species. **Gonads** are the primary reproductive organs which produce the gametes (egg or ovum); a pair of testes (singular = testis) produces sperms in males and a pair of ovaries produces ovum in females.

Normally, most of the animals including humans are either definite males or definite females. However, in some organisms like earthworms and snails, both sexes may be present in the same organism and this condition is known as **hermaphroditism.**

In humans and most of the higher animals, reproduction occurs sexually, i.e. by mating. However, there are some species like insects which can produce offsprings without mating.

Reproductive organs include:

1. Primary sex organs
2. Accessory sex organs.

Primary Sex Organs

Testes are the primary sex organs or gonads in males.

Accessory Sex Organs

Accessory sex organs in males are:

1. Seminal vesicles
2. Prostate gland

3. Urethra
4. Penis.

External and Internal Genitalia

Reproductive organs are generally classified into two groups, namely external genitalia (genital organs) and internal genitalia. External genital organs in males are scrotum, penis and urethra. Remaining sex organs constitute the internal genitalia.

■ FUNCTIONAL ANATOMY OF TESTES

Testes are the **primary sex organs** or gonads in males. There are two testes in almost all the species. In human beings, both the testes are ovoid or walnut-shaped bodies that are located and suspended in a sac-like structure called **scrotum.**

Each testis weighs about 15 to 19 g and measures about 5 × 3 cm. Testis is made up of about 900 coiled tubules known as **seminiferous tubules,** which produce sperms. Seminiferous tubules continue as the vas efferens, which form the **epididymis.** It is continued as **vas deferens.**

Vas deferens is also called **ductus deferens, spermatic deferens** or **sperm duct.** From epididymis in scrotum, the vas deferens extends on its one side upwards into abdominal cavity via inguinal canal. Terminal portion of vas deferens is called **ampulla** (Fig. 74.1). Ampulla of vas deferens joins ducts of seminal vesicle of same side, to form **ejaculatory duct.**

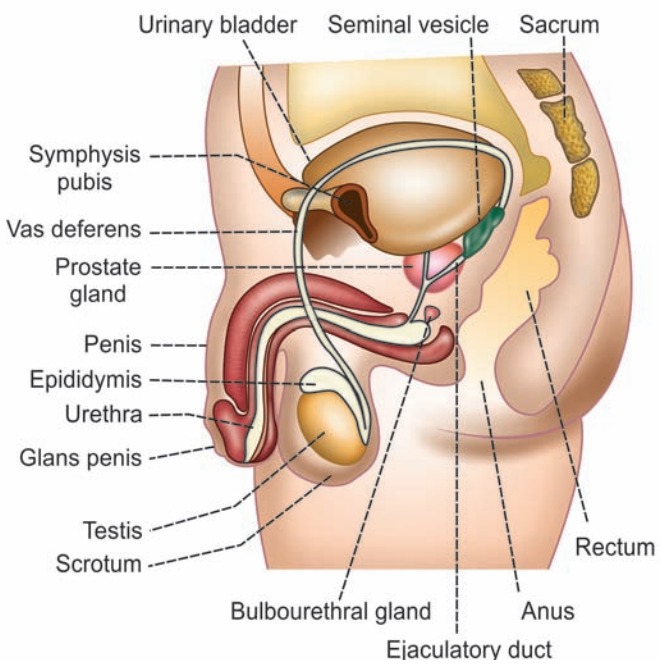


FIGURE 74.1: Male reproductive system and other organs of pelvis

Thus, there are two ejaculatory ducts each of which receives sperm from vas deferens and secretions of seminal vesicle on its own side. Both the ejaculatory ducts empty into a single **urethra.** Actually, ejaculatory ducts open into prostatic part of urethra.

■ COVERINGS OF TESTIS

Each testis is enclosed by three coverings.

1. *Tunica Vasculosa*

Tunica vasculosa is the innermost covering. It is made up of connective tissue and it is rich in blood vessels

2. *Tunica Albuginea*

Tunica albuginea is the middle covering. It is a dense fibrous capsule

3. *Tunica Vaginalis*

Tunica vaginalis is the outermost closed cleft like covering, formed by **mesothelial cells.** It is formed by visceral and parietal layers, which glide on one another and allow free movement of testes. Visceral layer of tunica vaginalis adheres to tunica albuginea and the parietal layer lines the inner surface of the scrotum.

Anterior and lateral surfaces of testis are covered by all the three layers. Posterior surface is covered by tunica albuginea only.

■ PARENCHYMA OF TESTIS

Lobules of Testis

Tunica albuginea on the posterior surface of testis is thickened to form the **mediastinum testis.** From this, the connective tissue septa called **septula testis** radiate into testis and bind with tunica albuginea at various points. Because of this, testis is divided into a number of **pyramidal lobules,** with bases directed towards the periphery and the apices towards the mediastinum (Fig. 74.2).

The septula do not form complete partition so the lobules of testis anastomose with one another at many places. Each testis has about 200 to 300 lobules.

Seminiferous Tubules

Each lobule contains 1 to 4 coiled tubules known as the seminiferous tubules, which are surrounded and supported by interlobular connective tissue. Seminiferous tubules do not end bluntly, but form single, double or triple arches. Limbs of an arch are not in the same lobule (fig. 74.2). Other details of seminiferous tubules are given below.

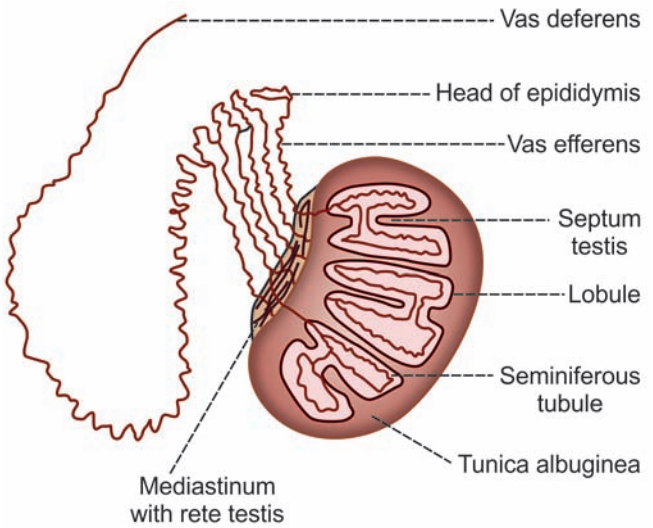


FIGURE 74.2: Structure of testis

Rete Testis

Rete testis is a network of thin-walled channels present in mediastinum. All the seminiferous tubules open into the rete testis.

Vas Efferens

From rete testis, 8 to 15 tubules called vas efferens arise. Vas efferens join together and form the head of epididymis and then converge to form the duct of epididymis (Fig. 74.3).

Epididymis

Duct of epididymis is an enormously convoluted tubule, with a length of about 4 meter. It begins at head, where it receives vas efferens.

Vas Deferens

At the caudal pole of testis, epididymis turns sharply upon itself and continues as vas deferens, without any definite demarcation.

Interstitial Cells of Leydig

Interstitial cells of Leydig are the hormone secreting cells of testis, lying in between the seminiferous tubules.

■ SEMINIFEROUS TUBULES

Seminiferous tubules are thread-like convoluted tubular structures which produce the spermatozoa or sperms. There are about 400 to 600 seminiferous tubules in each testis. Each tubule is 30 to 70 cm long with a diameter of 150 to 300 μ.

Wall of the seminiferous tubule is formed by three layers:

1. Outer capsule or tunica propria, formed by fibro-elastic connective tissue
2. Thin homogeneous basement membrane
3. Complex stratified epithelium, which consists of two types of cells:
   i. Spermatogenic cells or germ cells
   ii. Sertoli cells or supporting cells.

Spermatogenic Cells

Spermatogenic cells or germ cells present in seminiferous tubules are **precursor cells** of spermatozoa. These cells lie in between **Sertoli cells** and are arranged in an orderly manner in 4 to 8 layers.

In children, the testis is not fully developed. Therefore, the **spermatogenic cells** are in primitive stage called **spermatogonia.** With the onset of puberty, spermatogonia develop into sperms through different stages.

Stages of spermatogenic cells

Different stages of spermatogenic cells seen from periphery to the lumen of seminiferous tubules are:

1. Spermatogonium
2. Primary spermatocyte
3. Secondary spermatocyte
4. Spermatid.

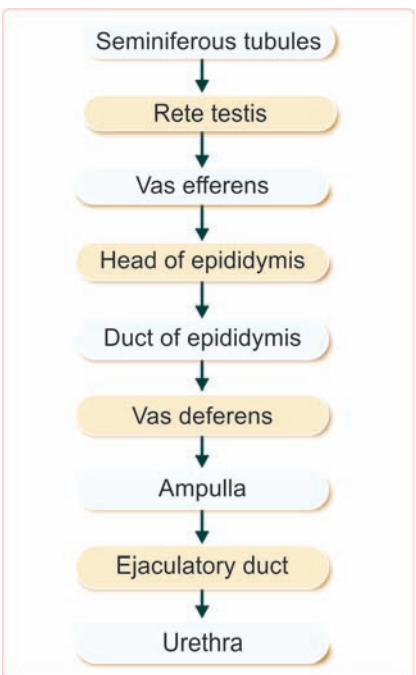


FIGURE 74.3: Pathway for the passage of sperms

Sertoli Cells

Sertoli cells are the **supporting cells** for spermatogenic cells in seminiferous tubules. These cells are also called **sustentacular cells** or **nurse cells.**

Sertoli cells are the large and tall irregular columnar cells, extending from basement membrane to lumen of the seminiferous tubule. Germ cells present in seminiferous tubule are attached to Sertoli cells by means of cytoplasmic connection. This attachment between germ cells and Sertoli cells exists till the matured spermatozoa are released into the lumen of seminiferous tubules.

Functions of Sertoli cells

Sertoli cells provide support, protection and nourishment for the spermatogenic cells present in seminiferous tubules.

Sertoli cells:

1. Support and **nourish** the spermatogenic cells till the spermatozoa are released from them
2. Secrete the enzyme **aromatase,** which converts androgens into estrogen
3. Secrete **androgen-binding protein** (ABP), which is essential for testosterone activity, especially during spermatogenesis
4. Secrete **estrogen-binding protein** (EBP)
5. Secrete **inhibin,** which inhibits FSH release from anterior pituitary
6. Secrete **activin,** which has opposite action of inhibin (increases FSH release)
7. Secrete **müllerian regression factor** (MRF) in fetal testes. MRF is also called **müllerian inhibiting substance** (MIS). MRF is responsible for the regression of müllerian duct during sex differentiation in fetus.

Blood-testes Barrier

Blood-testes barrier is a mechanical barrier that separates blood from seminiferous tubules of the testes. It is formed by tight junctions between the adjacent Sertoli cells, near the basal membrane of seminiferous tubule.

Functions of blood-testes barrier

1. Protection of seminiferous tubules

Blood-testes barrier protects the seminiferous tubules and spermatogenic cells by preventing the entry of toxic substances from blood and fluid of the surrounding tissues into the lumen of seminiferous tubules. However, blood-testes barrier permits substances essential for spermatogenic cells.

Substances prevented by blood-testes barrier:

i. Large molecules including proteins, polysaccharides and cytotoxic substances
ii. Medium-sized molecules like galactose.

Substances permitted by blood-testes barrier:

i. Nutritive substances essential for spermatogenic cells
ii. Hormones necessary for spermatogenesis
iii. Water.

2. Prevention of autoimmune disorders

Blood-testes barrier also prevents the development of autoimmune disorders by inhibiting the movement of antigenic products of spermatogenesis, from testis into blood.

Damage of blood-testes barrier

Blood-testes barrier is commonly damaged by trauma or viral infection like **mumps.** Whenever, the blood-testes barrier is damaged the sperms enter the blood. The immune system of the body is activated, resulting in the production of **autoantibodies** against sperms. The antibodies destroy the germ cells, leading to consequent **sterility.**

■ FUNCTIONS OF TESTES

Testes performs two functions:

1. Gametogenic function: Spermatogenesis
2. Endocrine function: Secretion of hormones.

■ GAMETOGENIC FUNCTIONS OF TESTES – SPERMATOGENESIS

Spermatogenesis is the process by which the male gametes called **spermatozoa** (sperms) are formed from the primitive **spermatogenic cells** (spermatogonia) in the testis (Fig. 74.4). It takes 74 days for the formation of sperm from a **primitive germ cell.** Throughout the process of spermatogenesis, the spermatogenic cells have cytoplasmic attachment with Sertoli cells. **Sertoli cells** supply all the necessary materials for spermatogenesis through the cytoplasmic attachment.

■ STAGES OF SPERMATOGENESIS

Spermatogenesis occurs in four stages:

1. Stage of proliferation
2. Stage of growth
3. Stage of maturation
4. Stage of transformation.

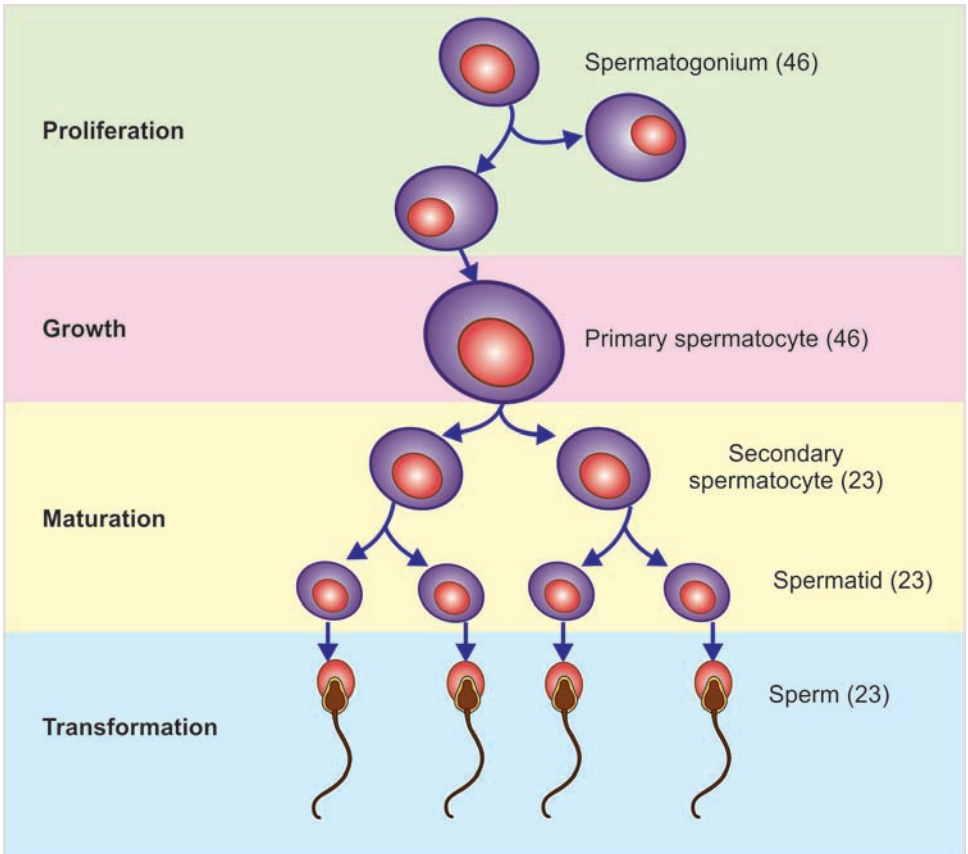


FIGURE 74.4: Spermatogenesis. Number in parenthesis indicate chromosomal number

1. *Stage of Proliferation*

Each **spermatogonium** contains **diploid number** (23 pairs) of chromosomes. One member of each pair is from maternal origin and the other one from paternal origin. The 23 pairs include 22 pairs of **autosomal chromosomes** and one pair of **sex chromosomes.** Sex chromosomes are one X chromosome and one Y chromosome.

During the proliferative stage, spermatogonia divide by mitosis, without any change in chromosomal number. In man, there are usually seven generations of spermatogonia. The last generation enters the stage of growth as **primary spermatocyte.**

During this stage, the spermatogonia migrate along with Sertoli cells towards the lumen of seminiferous tubule.

2. *Stage of Growth*

In this stage, the primary spermatocyte grows into a large cell. Apart from growth, there is no other change in spermatocyte during this stage.

3. *Stage of Maturation*

After reaching the full size, each primary spermatocyte quickly undergoes meiotic or maturation division, which occurs in two phases:

First phase

In the first phase, each **primary spermatocyte** divides into two **secondary spermatocytes.** The significance of the first meiotic division is that each secondary spermatocyte receives only the **haploid** or **half the number of chromosomes.** 23 chromosomes include 22 autosomes and a X or a Y chromosome.

Second phase

During this phase, each secondary spermatocyte undergoes second meiotic division, resulting in two smaller cells called **spermatids.** Each spermatid has **haploid** number of chromosomes.

4. *Stage of Transformation*

There is no further division. Spermatids are transformed into matured **spermatozoa** (sperms), by means of **spermeogenesis** and released by **spermination.**

Spermeogenesis

Spermeogenesis is the process by which spermatids become matured spermatozoa.

Changes taking place during spermeogenesis:

i. Condensation of nuclear material
ii. Formation of acrosome, mitochondrial spiral filament and tail structures
iii. Removal of extraneous (extra volume of nonessential) cytoplasm.

Spermination

Spermination is the process by which the matured sperms are released from Sertoli cells into the lumen of seminiferous tubules.

Refer Chapter 77 for structure of sperm.

■ FACTORS AFFECTING SPERMATOGENESIS

Spermatogenesis is influenced by:

1. Sertoli cells
2. Hormones
3. Other factors.

1. *Role of Sertoli Cell in Spermatogenesis*

Sertoli cells influence spermatogenesis by:

i. Supporting and nourishing the germ cells
ii. Providing hormonal substances necessary for spermatogenesis
iii. Secreting androgen-binding protein (ABP), which is essential for testosterone activity, particularly on spermatogenesis
iv. Releasing sperms into the lumen of seminiferous tubules (spermination).

2. *Role of Hormones in Spermatogenesis*

Spermatogenesis is influenced by many hormones, which act either directly or indirectly: Table 74.1 gives the hormones essential for each stage of spermatogenesis.

Hormones necessary for spermatogenesis are:

i. Follicle-stimulating hormone (FSH)
ii. Testosterone
iii. Estrogen
iv. Luteinizing hormone (LH)
v. Growth hormone (GH)
vi. Inhibin
vii. Activin.

i. *Follicule-stimulating hormone*

Follicule-stimulating hormone is responsible for the **initiation of spermatogenesis.** It binds with Sertoli cells and spermatogonia and induces the proliferation of spermatogonia. It also stimulates the formation of estrogen and androgen-binding protein from Sertoli cells (Fig. 74.5).

ii. *Testosterone*

Testosterone is responsible for the sequence of remaining stages in spermatogenesis. It is also responsible for the **maintenance of spermatogenesis.** Testosterone activity is largely influenced by androgen-binding protein.

iii. *Estrogen*

Estrogen is formed from testosterone in Sertoli cells. It is necessary for **spermeogenesis.**

iv. *Luteinizing Hormone*

In males, this hormone is called **interstitial cell-stimulating** hormone. It is essential for the **secretion of testosterone** from Leydig cells.

v. *Growth Hormone*

Growth hormone is essential for the **general metabolic processes** in testis. It is also necessary for the proliferation of spermatogonia. In pituitary dwarfs, the spermatogenesis is severely affected.

vi. *Inhibin*

Inhibin is a peptide hormone and serves as a transforming growth factor. It is secreted by Sertoli cells. In females, it is secreted by granulosa cells of ovarian follicles. Its secretion is stimulated by FSH.

Inhibin plays an important role in the **regulation of spermatogenesis** by inhibiting FSH secretion through feedback mechanism. FSH secreted from anterior pituitary induces spermatogenesis by stimulating Sertoli cells. It also stimulates the secretion of inhibin from Sertoli cells. So, when the rate of spermatogenesis increases, there is a simultaneous increase in inhibin secretion also. Inhibin in turn, acts on anterior pituitary and inhibits the secretion of FSH, leading to decrease in the pace of spermatogenesis.

TABLE 74.1: Hormones necessary for spermatogenesis

Stage of spermatogenesis	Hormones necessary
Stage of proliferation	Follicle-stimulating hormone Growth hormone
Stage of growth	Testosterone Growth hormone
Stage of maturation	Testosterone Growth hormone
Stage of transformation	Testosterone Estrogen

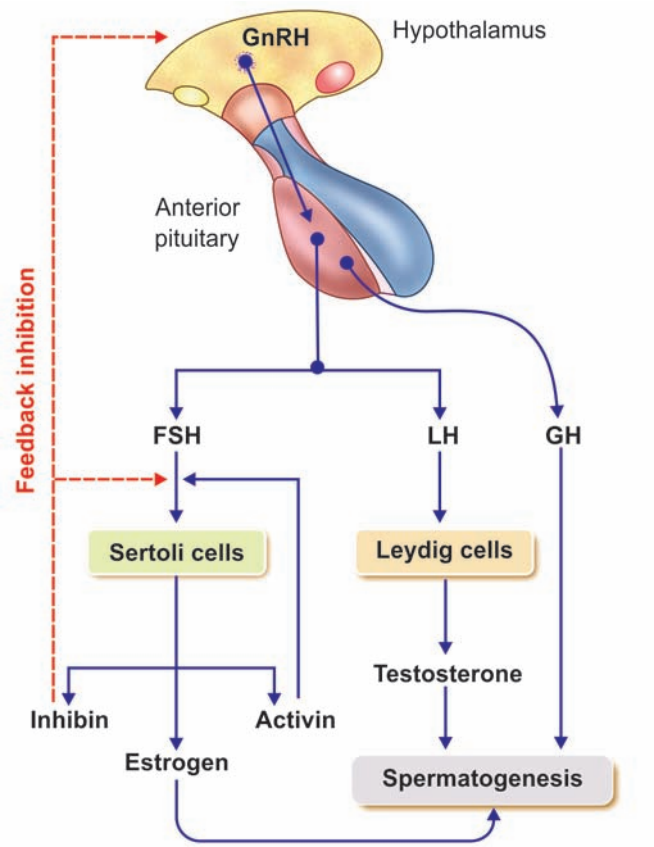


FIGURE 74.5: Role of hormones in spermatogenesis. Blue arrow = Stimulation, Red dotted arrow = inhibition, GnRH = Gonadotropin-releasing hormone, FSH = Follicle-stimulating hormone, LH = Lutinizing hormone, GH = Growth hormone.

It is believed that inhibin also inhibits FSH secretion indirectly by inhibiting GnRH secretion from hypothalamus.

vii. *Activin*

Activin is also a peptide hormone secreted in gonads along with inhibin. The exact location of its secretion in testis is not known. It is suggested that activin is secreted by Sertoli cells and Leydig cells.

Activin has opposite actions of inhibin. It increases the secretion of FSH and accelerates spermatogenesis.

3. *Role of Other Factors in Spermatogenesis*

i. *Increase in body temperature*

Increase in body temperature prevents spermatogenesis. Normally, the temperature in scrotum is about 2°C less than the body temperature. This low temperature is essential for spermatogenesis. When the temperature increases, the spermatogenesis stops. It is very common in **cryptorchidism** (undescended testes).

In cryptorchidism, the testes are in the abdomen, where the temperature is always higher than that of scrotum. High temperature in the abdomen causes degeneration of seminiferous tubules and stoppage of spermatogenesis.

ii. *Diseases*

Infectious diseases such as mumps cause degeneration of seminiferous tubules and stoppage of spermatogenesis.

ENDOCRINE FUNCTIONS OF TESTES

HORMONES SECRETED BY TESTES

Testes secrete male sex hormones, which are collectively called the **androgens.**

Androgens secreted by testes are:

1. Testosterone
2. Dihydrotestosterone
3. Androstenedione.

Among these three androgens, testosterone is secreted in large quantities. However, dihydrotestosterone is more active.

Female sex hormones, namely estrogen and progesterone are also found in testes. Two more hormones activin and inhibin are also secreted in testes. However, these two hormones do not have **androgenic actions.**

Source of Secretion of Androgens

Androgens are secreted in large quantities by testes and in small quantity by adrenal cortex.

Testes

In testes, androgens are secreted by the interstitial cells of Leydig, which form 20% of mass of adult testis. Leydig cells are numerous in newborn male baby and in adult male. But in childhood, these cells are scanty or nonexisting. So, the secretion of androgens occurs in newborn babies and after puberty.

Adrenal cortex

Androgens secreted by zona reticularis of adrenal cortex are testosterone, androstenedione and dehydroepiandrosterone. Adrenal androgens do not have any significant physiological actions because of their small quantity. In abnormal conditions, the hypersecretion of adrenal androgens results in sexual disorders (Chapter 70).

Chemistry

Testosterone is a C_{19} steroid.

Synthesis

Androgens are steroid hormones synthesized from cholesterol. Androgens are also synthesized directly from acetate. Synthesis of male sex hormones is given in Fig. 70.2, Chapter 70.

Plasma Level and Transport

Plasma level of testosterone in an adult male varies between 300 and 700 ng/dL. In adult female, the testosterone level is 30 to 60 mg/dL.

Two thirds of testosterone is transported in plasma by **gonadal steroid-binding globulin.** It is β-globulin in nature and it is also called **sex steroid-binding globulin.** The remaining one third of testosterone is transported by **albumin.**

Metabolism

In many target tissues, testosterone is converted into **dehydrotestosterone,** which is the most active androgen. In some of the tissues such as adipose tissue, hypothalamus and liver, testosterone is converted into **estradiol.** Major portion of testosterone is degraded in liver. It is converted into inactive forms of **androsterone** and **dehydroepiandrosterone.** These two substances are later conjugated and excreted through urine.

■ TESTOSTERONE SECRETION IN DIFFERENT PERIODS OF LIFE

Testosterone secretion starts at 7th week of fetal life by fetal genital ridge. Fetal testes begin to secrete testosterone at about 2nd to 4th month of fetal life. In fetal life, testosterone secretion from testes is stimulated by human chorionic gonadotropins, secreted by placenta.

But in childhood, practically no testosterone is secreted approximately until 10 to 12 years of age. Afterwards, the testosterone secretion starts and it increases rapidly at the onset of puberty and lasts through most of the remaining part of life. The secretion starts decreasing after 40 years and becomes almost zero by the age of 90 years (Fig. 74.6).

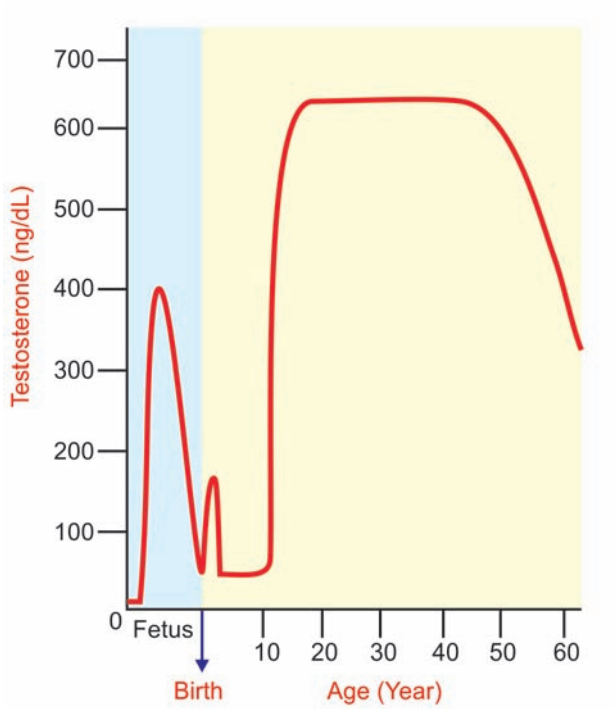


FIGURE 74.6: Plasma testosterone in different ages of male humans

■ FUNCTIONS OF TESTOSTERONE

In general, testosterone is responsible for the distinguishing characters of masculine body. It also plays an important role in fetal life.

Functions of Testosterone in Fetal Life

Testosterone performs three functions in fetus:

1. Sex differentiation in fetus
2. Development of accessory sex organs
3. Descent of the testes.

1. *Sex differentiation in fetus*

Sex chromosomes are responsible for the determination of sex of the fetus (Chapter 84), whereas testosterone is responsible for the sex differentiation of fetus.

Fetus has two genital ducts:

i. **Müllerian duct,** which gives rise to female accessory sex organs such as vagina, uterus and fallopian tube

ii. **Wolffian duct,** which gives rise to male accessory sex organs such as epididymis, vas deferens and seminal vesicles.

If testosterone is secreted from the genital ridge of the fetus at about 7th week of intrauterine life, the müllerian duct system disappears and male sex organs develop from Wolffian duct.

In addition to testosterone, **müllerian regression factor** (MRF) secreted by Sertoli cells is also responsible for regression of müllerian duct.

In the absence of testosterone, Wolffian duct regresses and female sex organs develop from müllerian duct.

2. *Development of accessory sex organs and external genitalia*

Testosterone is also essential for the growth of the external genitalia, viz. penis and scrotum and other accessory sex organs, namely genital ducts, seminal vesicles and prostate.

3. Descent of testes

Descent of testes is the process by which testes enter scrotum from abdominal cavity. Initially, testes are developed in the abdominal cavity and are later pushed down into the scrotum through inguinal canal, just before birth. The process by which testes enter the scrotum is called the descent of testes. Testosterone is necessary for descent of testes.

Cryptorchidism

Cryptorchidism is a congenital disorder characterized by the failure of one or both the testes to descent from abdomen into scrotum. In such case, the testes are called **undescended testes.** Males with untreated testes are prone for **testicular cancer.**

Treatment

Administration of testosterone or gonadotropic hormones (which stimulate Leydig cells) causes descent of testes, provided the **inguinal canal** is large enough to allow the passage of testes. Surgery is required if the inguinal canal is narrow.

Functions of Testosterone in Adult Life

Testosterone has two important functions in adult:
1. Effect on sex organs
2. Effect on secondary sexual characters.

1. *Effect on sex organs*

Testosterone increases the size of penis, scrotum and the testes after puberty. All these organs are enlarged at least 8 folds between the onset of puberty and the age of 20 years, under the influence of testosterone. Testosterone is also necessary for spermatogenesis.

2. *Effect on secondary sexual characters*

Secondary sexual characters are the physical and behavioral characteristics that distinguish the male from female. These characters appear at the time of puberty in humans. Testosterone is responsible for the development of secondary sexual characters in males.

Secondary sexual characters in males:

i. *Effect on muscular growth*

One of the most important male sexual characters is the development of musculature after puberty. Muscle mass increases by about 50%, due to the anabolic effect of testosterone on proteins. Testosterone accelerates the transport of amino acids into the muscle cells, synthesis of proteins and storage of proteins. Testosterone also decreases the breakdown of proteins.

ii. *Effect on bone growth*

After puberty, testosterone increases the thickness of bones by increasing the bone matrix and deposition of calcium. It is because of the **protein anabolic activity** of testosterone. Deposition of calcium is secondary to the increase in bone matrix.

In addition to increase in the size and strength of bones, testosterone also causes early fusion of epiphyses of long bones with shaft. So, if testes are removed before puberty, the fusion of epiphyses is delayed and the height of the person increases.

iii. *Effect on shoulder and pelvic bones*

Testosterone causes broadening of shoulders and it has a specific effect on pelvis, which results in:
a. Lengthening of pelvis
b. Funnel-like shape of pelvis.
c. Narrowing of pelvic outlet.

Thus, pelvis in males is different from that of females, which is broad and round or oval in shape.

iv. *Effect on skin*

Testosterone increases the thickness of skin and ruggedness of subcutaneous tissue. These changes in skin are due to the deposition of proteins in skin. It also increases the quantity of melanin pigment, which is responsible for the deepening of the skin color.

Testosterone enhances the secretory activity of sebaceous glands. So, at the time of puberty, when the body is exposed to sudden increase in testosterone secretion, the excess secretion of sebum leads to development of **acne** on the face. After few years, the skin gets adapted to testosterone secretion and the acne disappears.

v. *Effect on hair distribution*

Testosterone causes male type of hair distribution on the body, i.e. hair growth over the pubis, along linea alba up to umbilicus, on face, chest and other parts of the body such as back and limbs. In males, the pubic

hair has the base of the triangle downwards where as in females it is upwards. Testosterone decreases the hair growth on the head and may cause baldness, if there is genetic background.

vi. *Effect on voice*

At the time of adolescence, the boys have a **cracking voice.** It is because of the testosterone effect, which causes:

a. Hypertrophy of laryngeal muscles
b. Enlargement of larynx and lengthening
c. Thickening of vocal cords.

Later, the cracking voice changes gradually into a typical adult male voice with a bossing sound.

vii. *Effect on basal metabolic rate*

At the time of puberty and earlier part of adult life, the testosterone increases the basal metabolic rate to about 5% to 10% by its anabolic effects on protein metabolism.

viii. *Effect on electrolyte and water balance*

Testosterone increases the sodium reabsorption from renal tubules, along with water reabsorption. It leads to increase in ECF volume.

ix. *Effect on blood*

Testosterone has got **erythropoietic action.** So, after puberty, testosterone causes mild increase in RBC count. It also increases the blood volume by increasing the water retention and ECF volume.

■ MODE OF ACTION OF TESTOSTERONE

Testosterone combines with receptor proteins. The testosterone-receptor complex migrates to nucleus, binds with a nuclear protein and induces the DNA-RNA transcription process. In 30 minutes, the RNA polymer is activated and the concentration of RNA increases. The quantity of DNA also increases.

So, the testosterone primarily stimulates the protein synthesis in the target cells, which are responsible for the development of secondary sexual characters.

Testosterone is converted into dihydrotestosterone (DHT) in the target cells of some accessory sex organs such as epididymis and penis. DHT combines with receptor proteins and the DHT-receptor complex induces the DNA-RNA transcription process. DHT-receptor complex is more stable than testosterone-receptor complex.

In brain, testosterone is converted into estrogen (estradiol).

■ REGULATION OF TESTOSTERONE SECRETION

In Fetus

During fetal life, the testosterone secretion from testes is stimulated by **human chorionic gonadotropin,** which has the properties similar to those of luteinizing hormone. Human chorionic gonadotropin stimulates the development of Leydig cells in the fetal testes and promotes testosterone secretion.

In Adults

Luteinizing hormone (LH) or **interstitial cell stimulating** hormone (ICSH) stimulates the Leydig cells and the quantity of testosterone secreted is directly proportional to the amount of LH available.

Secretion of LH from anterior pituitary gland is stimulated by luteinizing hormone releasing hormone (LHRH) from hypothalamus.

Feedback Control

Testosterone regulates its own secretion by **negative feedback** mechanism. It acts on hypothalamus and inhibits the secretion of LHRH. When LHRH secretion is inhibited, LH is not released from anterior pituitary, resulting in stoppage of testosterone secretion from testes. On the other hand, when testosterone production is low, lack of inhibition of hypothalamus leads to secretion of testosterone through LHRH and LH (Fig. 74.7).

■ ANABOLIC STEROIDS

Anabolic steroids are the synthetic forms of testosterone, which are used to increase the growth of muscles and bones. Like androgens, these steroids also increase the growth of muscles and bones by accelerating protein synthesis (anabolic effect). These drugs are also called **anabolic-androgenic steroids** (AAS).

Therapeutic Uses of Anabolic Steroids

1. Growth stimulation
2. Bone marrow stimulation
3. Hormone replacement therapy
4. Induction of puberty in males.

Abuse of Anabolic Steroids

Anabolic steroids are commonly used by athletes to improve their performances during competitions, particularly in professional sports. Organizations of many sports have banned the use of anabolic steroids by their athletes.

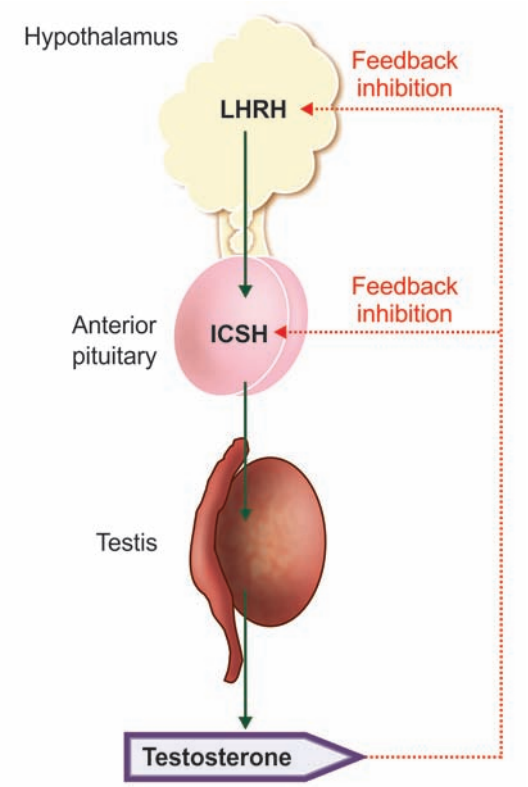


FIGURE 74.7: Regulation of testosterone secretion. LHRH = Luteinizing hormone-releasing hormone, ICSH = Interstitial cell-stimulating hormone.

■ PRODUCTION OF FEMALE SEX HORMONES IN MALES

In addition to androgens, female sex hormones are also produced in testes.

Estrogen

Small amount of estrogen is produced in males. Estrogen level in plasma of normal adult male is 12 to 34 pg/mL. Estrogens have three sources of production in males.

1. *Adrenal Cortex*

Adrenal cortex secretes small quantity of estrogen. Refer Chapter 70 for details.

2. *Testes*

Up to 20% of estrogen in males is produced in testes. Estrogen is formed from androgens in Sertoli cells of testes, by the influence of the enzyme aromatase.

3. *Other Organs*

About 80% of estrogen is formed from androgens in other organs, particularly liver.

Progesterone

Progesterone is also produced from androgens in males though the quantity is very less. Plasma progesterone level in normal adult male is 0.3 ng/mL.

■ MALE ANDROPAUSE OR CLIMACTERIC

Male andropause or climacteric is the condition in men, characterized by emotional and physical changes in the body, due to low androgen level with aging. It is also called **viropause.**

After the age of 50, testosterone secretion starts declining. It is accompanied by decrease in number and secretory activity of Leydig cells. Low level of testosterone increases the secretion of FSH and LH, which leads to some changes in the body. It does not affect most of the men. But some men develop symptoms similar to those of **female menopausal syndrome** (Chapter 82). Common symptoms are hot flashes, illusions of suffocation and mood changes.

■ APPLIED PHYSIOLOGY

■ EFFECTS OF EXTIRPATION OF TESTES

Extirpation (removal) of testes is called castration. Effects of castration depend upon the age when testes are removed.

1. *Effects of Extirpation of Testes before Puberty – Eunuchism*

If a boy looses the testes before puberty, he continues to have infantile sexual characters throughout his life and this condition is called eunuchism. Height of the person is slightly more but the bones are weak and thin. Muscles become weak and shoulder remains narrow.

Sex organs do not increase in size and the male secondary sexual characters do not develop. The voice remains like that of a child.

There is abnormal deposition of fat on buttocks, hip, pubis and breast, resembling the feminine distribution.

2. *Effects of Extirpation of Testes Immediately after Puberty*

If testes are removed after puberty, some of the male secondary sexual characters revert to those of a child and other masculine characters are retained.

Sex organs are depressed. Seminal vesicles and prostate undergo atrophy. Penis remains smaller. Voice remains mostly masculine but other secondary sexual characters like masculine hair distribution, musculature and thickness of bones are lost. There may be loss of sexual desire and sexual activities.

3. *Effect of Extirpation of Testes in Adults*

Removal of testes in adults does not cause loss of secondary sexual characters. But, accessory sex organs start degenerating. The sexual desire is not totally lost. Erection occurs but ejaculation is rare because of degeneration of accessory sex organs and lack of sperms.

■ HYPERGONADISM IN MALES

Hypergonadism is the condition characterized by hypersecretion of sex hormones from gonads.

Cause

Hypergonadism in males is mainly due to the tumor of Leydig cells. It is common in **prepubertal boys** who develop **precocious pseudopuberty.**

Symptoms

There is a rapid growth of musculature and bones. But, the height of the person is less because of early closure of epiphysis. There is excess development of sex organs and secondary sexual characters.

The tumors also secrete estrogenic hormones, which cause **gynecomastia** (the enlargement of breasts).

■ HYPOGONADISM IN MALES

Hypogonadism is a condition characterized by reduction in the functional activity of gonads.

Causes

Hypogonadism in males is due to various abnormalities of testes:

1. Congenital nonfunctioning of testes
2. Under-developed testes due to absence of human chorionic gonadotropins in fetal life
3. Cryptorchidism, associated with partial or total degeneration of testes
4. Castration
5. Absence of androgen receptors in testes
6. Disorder of the gonadotropes (cells secreting gonadotropins) in anterior pituitary
7. Hypothalamic disorder.

Signs and Symptoms

Clinical picture of male hypogonadism depends upon whether the testicular deficiency develops before or after puberty.

Before puberty

Features of hypogonadism are similar to those developed due to extirpation of testes before puberty, which are described above.

After puberty

Symptoms are similar to those developed due to the removal of testes after puberty (see above).

In adults

Same symptoms, which develop after extirpation of testes, occur in this condition.

Hypogonadism caused by testicular disorders increases the gonadotropin secretion and the condition is called **hypergonadotropic hypogonadism.** Hypogonadism that occurs due to deficiency of gonadotropins (pituitary or hypothalamic disorder) is called **hypogonadotropic hypogonadism.**

Fröhlich Syndrome

Fröhlich syndrome is the disorder characterized by obesity and hypogonadism in adolescent boys. It is also called **adiposogenital syndrome** or **hypothalamic eunuchism.** Refer Chapter 66 for details.

■ ACCESSORY SEX ORGANS IN MALES

Seminal Vesicles

Seminal vesicles are explained in Chapter 75.

Prostate gland

Prostate gland is explained in Chapter 76.

Urethra

Urethra in male has both reproductive and urinary functions. Refer Chapter 57 for details of urethra. Urethra contains mucus glands throughout its length, which are called **glands of Littre.** The bilateral **bulbourethral glands** or **Cowper** glands also open into the urethra.

Penis

Penis is the male genital organ. Urethra passes through penis and opens to the exterior. Penis is formed by three erectile tissue masses, i.e. a paired **corpora cavernosa** and an unpaired **corpus spongiosum.** Corpus spongiosum surrounds the urethra and terminates distally to form **glans penis.**

Seminal Vesicles

Chapter 75

STRUCTURE OF SEMINAL VESICLES

Seminal vesicles are the paired glands situated in lower abdomen on either side of prostate gland behind urinary bladder. Each seminal vesicle is a hollow sac of irregular shape and is lined by complexly folded mucous membrane.

Epithelial cells of the mucous membrane are secretory in nature and secrete seminal fluid. Duct of seminal vesicle from each side joins with **ampulla of vas deferens** to form **ejactulatory duct.** Thus seminal fluid is emptied into ejaculatory ducts, which open into urethra. Refer Chapter 57 for details.

PROPERTIES AND COMPOSITION OF SEMINAL FLUID

PROPERTIES

Seminal fluid is mucoid and viscous in nature. It is neutral or slightly alkaline in reaction. It adds to the bulk of semen as it forms 60% of the total semen.

COMPOSITION

Seminal vesicles secrete several important substances. Refer Figure 77.1 for the products of seminal fluid.

FUNCTIONS OF SEMINAL FLUID

NUTRITION TO SPERMS

Fructose and other nutritive substances in seminal fluid are utilized by sperms after being ejaculated into the female genital tract.

CLOTTING OF SEMEN

Immediately after ejaculation, semen **clots** because of the conversion of fibrinogen from seminal fluid into fibrin.

FERTILIZATION

Prostaglandin of seminal fluid enhances fertilization of ovum by:

1. Increasing the receptive capacity of cervical mucosa for sperms
2. Initiating **reverse peristaltic movement** of uterus and fallopian tubes. This in turn, increases the rate of transport of sperms in female genital tract during coitus (oxytocin is also responsible for this process).

Chapter 76

Prostate Gland

STRUCTURE OF PROSTATE GLAND

Human prostate gland weighs about 40 g. It consists of 20 to 30 separate glands, which open separately into the urethra. These glands are **tubuloalveolar** in nature. Epithelial lining of these glands is made up of columnar cells. Prostate secretes **prostatic fluid,** which is emptied into **prostatic urethra** through **prostatic sinuses** (Chapter 57).

PROPERTIES AND COMPOSITION OF PROSTATIC FLUID

PROPERTIES

Prostate fluid is a thin, milky and alkaline fluid. It forms 30% of total semen.

COMPOSITION

Refer Figure 77.1 for the products secreted by prostate gland.

FUNCTIONS OF PROSTATIC FLUID

MAINTENANCE OF SPERM MOTILITY

Prostatic fluid provides optimum pH for the motility of sperms. Generally, sperms are nonmotile at a pH of less than 6.0. There are some factors, which decrease the pH and motility of sperm both in vas deferens and female genital tract.

In vas deferens

End products of metabolic activities in the sperm make the fluid in vas deferens acidic, so that the sperms are nonmotile.

In female genital tract

Vaginal secretions in females are highly acidic with a pH of 3.5 to 4.0. So, when semen is ejaculated into female genital tract at coitus, sperms are nonmotile initially.

However, the alkaline prostatic secretion, which is also present in semen neutralizes the acidity in vagina and maintains a pH of 6.0 to 6.5. At this pH, the sperms become motile and chances of fertilization are enhanced.

CLOTTING OF SEMEN

The clotting enzymes present in prostatic fluid convert fibrinogen (from seminal vesicles) into **coagulum.** It is essential for holding the sperms in uterine cervix.

LYSIS OF COAGULUM

The coagulum is dissolved by fibrinolysin of prostatic fluid, so that the sperms become motile.

■ APPLIED PHYSIOLOGY – ENLARGEMENT OF PROSTATE GLAND

Enlargement of prostate gland is of two types:

1. Benign enlargement
2. Malignant enlargement.

1. *Benign enlargement*

Hyperplasia of glandular structures and connective tissues causes benign **(nonmalignant)** enlargement of prostate gland. It occurs in some men after 60 years of age, due to unknown causes.

Enlarged prostate gland stretches the urethra and obstructs urine outflow from bladder.

Common symptoms are increase in the frequency of urination, difficulty in urination, dribbling of urine after urination and occasional renal failure.

2. *Malignant enlargement*

Malignant enlargement **(cancer)** of prostate gland also causes obstruction of urinary passage. In addition, the **metastasis** (spread of cancer from primary site to other places) affects the other tissues, particularly bones.

Chapter 77

Semen

INTRODUCTION

Semen is a white or grey fluid that contains sperms. It is the collection of fluids from testes, seminal vesicles, prostate gland and bulbourethral glands. Semen is discharged during sexual act and the process of discharge of semen is called **ejaculation.**

Testes contribute sperms. Prostate secretion gives milky appearance to the semen. Secretions from seminal vesicles and bulbourethral glands provide mucoid consistency to semen.

NATURE OF SEMEN

At the time of ejaculation, human semen is liquid in nature. Immediately, it coagulates and after some time it becomes liquid once again **(secondary liquefaction).**

Fibrinogen secreted from the seminal vesicle is converted into a weak **coagulum** by the clotting enzymes secreted from prostate gland. Coagulum is liquefied after about 30 minutes, as it is lysed by fibrinolysin produced in prostate gland.

When semen is ejaculated, the sperms are non-motile due to the viscosity of coagulum. When the coagulum dissolves, the sperms become motile.

PROPERTIES OF SEMEN

1. Specific gravity : 1.028
2. Volume : 2 mL to 6 mL per ejaculation
3. Reaction : It is alkaline with a pH of 7.5. Alkalinity is due to the prostate fluid.

COMPOSITION OF SEMEN

Semen contains 10% sperms and 90% of fluid part, which is called **seminal plasma.** Seminal plasma contains the products from seminal vesicle and prostate gland (Fig. 77.1). It also has small amount of secretions from the mucus glands, particularly the bulbourethral glands.

SPERM

Sperm is the **male gamete (reproductive cell),** developed in the testis. It is also called **spermatozoon** (plural = spermatozoa). Matured sperm is 60 μ long.

Sperm Count

Total count of sperm is about 100 to 50 million/mL of semen. **Sterility** occurs when the sperm count falls below 20 million/mL.

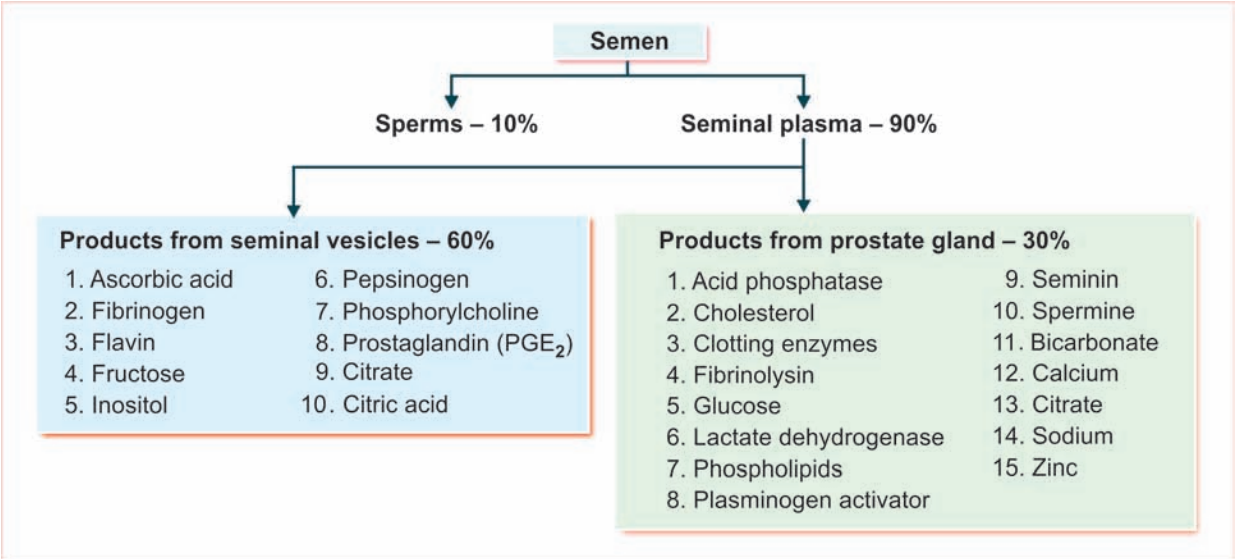


FIGURE 77.1: Composition of semen

Though the sperms can be stored in male genital tract for longer periods, after ejaculation the survival time is only about 24 to 48 hours at a temperature equivalent to body temperature.

Rate of motility of sperm in female genital tract is about 3 mm/minute. Sperms reach the fallopian tube in about 30 to 60 minutes after sexual intercourse. Uterine contractions during sexual act facilitate the movement of sperms.

Structure of Sperm

Sperm consists of four parts (Fig. 77.2):

1. Head
2. Neck
3. Body
4. Tail.

1. *Head*

Head of sperm is oval in shape (in front view), with a length of 3 to 5 μ and width of up to 3 μ. Anterior portion of head is thin.

Head is covered by a thin cell membrane and it is formed by a condensed nucleus with a thin cytoplasm. Anterior two thirds of the head is called **acrosome** or **galea capitis.**

Acrosome

Acrosome is the thick cap like anterior part of sperm head. It develops from Golgi apparatus and it is made up of mucopolysaccharide and acid phosphatase. Acrosome also contains hyaluronidase and proteolytic

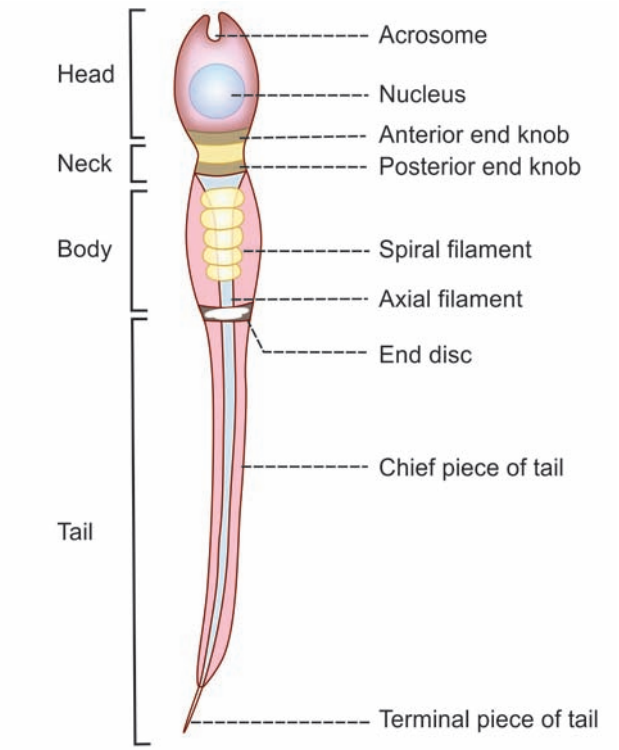


FIGURE 77.2: Human sperm

enzymes, which are essential for the sperm to fertilize the ovum.

2. *Neck*

Head is connected to the body by a short neck. Its anterior end is formed by thick disk-shaped anterior end

knob, which is also called **proximal centriole.** Posterior end is formed by another similar structure known as **posterior end knob.** It gives rise to the **axial filament** of body.

Often, the neck and body of sperm are together called **midpiece.**

3. *Body*

Body is cylindrical with a length of 5 to 9 μ and the thickness of 1 μ. The body of the sperm consists of a central core called **axial filament,** covered by thin cytoplasmic capsule.

Axial filament starts from posterior end knob of the neck. It passes through the body and a perforated disc called **end disk** or **end ring centriole.** Finally, the axial filament reaches the tail as **axial thread.**

In the body, the axial filament is surrounded by a closely wound spiral filament consisting of mitochondria.

4. *Tail*

Tail of the sperm consists of two segments:

i. *Chief or main piece:* It is enclosed by cytoplasmic capsule and has an axial thread. It is 40 to 50 μ long
ii. *Terminal or end piece:* It has only the axial filament.

■ PRODUCTS FROM SEMINAL VESICLES

Products of seminal vesicles are given in Figure 77.1.

■ PRODUCTS FROM PROSTATE GLAND

Products of prostate gland are given in Figure 77.1.

■ SEMEN ANALYSIS

Analysis of semen evaluates the qualities of semen, which is useful to investigate the infertility.

Parameters of semen analysis:

1. Volume
2. Reaction and pH
3. Liquefaction
4. Sperm count
5. Morphology of sperm
6. Motility of sperms
7. Pus cells and RBCs
8. Fructose level.

■ QUALITIES OF SEMEN REQUIRED FOR FERTILITY

Minimum required qualities of semen for fertility are:

1. Volume of semen per ejaculation must be at least 2 mL
2. Sperm count must be at least 20 million/mL
3. Number of sperms in each ejaculation must be at least 40 million
4. 75% of sperms per ejaculation must be alive
5. 50% of sperms must be motile
6. 30% of sperms must have normal shape and structure
7. Sperms with head defect must be less than 35%
8. Sperms with midpiece defect must be less than 20%
9. Sperms with tail defect must be less than 20%.

■ APPLIED PHYSIOLOGY

Azoospermia

Azoospermia is the condition characterized by lack of sperm in semen. It is a **congenital** disease. It is also caused by excess use of corticosteroids and androgens.

Oligozoospermia

Oligozoospermia is the low sperm count with less than 20 million of sperms/mL of semen. Oligozoospermia causes **infertility.**

Teratozoospermia

Teratozoospermia is the condition characterized by presence of sperms with abnormal morphology. It is also called **teratospermia.** It occurs in **Crohn's disease, Hodgkin disease** and **celiac disease.** The abnormal morphology of sperm results in **infertility.**

Aspermia

Aspermia is the lack of semen. It occurs due to retrograde ejaculation. **Retrograde ejaculation** is the entrance of semen into urinary bladder instead of entering urethra. It is due to dysfunction of sphincter of the bladder, which is caused by prostatic surgery or excess use of drugs. Aspermia leads to **infertility.**

Oligospermia

Oligospermia is a genetic disorder characterized by low volume of semen.

Hematospermia

Hematospermia is the appearance of blood in sperm. It occurs due to infection of urethra or prostate. It is also common in **congenital bleeding disorder.**

Female Reproductive System

Chapter 78

FEMALE REPRODUCTIVE ORGANS

Female reproductive system comprises of primary sex organs and accessory sex organs (Fig. 78.1).

PRIMARY SEX ORGANS

Primary sex organs are a pair of ovaries, which produce eggs or ova and secrete female sex hormones, the estrogen and progesterone. Details of structure and functions of ovary are given in Chapter 79.

ACCESSORY SEX ORGANS

Accessory sex organs in females are:

1. *A system of genital ducts:* Fallopian tubes, uterus, cervix and vagina (Figs. 78.2 and 78.3)

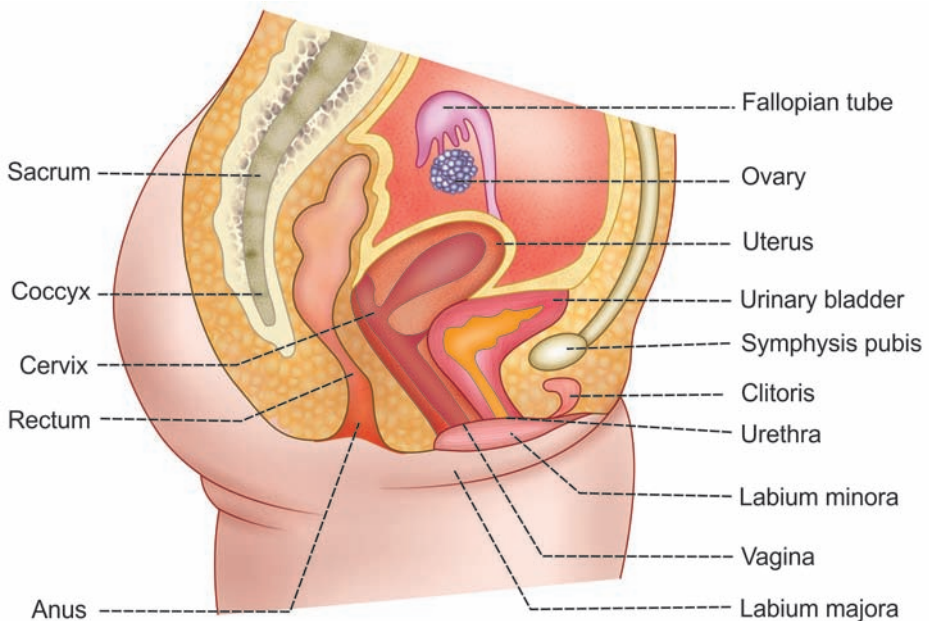


FIGURE 78.1: Female reproductive organs and other organs of pelvis

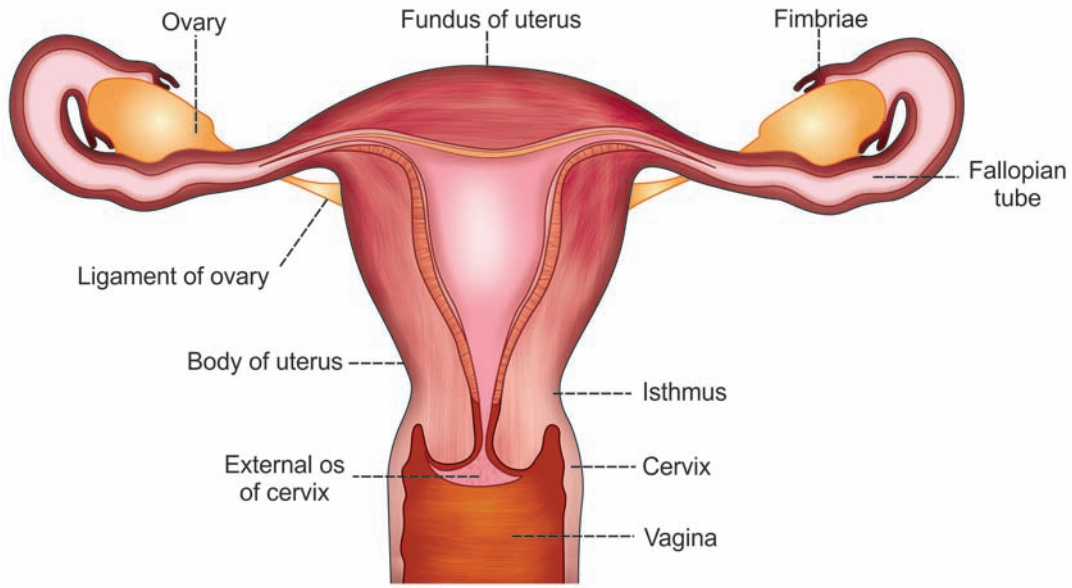


FIGURE 78.2: Female reproductive system

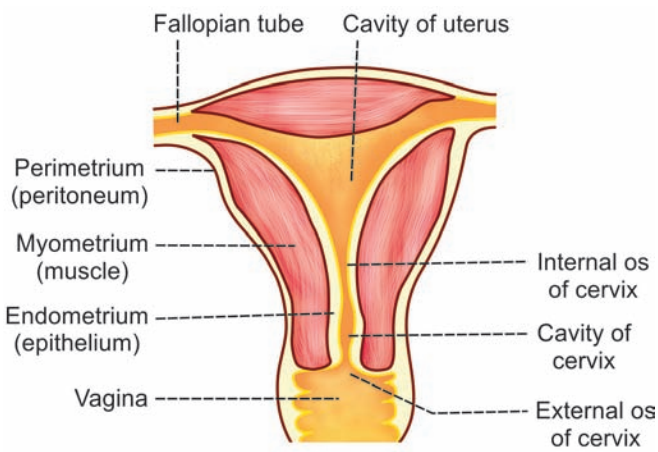


FIGURE 78.3: Section of uterus

2. *External genitalia:* Labia majora, labia minora and clitoris.

Mammary glands are not the female genital organs but are the important glands of female reproductive system.

■ FUNCTIONAL ANATOMY OF ACCESSORY SEX ORGANS

Uterus

Uterus is otherwise known as **womb.** It lies in the pelvic cavity, in between the rectum and urinary bladder. Uterus is a hollow muscular organ with a thick wall. It has a central cavity, which opens into vagina through cervix. On either side at its upper part, the fallopian tubes open. Uterus communicates with peritoneal cavity through fallopian tubes.

Virgin uterus is pyriform in shape and is flattened anteroposteriorly. It measures about 7.5 cm in length, 5 cm in breadth at its upper part and about 2.5 cm in thickness. There is a constriction almost at the middle of uterus called **isthmus.**

Divisions of uterus

Uterus is divided into three portions:
1. Fundus (above the entrance points of fallopian tubes)
2. Body (between fundus and isthmus)
3. Cervix (below isthmus).

Structure of uterus

Uterus is made up of three layers:
1. Serous or outer layer
2. Myometrium or middle muscular layer
3. Endometrium or inner mucus layer.

1. *Serous or outer layer*

Serous or outer layer is the covering of uterus derived from peritoneum. Anteriorly, it covers the uterus completely, but posteriorly it covers only up to the isthmus.

2. *Myometrium or middle muscular layer*

Myometrium is the thickest layer of uterus and it is made up of smooth muscle fibers.

Smooth muscle fibers of myometrium are arranged in three layers:

i. External myometrium with transversely arranged muscle fibers

ii. Middle myometrium with muscle fibers arranged longitudinally, obliquely and transversely
iii. Internal myometrium with circular muscle fibers.

Muscular layer is interdisposed with blood vessels, nerve fibers, lymphatic vessels and areolar tissues.

3. *Endometrium or inner mucus layer*

Endometrium is smooth and soft with pale red color. It is made up of ciliated columnar epithelial cells.

Surface of the endometrium has minute orifices, through which tubular follicles of endometrium open. Endometrium also contains connective tissue in which the uterine glands are present. Uterine glands are lined by ciliated columnar epithelial cells.

Changes in uterus

Uterus changes its size, structure and function in different phases of sexual life.

Just before menstruation, uterus is enlarged, becomes more vascular. The endometrium thickens with more blood supply. This layer is desquamated during menstruation and reformed after menstrual period.

During pregnancy, uterus is enlarged very much with increase in weight. After parturition (delivery), it comes back to its original size but the cavity remains larger. In old age, uterus is atrophied.

Cervix

Cervix is the lower constricted part of uterus. It is divided into two portions:

1. Upper supravaginal portion, which communicates with body of uterus through **internal os** (orifice) of cervix. Mucus membrane of this portion has glandular follicles, which secrete mucus.
2. Lower vaginal portion, which projects into the anterior wall of the vagina and it communicates with vagina through **external os** (orifice) of cervix. Mucus membrane of this portion is formed by stratified epithelial cells.

Vagina

Vagina is a short tubular organ. It is lined by mucus membrane, which is formed by stratified epithelial cells.

SEXUAL LIFE IN FEMALES

Lifespan of a female is divided into three periods.

FIRST PERIOD

First period extends from birth to puberty. During this period, primary and accessory sex organs do not function. These organs remain quiescent. Puberty occurs at the age of 12 to 15 years.

SECOND PERIOD

Second period extends from onset of puberty to the onset of menopause. First menstrual cycle is known as **menarche.** Permanent stoppage of the menstrual cycle in old age is called **menopause,** which occurs at the age of about 45 to 50 years. During the period between menarche and menopause, women menstruate and reproduce.

THIRD PERIOD

Third period extends after menopause to the rest of the life.

Ovary

Chapter 79

INTRODUCTION

Ovary is the gonad or **primary sex organs** in females. A woman has two ovaries. Ovaries have two functions, gametogenic and endocrine functions. Gametogenic function is the production and release of **ovum** or egg, which is the **female gamete** (reproductive cell). Endocrine function of ovaries is the secretion of female sex hormones.

FUNCTIONAL ANATOMY OF OVARY

Ovaries are flattened ovoid bodies, with dimensions of 4 cm in length, 2 cm in width and 1 cm in thickness. Each ovary is attached at hilum to the broad ligament, by means of mesovarium and ovarian ligament.

Each ovary has two portions:

1. Medulla
2. Cortex.

MEDULLA

Medulla or zona vasculosa is the central deeper portion of the ovary. It has the stroma of loose connective tissues. It contains blood vessels, lymphatics, nerve fibers and bundles of smooth muscle fibers near the hilum.

CORTEX

Cortex is the outer broader portion and has compact cellular layers. It is interrupted at the hilum, where the medulla is continuous with **mesovarium.** Cortex is lined by the germinal epithelium underneath a fibrous layer known as **'tunica albuginea'.**

Cortex consists of the following structures:

i. Glandular structures, which represent ovarian follicles at different stages
ii. Connective tissue cells
iii. Interstitial cells, which are clusters of epithelial cells with fine lipid granules formed mainly from theca interna.

Ovarian Follicles

In the intrauterine life, outer part of cortex contains the **germinal epithelium,** which is derived from the **germinal ridges.** When fetus develops, the germinal epithelium gives rise to a number of primordial ova. The primordial ova move towards the inner substance of cortex. A layer of spindle cells called **granulose cells** from the ovarian stroma surround the ova. Primordial ovum along with granulosa cells is called the **primordial follicle** (Fig. 79.1).

At 7th or 8th month of intrauterine life, about 6 million primordial follicles are found in the ovary. But at the time of birth, only 1 million primordial follicles are seen in both the ovaries and the rest of the follicles degenerate. At the time of puberty, the number decreases further to about 300,000 to 400,000. After menarche, during every menstrual cycle, one of the follicles matures

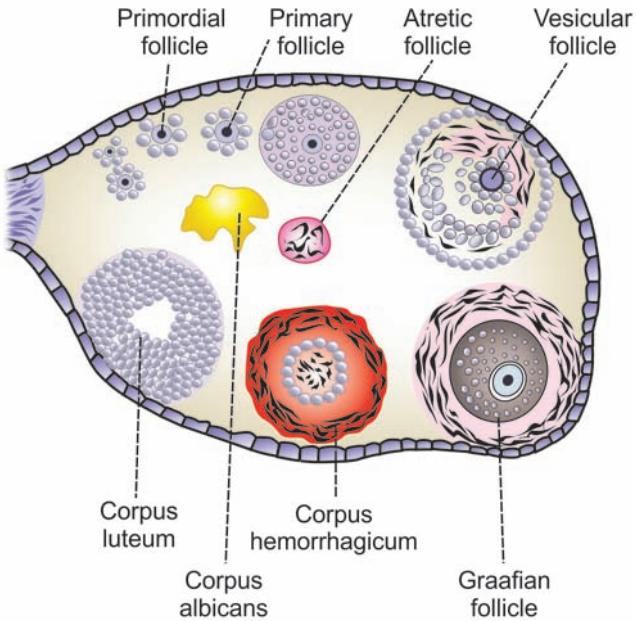


FIGURE 79.1: Ovarian follicles and corpus luteum

and releases its ovum. During every menstrual cycle, only one ovum is released from any one of the ovaries.

During every cycle, many of the follicles degenerate. The degeneration of the follicles is called **atresia** and the degenerated follicles are known as **atretic follicles.** The atretic follicles become fibrous and the fibrotic follicles are called the **corpus fibrosa.** Atresia occurs at all levels of follicles. Usually, the degenerated follicles disappear without leaving any scar.

Functions of Ovaries

Ovaries are the primary sex organs in females. Functions of ovaries are:

1. Secretion of female sex hormones
2. Oogenesis
3. Menstrual cycle.

Sex hormones are discussed in this Chapter. Oogenesis and menstrual cycle are explained in the next Chapter.

■ OVARIAN HORMONES

Ovary secretes the female sex hormones estrogen and progesterone. Ovary also secretes few more hormones, namely inhibin (Chapter 80), relaxin (Chapter 84) and small quantities of androgens.

■ ESTROGEN

Source of Secretion

In a normal non-pregnant woman, estrogen is secreted in large quantity by theca interna cells of ovarian follicles and in small quantity by corpus luteum of the ovaries. Estrogen secretion is predominant at the later stage of follicular phase before ovulation (Chapter 80).

Estrogen is derived from androgens, particularly androstenedione, which is secreted in theca interna cells. Androstenedione migrates from theca cells to granulosa cells, where it is converted into estrogen by the activity of the enzyme aromatase.

A small quantity of estrogen is also secreted by adrenal cortex. In pregnant woman, a large amount of estrogen is secreted by the placenta.

Chemistry

Estrogen is a C_{18} steroid.

Different Forms

Estrogen is present in three forms in plasma:

1. β-estradiol
2. Estrone
3. Estriol.

All the three forms of estrogen are present in significant quantities in plasma. The quantity and potency of β-estradiol are more than those of estrone and estriol.

Plasma Level

Plasma level of estrogen in females at normal reproductive age varies during different phases of menstrual cycle. In follicular phase, it is 30 to 200 pg/mL (Fig. 80.4). In normal adult male, estrogen level is 12 to 34 pg/mL.

Half-life

Half-life of estrogen is 30 to 60 minutes.

Synthesis

The different forms of estrogen are synthesized from the cholesterol or acetate. If estrogen is formed from acetate, first acetate is converted into cholesterol.

Pathway for synthesis of estrogen

Acetate → Cholesterol → Pregnenolone
↓
Estrogen ← Testosterone ← Progesterone

During synthesis of estrogen, progesterone and testosterone are synthesized first (Fig. 70.2). Then, before leaving the ovaries, almost all the testosterone and much of the progesterone are converted into estrogen. About 1/15 of testosterone is secreted into the plasma of the female by the ovaries.

Transport in Plasma

Estrogen is transported mainly by the plasma protein, **albumin.** A small quantity of estrogen is also transported by **globulin.** The binding of estrogen with the plasma protein is loose, so that the hormones are released into the tissues easily.

Metabolism

Estrogen is degraded mainly in the liver. Here, it is conjugated with glucuronides and sulfates. About one fifth of the conjugated products are excreted in the bile. Most of the remaining part is excreted in the urine. Liver also converts the potent active beta estradiol into the almost inactive estrogen, the estriol.

■ FUNCTIONS OF ESTROGEN

Major function of estrogen is to promote cellular proliferation and tissue growth in the sexual organs and in other tissues, related to reproduction. In childhood, the estrogen is secreted in small quantity. During puberty, the secretion increases sharply, resulting in changes in the sexual organs. Effects of estrogen are:

1. *Effect on Ovarian Follicles*

Estrogen promotes the growth of ovarian follicles by increasing the proliferation of the follicular cells. It also increases the secretory activity of theca cells (Refer Chapter 80 for details).

2. *Effect on Uterus*

Estrogen produces the following changes in uterus:

i. Enlargement of uterus to about double of its childhood size due to the proliferation of endometrial cells
ii. Increase in the blood supply to endometrium
iii. Deposition of glycogen and fats in endometrium
iv. Proliferation and dilatation of blood vessels of endometrium
v. Proliferation and dilatation of the endometrial glands, which become more tortuous with increased blood flow
vi. Increase in the spontaneous activity of the uterine muscles and their sensitivity to oxytocin
vii. Increase in the contractility of the uterine muscles.

All these changes prepare uterus for pregnancy.

3. *Effect on Fallopian Tubes*

Estrogen:

i. Acts on the mucosal lining of the fallopian tubes and increases the number and size of the epithelial cells, especially the ciliated epithelial cells lining the fallopian tubes
ii. Increases the activity of the cilia, so that the movement of ovum in the fallopian tube is facilitated
iii. Enhances the proliferation of glandular tissues in fallopian tubes.

All these changes are necessary for the fertilization of ovum.

4. *Effect on Vagina*

Estrogen:

i. Changes the vaginal epithelium from cuboidal into stratified type; the stratified epithelium is more resistant to trauma and infection
ii. Increases the layers of the vaginal epithelium by proliferation
iii. Reduces the pH of vagina, making it more acidic.

All these changes are necessary for the prevention of certain common vaginal infections such as **gonorrheal vaginitis.** Such infections can be cured by the administration of estrogen.

5. *Effect on Secondary Sexual Characters*

Estrogen is responsible for the development of secondary sexual characters (Chapter 74) in females.

Secondary sexual characters in female

i. *Hair distribution:* Hair develops in the pubic region and axilla. In females, pubic hair has the base of the triangle upwards. Body hair growth is less. Scalp hair grows profusely
ii. *Skin:* Skin becomes soft and smooth. Vascularity of skin also increases
iii. *Body shape:* Shoulders become narrow, hip broadens, thighs converge and the arms diverge. Fat deposition increases in breasts and buttocks
iv. *Pelvis:*
    a. Broadening of pelvis with increased transverse diameter
    b. Round or oval shape of pelvis
    c. Round or oval=shaped pelvic outlet.

Thus, pelvis in females is different from that of males, which is funnel shaped.

iv. *Voice:* Larynx remains in prepubertal stage, which produces high-pitch voice.

6. *Effect on Breast*

Estrogen causes:

i. Development of stromal tissues of breasts
ii. Growth of an extensive ductile system
iii. Deposition of fat in the ductile system.

All these effects prepare the breasts for lactation. Estrogen causes development of lobules and alveoli of the breasts, to some extent. However, progesterone is necessary for the full growth of breast and prolactin is necessary for its function.

7. *Effect on Bones*

Estrogen increases **osteoblastic activity.** So, at the time of puberty, the growth rate increases enormously. But, at the same time, estrogen causes early fusion of the epiphysis with the shaft. This effect is much stronger in females than the similar effect of testosterone in males. As a result, the growth of the females usually ceases few years earlier than in the males.

In old age, the estrogen is not secreted or it becomes scanty. It leads to **osteoporosis,** in which the bones become extremely weak and **fragile.** Because of this, the bones are highly susceptible for **fractures** (Chapter 68).

8. *Effect on Metabolism*

i. *On protein metabolism*

Estrogen induces anabolism of proteins, by which it increases the total body protein.

ii. *On fat metabolism*

Estrogen causes deposition of fat in the subcutaneous tissues, breasts, buttocks and thighs. The overall specific gravity of the female body is considerably lesser than that of males because of fat deposition.

9. *Effect on Electrolyte Balance*

Estrogen causes sodium and water retention from the renal tubules. This effect is normally insignificant but in pregnancy, it becomes more significant.

Mode of Action of Estrogen

Estrogen receptors situated on nuclear membrane of target cells are of two types namely **α and β estrogen receptors.** The α-estrogen receptors are present in uterus, liver, heart and kidneys. The β estrogen receptors are present in ovaries and other tissues.

Estrogen acts through genes.

Regulation of Estrogen Secretion

Estrogen secretion is regulated by follicle-stimulating hormone (FSH) released from anterior pituitary. Release of FSH is stimulated by the gonadotropin-releasing hormone (GnRH) secreted from hypothalamus.

Theca cells and granulosa cells have many FSH receptors. After binding with the receptors, FSH acts via cAMP and stimulates the secretory activities of theca and granulosa cells. Estrogen inhibits secretion of FSH and GnRH by **negative feedback.** Inhibin secreted by granulosa cells (Chapter 80) also decreases estrogen secretion, by inhibiting the secretion of FSH and GnRH (Fig. 79.2).

■ PROGESTERONE

Source of Secretion

In non-pregnant woman, a small quantity of progesterone is secreted by theca interna cells of ovaries during the first half of menstrual cycle, i.e. during follicular stage. But, a large quantity of progesterone is secreted during the latter half of each menstrual cycle, i.e. during secretory phase by the corpus luteum. Small amount of progesterone is secreted from adrenal cortex also.

In pregnant woman, large amount of progesterone is secreted by the corpus luteum in the first trimester. In the second trimester, corpus luteum degenerates. Placenta

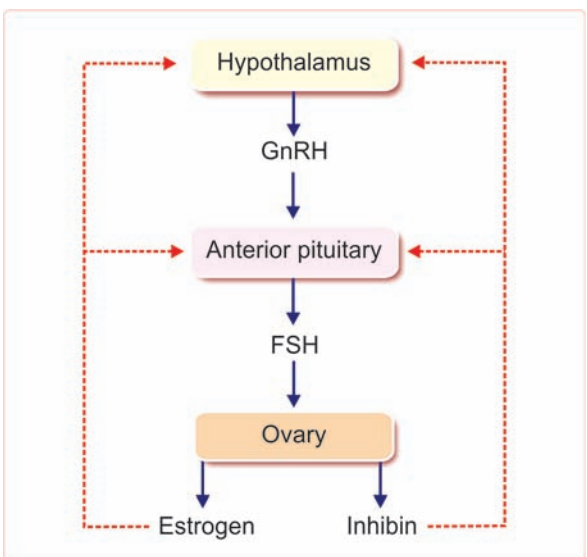


FIGURE 79.2: Regulation of estrogen secretion. Red dotted lines indicate inhibition.

secretes large quantity of progesterone in second and third trimesters.

Chemistry

Progesterone is a C_{21} steroid.

Half-life

Half-life of progesterone is 4 to 5 minutes.

Synthesis

Progesterone is synthesized from acetate or cholesterol in the ovaries, along with estrogen (Fig. 70.2, Chapter 70).

Plasma Level

Plasma level of progesterone in females at normal reproductive age varies during different phases of menstrual cycle. In follicular phase, it is about 0.9 ng/mL (Fig. 80.4). In normal adult male, progesterone level is 0.3 ng/mL.

Transport in Blood

Like estrogen, progesterone is also transported in the blood by the plasma proteins – **albumin** and **globulin.**

Metabolism

Within few minutes after secretion, almost all the progesterone is degraded into other steroids, which do not have progesterone effect. The degradation occurs in liver. The main end product of progesterone degradation is pregnanediol, which is conjugated with glucuronic acid and excreted in the urine.

■ FUNCTIONS OF PROGESTERONE

Progesterone is concerned mainly with the final preparation of the uterus for pregnancy and the breasts for lactation. The effects of progesterone are:

1. *Effect on Fallopian Tubes*

Progesterone promotes the secretory activities of mucosal lining of the fallopian tubes. Secretions of fallopian tubes are necessary for nutrition of the fertilized ovum, while it is in fallopian tube before implantation.

2. *Effect on the Uterus*

Progesterone promotes the secretory activities of uterine **endometrium** during the secretory phase of the menstrual cycle. Thus, the uterus is prepared for implantation of the fertilized ovum.

Progesterone:

i. Increases the thickness of the endometrium by increasing the number and size of the cells
   Thickness of endometrium increases from 1 mm thickness at the beginning of secretory phase to about 5 to 6 mm at the end of secretory phase.
ii. Increases the size of uterine glands and these glands become more tortuous
iii. Increases the secretory activities of epithelial cells of uterine glands
iv. Increases the deposition of lipid and glycogen in the stromal cells of endometrium
v. Increases the blood supply to endometrium. It is due to increase in size of the vessels and vasodilatation
vi. Decreases the frequency of uterine contractions during pregnancy. Because of this, the expulsion of the implanted ovum is prevented.

3. *Effect on Cervix*

Progesterone increases the thickness of cervical mucosa and thereby inhibits the transport of sperm into uterus. This effect is utilized in the contraceptive actions of minipills.

4. *Effect on the Mammary Glands*

Progesterone promotes the development of lobules and alveoli of mammary glands by proliferating and enlarging the alveolar cells. It also makes the breasts secretory in nature. It makes the breasts to swell by increasing the secretory activity and fluid accumulation in the subcutaneous tissue.

5. *Effect on Hypothalamus*

Progesterone inhibits the release of LH from hypothalamus through feedback effect. This effect is utilized for its contraceptive action.

6. *Thermogenic Effect*

Progesterone increases the body temperature after ovulation. The mechanism of thermogenic action is not known. It is suggested that progesterone increases the body temperature by acting on hypothalamic centers for temperature regulation.

7. *Effect on Respiration*

During luteal phase of menstrual cycle and during pregnancy, progesterone increases the ventilation via respiratory center. This decreases the partial pressure of carbon dioxide in the alveoli.

8. *Effect on Electrolyte Balance*

Progesterone increases the reabsorption of sodium and water from the renal tubules. However, in large doses, it is believed to cause excretion of sodium and water. This may be due to an indirect effect, i.e. progesterone combines with the same receptors, which bind with aldosterone. So, the action of aldosterone is blocked, leading to the excretion of sodium and water.

Mode of Action of Progesterone

The progesterone receptors situated on the nuclear membrane of target cells are of two types, namely A-progesterone receptors and B-progesterone receptors. Exact location of each type of progesterone receptor is not clear.

Like estrogen, progesterone also acts through genes.

Regulation of Progesterone Secretion

LH from anterior pituitary activates the corpus luteum to secrete progesterone. Secretion of LH is influenced by the gonadotropin-releasing hormone secreted in hypothalamus. Progesterone inhibits the release of LH from anterior pituitary by **negative feedback.**

Chapter 80

Menstrual Cycle

INTRODUCTION

DEFINITION

Menstrual cycle is defined as cyclic events that take place in a rhythmic fashion during the reproductive period of a woman's life. Menstrual cycle starts at the age of 12 to 15 years, which marks the onset of puberty. The commencement of menstrual cycle is called **menarche.** Menstrual cycle ceases at the age of 45 to 50 years. Permanent cessation of menstrual cycle in old age is called **menopause.**

DURATION OF MENSTRUAL CYCLE

Duration of menstrual cycle is usually 28 days. But, under physiological conditions, it may vary between 20 and 40 days.

CHANGES DURING MENSTRUAL CYCLE

During each menstrual cycle, series of changes occur in ovary and accessory sex organs.

These changes are divided into 4 groups:

1. Ovarian changes
2. Uterine changes

3. Vaginal changes
4. Changes in cervix.

All these changes take place simultaneously.

OVARIAN CHANGES DURING MENSTRUAL CYCLE

Changes in the ovary during each menstrual cycle occur in two phases:

A. Follicular phase
B. Luteal phase.

Ovulation occurs in between these two phases.

FOLLICULAR PHASE

Follicular phase extends from the 5th day of the cycle until the time of ovulation, which takes place on 14th day. Maturation of ovum with development of ovarian follicles takes place during this phase.

Ovarian Follicles

Ovarian follicles are glandular structures present in the cortex of ovary. Each follicle consists of the ovum surrounded by epithelial cells, namely **granulosa cells.** The follicles gradually grow into a matured follicle through various stages.

Different follicles:

1. Primordial follicle
2. Primary follicle
3. Vesicular follicle
4. Matured follicle or graafian follicle.

1. *Primordial Follicle*

At the time of puberty, both the ovaries contain about 400,000 primordial follicles. Diameter of the primordial follicle is about 15 to 20 µ and that of ovum is about 10 µ.

Each primordial follicle has an ovum, which is incompletely surrounded by the granulosa cells (Chapter 79, Fig. 79.1). These cells provide nutrition to the ovum during childhood.

Granulosa cells also secrete the **oocyte maturation inhibiting factor,** which keeps ovum in the immature stage. All the ova present in the ovaries are formed before birth. No new ovum is developed after birth.

At the onset of puberty, under the influence of FSH and LH the primordial follicles start growing through various stages.

2. *Primary Follicle*

Primordial follicle becomes the primary follicle, when ovum is completely surrounded by the granulosa cells. During this stage, the follicle and the ovum increase in size. Diameter of the follicle increases to 30 to 40 µ and that of ovum increases to about 20 µ. The follicle is not covered by a definite connective tissue capsule.

Changes taking place during development of primary follicle

i. Proliferation of granulosa cells and increase in size of the follicle
ii. Increase in size of the ovum
iii. Onset of formation of connective tissue capsule around the follicle.

Primary follicles develop into vesicular follicles.

3. *Vesicular Follicle*

Under the influence of FSH, about 6 to 12 primary follicles start growing and develop into vesicular follicles.

Changes taking place during the development of vesicular follicle

i. Changes in granulosa cells
ii. Changes in ovum
iii. Formation of capsule.

i. *Changes in granulosa cells*

a. First, the proliferation of granulosa cells occurs
b. A cavity called **follicular cavity** or **antrum** is formed in between the granulosa cells
c. Antrum is filled with a serous fluid called the **liquor folliculi**
d. With continuous proliferation of granulosa cells, the follicle increases in size
e. Antrum with its fluid also increases in size
f. Ovum is pushed to one side and it is surrounded by granulosa cells, which forms the **germ hill** or **cumulus oophorus**
g. Granulosa cells, which line the antrum form **membrana granulosa**
h. Cells of germ hill become columnar and form **corona radiata.**

ii. *Changes in ovum*

a. First, the ovum increases in size and its diameter increases to 100 to 150 µ
b. Nucleus becomes larger and vesicular
c. Cytoplasm becomes granular
d. Thick membrane is formed around the ovum, which is called zona pellucida
e. A narrow cleft appears between ovum and zona pellucida. This cleft is called **perivitelline space.**

iii. Formation of capsule

Spindle cells from the stroma of ovarian cortex are modified and form a covering sheath around the follicle. The covering sheath is known as **follicular sheath** or **theca folliculi.**

Theca folliculi divides into two layers:

a. Theca interna
b. Theca externa.

a. *Theca interna*

Theca interna is the inner vascular layer with loose connective tissue. This layer also contains special type of epithelial cells with lipid granules and some delicate collagen fibers.

Epithelial cells become secretory in nature and start secreting the female sex hormones, especially estrogen. Hormones are released into the fluid of antrum.

b. *Theca externa*

Theca externa is the outer layer of follicular capsule and consists of thickly packed fibers and spindle-shaped cells.

After about 7th day of menstrual cycle, one of the vesicular follicles outgrows others and becomes the dominant follicle. It develops further to form graafian follicle. Other vesicular follicles degenerate and become **atretic** by means of **apoptosis.**

4. *Graafian Follicle*

Graafian follicle is the matured ovarian follicle with maturing ovum (Fig. 80.1). It is named after the Dutch physician and anatomist, **Regnier De Graaf.**

Changes taking place during the development of graafian follicle

i. Size of the follicle increases to about 10 to 12 mm. It extends through the whole thickness of ovarian cortex
ii. At one point, the follicle encroaches upon tunica albuginea and protrudes upon surface of the ovary. This protrusion is called **stigma.** At the stigma, the tunica albuginea becomes thin
iii. Follicular cavity becomes larger and distended with fluid
iv. Ovum attains maximum size
v. Zona pellucida becomes thick
vi. Corona radiata becomes prominent
vii. Small spaces filled with fluid appear between the cells of germ hill, outside the corona radiata. These spaces weaken the attachment of the ovum to the follicular wall
viii. Theca interna becomes prominent. Its thickness becomes double with the formation of rich capillary network

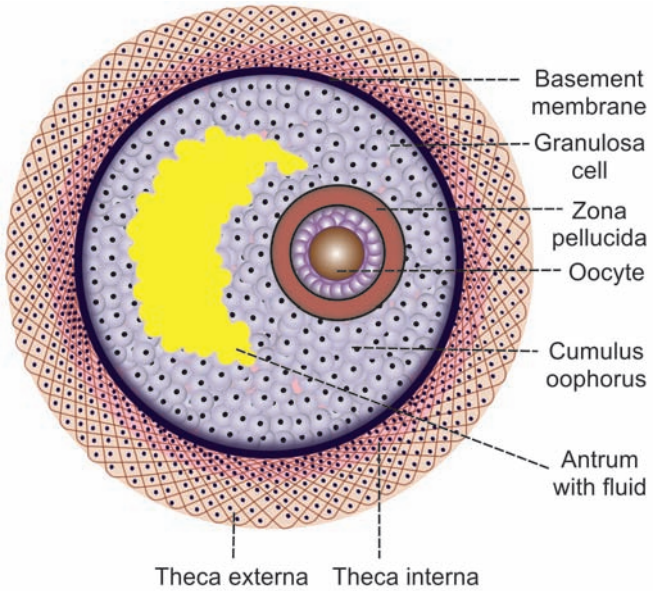


FIGURE 80.1: Graafian follicle

ix. On the 14th day of menstrual cycle, graafian follicle is ready for the process of ovulation.

■ OVULATION

Ovulation is the process by which the graafian follicle ruptures with consequent **discharge of ovum** into the abdominal cavity. It is influenced by LH. Ovulation occurs on 14th day of menstrual cycle in a normal cycle of 28 days. The ovum enters the fallopian tube.

Process of Ovulation

Mechanism of ovulation is not known clearly. Process of ovulation is explained in the next Chapter.

Stages of ovulation

1. Rupture of graafian follicles takes place at the stigma
2. Follicular fluid oozes out
3. Germ hillock is freed from wall
4. Ovum is expelled out into the abdominal cavity along with some amount of fluid and granulosa cells
5. From abdominal cavity, the ovum enters the fallopian tube through the fimbriated end.

Other details are given in the next Chapter.

Ovum becomes **haploid** before or during ovulation by the formation of polar bodies. After ovulation, the ovum is viable only for 24 to 48 hours. So it must be fertilized within that time.

Fertilized ovum is called **zygote.** Zygote moves from fallopian tube and reaches the uterus on 3rd day after ovulation. It is **implanted** in the uterine wall on 6th or 7th day.

If fertilization does not occur, ovum degenerates. Generally, only one ovum is released from one of the ovaries.

■ LUTEAL PHASE

Luteal phase extends between 15th and 28th day of menstrual cycle. During this phase, corpus luteum is developed and hence this phase is called luteal phase (Fig. 80.2).

Corpus Luteum

Corpus luteum is a glandular yellow body, developed from the ruptured graafian follicle after the release of ovum. It is also called **yellow body.**

Development of Corpus Luteum

Soon after the rupture of graafian follicle and release of ovum, the follicle is filled with **blood.** Now the follicle is called **corpus hemorrhagicum.** The blood clots slowly. Corpus hemorrhagicum does not degenerate immediately. It is transformed into corpus luteum.

Follicular cavity closes gradually by the healing of the wound. Blood clot is gradually replaced by a **serous fluid** containing fibrin. Corpus luteum obtains a diameter of 15 mm and remains in the ovary till the end of the cycle.

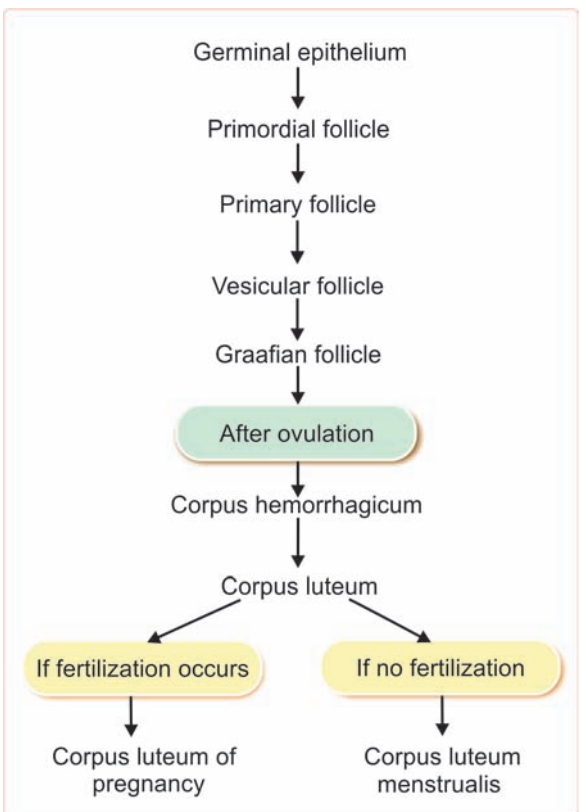


FIGURE 80.2: Ovarian follicle

Structure of Corpus Luteum

In the corpus luteum, **granulosa cells** and **theca interna cells** are transformed into **lutein cells** called granulosa lutein cells and theca lutein cells. The process which transforms the granulosa and theca cells into lutein cells is called **luteinization.**

Granulosa lutein cells contain fine lipid granules and the yellowish pigment granules. The **yellowish pigment** granules give the characteristic yellow color to corpus luteum.

Theca lutein cells contain only lipid granules and not the yellow pigment.

Follicular cavity is greatly reduced with irregular outline. It is filled with the serous fluid and remnants of blood clots.

Functions of Corpus Luteum

1. *Secretion of hormones*

Corpus luteum acts as a **temporary endocrine gland.** It secretes large quantity of progesterone and small amount of estrogen. Granulosa lutein cells secrete **progesterone** and theca lutein cells secrete **estrogen.** LH influences the secretion of these two hormones.

2. *Maintenance of pregnancy*

If pregnancy occurs, corpus luteum remains active for about 3 months, i.e. until placenta develops. Hormones secreted by corpus luteum during this period maintain the pregnancy.

Abortion occurs if corpus luteum becomes inactive or removed before third month of pregnancy, i.e. before placenta starts secreting the hormones.

Fate of Corpus Luteum

Fate of corpus luteum depends upon whether ovum is fertilized or not.

1. *If the ovum is not fertilized*

If fertilization does not take place, the corpus luteum reaches the maximum size about one week after ovulation. During this period, it secretes large quantity of progesterone with small quantity of estrogen. Then, it degenerates into the **corpus luteum menstrualis** or **spurium.** The cells decrease in size and the corpus luteum becomes smaller and involuted. Afterwards, the corpus luteum menstrualis is transformed into a

whitish scar called **corpus albicans.** The process by which corpus luteum undergoes regression is called **luteolysis.**

2. *If ovum is fertilized*

If ovum is fertilized and pregnancy occurs, the corpus luteum persists and increases in size. It attains a diameter of 20 to 30 mm and it is transformed into **corpus luteum graviditatis (verum)** or **corpus luteum of pregnancy.** It remains in the ovary for 3 to 4 months. During this period, it secretes large amount of progesterone with small quantity of estrogen, which are essential for the maintenance of pregnancy. After 3 to 4 months, placenta starts secreting these hormones and corpus luteum degenerates.

UTERINE CHANGES DURING MENSTRUAL CYCLE

During each menstrual cycle, along with ovarian changes, uterine changes also occur simultaneously (Fig. 80.3).

Uterine changes occur in three phases:

1. Menstrual phase
2. Proliferative phase
3. Secretory phase.

MENSTRUAL PHASE

After ovulation, if pregnancy does not occur, the thickened **endometrium** is shed or **desquamated.** This desquamated endometrium is expelled out through vagina along with blood and tissue fluid. The process of shedding and exit of uterine lining along with blood and fluid is called **menstruation** or **menstrual bleeding.** It lasts for about 4 to 5 days. This period is called menstrual phase or **menstrual period.** It is also called **menses, emmenia** or **catamenia.**

The day when bleeding starts is considered as the first day of the menstrual cycle.

Two days before the onset of bleeding, that is on 26th or 27th day of the previous cycle, there is a sudden reduction in the release of estrogen and progesterone from ovary. Decreased level of these two hormones is responsible for menstruation.

Changes in Endometrium during Menstrual Phase

i. Lack of estrogen and progesterone causes sudden involution of endometrium
ii. It leads to reduction in the thickness of endometrium, up to 65% of original thickness
iii. During the next 24 hours, the tortuous blood vessels in the endometrium undergo severe constriction. Endometrial vasoconstriction is because of three reasons:
   a. Involution of endometrium
   b. Actions of vasoconstrictor substances like prostaglandin, released from tissues of involuted endometrium
   c. Sudden lack of estrogen and progesterone (which are vasodilators)
iv. Vasoconstriction leads to **hypoxia,** which results in **necrosis** of the endometrium
v. Necrosis causes rupture of blood vessels and oozing of blood
vi. Outer layer of the **necrotic endometrium** is separated and passes out along with blood
vii. This process is continued for about 24 to 36 hours

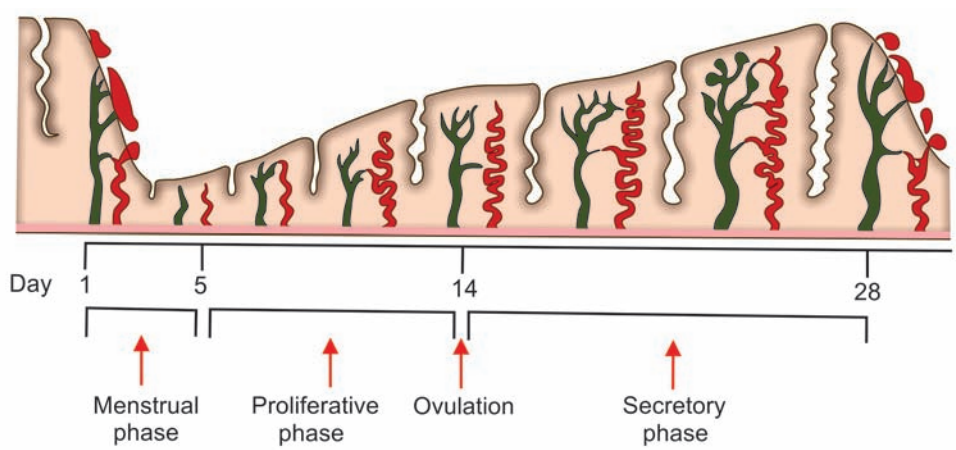


FIGURE 80.3: Uterine changes during menstrual cycle

viii. Within 48 hours after the reduction in the secretion of estrogen and progesterone, the superficial layers of endometrium are completely desquamated
ix. Desquamated tissues and the blood in the endometrial cavity initiate the contraction of uterus
x. Uterine contractions expel the blood along with desquamated uterine tissues to the exterior through vagina.

During normal menstruation, about 35 mL of **blood** along with 35 mL of **serous fluid** is expelled. The blood clots as soon as it oozes into the uterine cavity. **Fibrinolysin** causes **lysis of clot** in uterine cavity itself, so that the expelled menstrual fluid does not clot. However, in the pathological conditions involving uterus, the lysis of blood clot does not occur. So the menstrual fluid comes out with blood clot.

Menstruation stops between 3rd and 7th day of menstrual cycle. At the end of menstrual phase, the thickness of endometrium is only about 1 mm. This is followed by proliferative phase.

■ PROLIFERATIVE PHASE

Proliferative phase extends usually from 5th to 14th day of menstruation, i.e. between the day when menstruation stops and the day of ovulation. It corresponds to the follicular phase of ovarian cycle.

At the end of menstrual phase, only a thin layer (1 mm) of endometrium remains, as most of the endometrial stroma is desquamated.

Changes in Endometrium during Proliferative Phase

i. Endometrial cells proliferate rapidly
ii. Epithelium reappears on the surface of endometrium within the first 4 to 7 days
iii. Uterine glands start developing within the endometrial stroma
iv. Blood vessels appear in the stroma
v. Proliferation of endometrial cells occurs continuously, so that the endometrium reaches the thickness of 3 to 4 mm at the end of proliferative phase.

All these uterine changes during proliferative phase occur because of the influence of estrogen released from ovary. On 14th day, ovulation occurs under the influence of LH. This is followed by secretory phase.

■ SECRETORY PHASE

Secretory phase extends between 15th and 28th day of the menstrual cycle, i.e. between the day of ovulation and the day when menstruation of next cycle commences.

After ovulation, corpus luteum is developed in the ovary. It secretes a large quantity of progesterone along with a small amount of estrogen. Estrogen causes further proliferation of cells in uterus, so that the endometrium becomes more thick. Progesterone causes further enlargement of endometrial stroma and further growth of glands.

Under the influence of progesterone, the endometrial glands commence their secretory function. Many changes occur in the endometrium before commencing the secretory function.

Changes in Endometrium during Secretory Phase

i. Endometrial glands become more tortuous. Because of increase in size, the glands become tortuous to get accommodated within the endometrium
ii. Cytoplasm of stromal cells increases because of the deposition of glycogen and lipids
iii. Many new blood vessels appear within endometrial stroma. Blood vessels also become tortuous
iv. Blood supply to endometrium increases
v. Thickness of endometrium increases up to 6 mm.

Actually, secretory phase is the preparatory period, during which the uterus is prepared for implantation of ovum. All these uterine changes during secretory phase occur due to the influence of estrogen and progesterone. Estrogen is responsible for repair of damaged endometrium and growth of the glands. Progesterone is responsible for further growth of these structures and secretory activities in the endometrium.

If a fertilized ovum is implanted during this phase and if the implanted ovum starts developing into a fetus, then further changes occur in the uterus for the survival of the developing fetus. If the implanted ovum is unfertilized or if pregnancy does not occur, menstruation occurs after this phase and a new cycle begins.

■ CHANGES IN CERVIX AND VAGINA DURING MENSTRUAL CYCLE

■ CHANGES IN CERVIX DURING MENSTRUAL CYCLE

Mucus membrane of the cervix also shows cyclic changes during different phases of menstrual cycle.

Proliferative Phase

During proliferative phase, the mucus membrane of cervix becomes thinner and more alkaline due to the influence of estrogen. It helps in the survival and motility of spermatozoa.

Secretory Phase

During secretory phase, the mucus membrane of cervix becomes more thick and adhesive because of actions of progesterone.

■ VAGINAL CHANGES DURING MENSTRUAL CYCLE

Proliferative Phase

Epithelial cells of vagina are cornified. Estrogen is responsible for this.

Secretory Phase

Vaginal epithelium proliferates due to the actions of progesterone. It is also infiltrated with leukocytes. These two changes increase the resistance of vagina for infection.

■ REGULATION OF MENSTRUAL CYCLE

Regulation of menstrual cycle is a complex process that is carried out by a well organized regulatory system. The regulatory system is a highly integrated system, which includes hypothalamus, anterior pituitary and ovary with its growing follicle. In the whole scenario, the growing follicle has a vital role to play.

■ HORMONES INVOLVED IN REGULATION

The regulatory system functions through the hormones of **hypothalamo-pituitary-ovarian axis.**

Hormones involved in the regulation of menstrual cycle are:

1. Hypothalamic hormone: GnRH
2. Anterior pituitary hormones: FSH and LH
3. Ovarian hormones: Estrogen and progesterone.

Hormonal level during menstrual cycle is shown in Fig. 80.4.

Hypothalamic Hormone – GnRH

GnRH triggers the cyclic changes during menstrual cycle by stimulating secretion of FSH and LH from anterior pituitary. GnRH secretion depends upon two factors:

i. External factors like psychosocial events, which act on hypothalamus via cortex and many other brain centers
ii. Feedback effects of ovarian changes via ovarian hormones.

Anterior Pituitary Hormones – FSH and LH

FSH and LH modulate the ovarian and uterine changes by acting directly and/or indirectly via ovarian hormones. FSH stimulates the recruitment and growth of immature ovarian follicles. LH triggers ovulation and sustains corpus luteum.

Secretion of FSH and LH is under the influence of GnRH.

Ovarian Hormones – Estrogen and Progesterone

Estrogen and progesterone which are secreted by follicle and corpus luteum, show many activities during menstrual cycle. Ovarian follicle secretes large quantity of estrogen and corpus luteum secretes large quantity of progesterone.

Estrogen secretion reaches the peak twice in each cycle; once during follicular phase just before ovulation and another one during luteal phase (Fig. 80.4). On the other hand, progesterone is virtually absent during follicular phase till prior to ovulation. But it plays a critical role during luteal phase.

Estrogen is responsible for the growth of follicles. Both the steroids act together to produce the changes in uterus, cervix and vagina.

Both the ovarian hormones are under the influence of GnRH, which acts via FSH and LH. In addition, the secretion of GnRH, FSH and LH is regulated by ovarian hormones.

■ REGULATION OF OVARIAN CHANGES

Follicular Phase

1. The **biological clock** responsible to trigger the cyclic events is the **pulsatile secretion of GnRH,** at about every 2 hours (due to some mechanism that is not understood clearly)
2. Pulsatile release of GnRH stimulates the secretion of FSH and LH from anterior pituitary
3. LH induces the synthesis of androgens from theca cells of growing follicle
4. FSH promotes **aromatase activity** in granulosa cells of the follicle (Chapter 79), resulting in the conversion of androgens into estrogen. It also promotes follicular development
5. Estrogen is responsible for development and growth of graafian follicle. It also stimulates the secretory activities of theca cells
6. Estrogen also exerts a **double feedback control** on GnRH
   i. Initially, when estrogen secretion is moderate, it exerts a **negative feedback control** on GnRH so that GnRH secretion is inhibited. This leads to decrease in secretion of FSH and LH (negative feedback)
   ii. During later period of follicular phase, when a large amount of estrogen is secreted by the

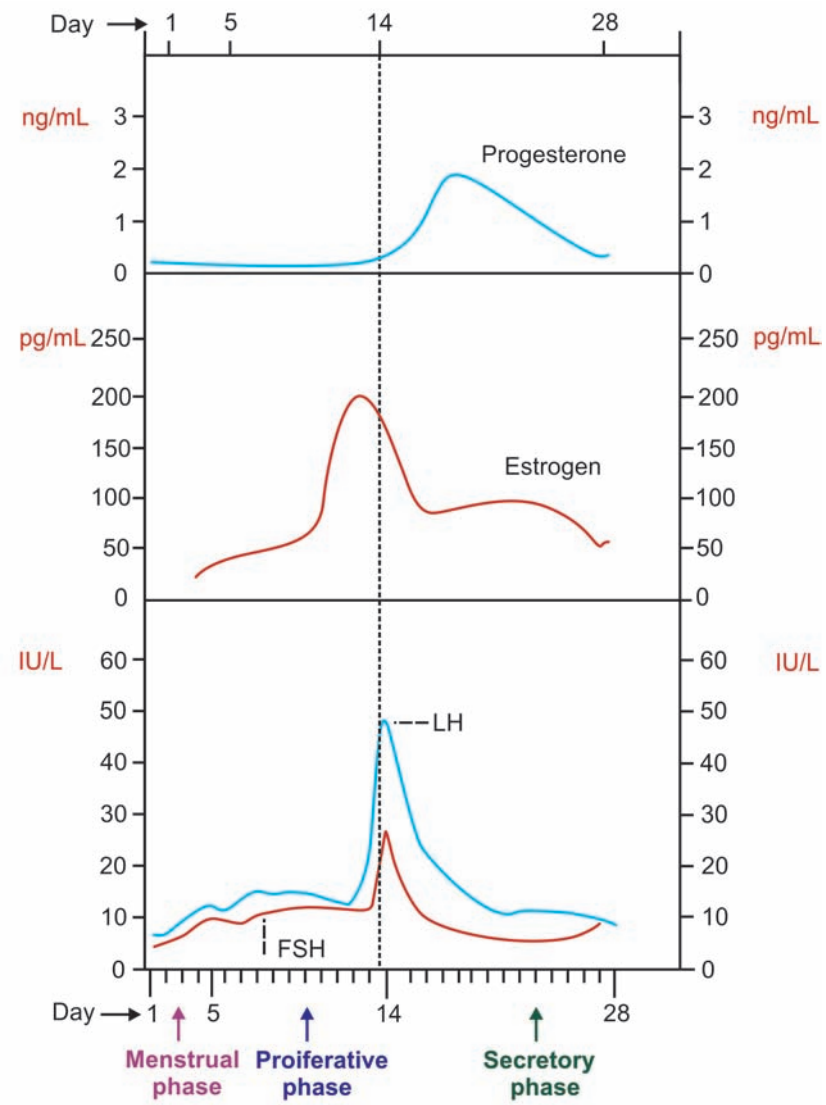


FIGURE 80.4: Hormonal level during menstrual cycle. LH = Luteinizing hormones, FSH = Follicle-stimulating hormone.

maturing follicle, it exerts a **positive feedback effect** on GnRH secretion. Now, GnRH secretion is increased, resulting in secretion of large quantity of FSH and LH. This in turn, facilitates the growth of graafian follicle

7. In addition, estrogen shows the following actions:
   i. Increases the number of FSH and LH receptors on the granulosa cells of follicles and increases the sensitivity of these cells for FSH and LH
   ii. Facilitates the faster growth of graafian follicle
8. LH is necessary to provide the final touches for the growth of graafian follicle. It stimulates the secretion of estrogen. At the same time, it stimulates the theca cells to secrete progesterone.

Ovulation

LH is important for ovulation. Without LH, ovulation does not occur even with a large quantity of FSH. The need for excessive secretion of LH for ovulation is known as **ovulatory surge for LH** or **luteal surge.**

Prior to ovulation, a large quantity of LH is secreted due to **positive feedback effect** of estrogen on GnRH, as mentioned above.

Luteal Phase

Role of LH

Ovarian changes during luteal phase depend mainly on LH.

Luteinizing hormone:

1. Induces development of corpus luteum from the follicle (devoid of ovum) by converting the granulosa cells into lutein cells
2. Stimulates corpus luteum to secrete progesterone and estrogen
3. Necessary for the maintenance of corpus luteum.

Role of FSH

FSH also plays a role during luteal phase.

Follicle-stimulating hormone:

1. Maintains the secretory activity of corpus luteum
2. Stimulates lutein cells to secrete inhibin, which in turn inhibits FSH secretion.

If the ovum is not fertilized or if implantation of ovum does not take place, the changes in the level of the hormones produce some effects on corpus luteum which are:

1. Progesterone and estrogen secreted from corpus luteum, inhibit the secretion of FSH and LH from anterior pituitary by **negative feedback**
2. Granulosa lutein cells secrete another hormone called inhibin (which is also secreted by Sertoli cells of testes in males: Chapter 74). Inhibin also inhibits the secretion of FSH and LH by **negative feedback**
3. In the absence of FSH and LH, the corpus luteum becomes inactive
4. Finally, the corpus luteum regresses by means of luteolysis; so progesterone and estrogen are not available
5. Absence of progesterone and estrogen induces the secretion of GnRH from hypothalamus
6. GnRH stimulates the secretion of FSH and LH from anterior pituitary
7. FSH and LH stimulate the new immature follicles, resulting in the commencement of next cycle.

■ REGULATION OF UTERINE CHANGES

Uterine changes during menstrual cycle are influenced by estrogen and progesterone.

Proliferative Phase

During proliferative stage, the repair of the damaged endometrium occurs mainly by estrogen.

Estrogen stimulates:

1. Proliferation of cells in endometrial stroma
2. Development of uterine glands and appearance of blood vessels in the endometrial stroma.

Secretory Phase

Secretory phase of uterine changes, coincides with luteal phase of ovarian cycle. Under the influence of FSH and LH from anterior pituitary, the corpus luteum secretes large amount of progesterone and small amount of estrogen. Progesterone is responsible for endometrial changes along with estrogen during this phase.

Progesterone stimulates:

1. Growth of endometrial glands and makes them more tortuous
2. Growth of blood vessels and makes them also tortuous, leading to increase in blood flow to endometrium
3. Secretory activities of endometrial glands.

Thus, during the secretory phase, the structure, blood flow and secretory functions of uterus are influenced by estrogen and progesterone secreted by corpus luteum.

Menstrual Phase

If pregnancy does not occur, menstrual phase occurs:

1. During the last two days of secretory phase, i.e. two days prior to onset of menstruation, the secretion of large quantity of progesterone and estrogen from corpus luteum inhibits the secretion of FSH and LH from anterior pituitary, by negative feedback
2. In the absence of LH and FSH, the corpus luteum becomes inactive and starts regressing
3. **Sudden withdrawal** (absence) of ovarian hormones progesterone and estrogen occurs
4. It leads to **menstrual bleeding.**

Lack of ovarian hormones causes the release of gonadotropins once again from anterior pituitary. It results in the onset of development of new follicles in ovary and the cycle repeats.

■ APPLIED PHYSIOLOGY – ABNORMAL MENSTRUATION

■ MENSTRUAL SYMPTOMS

Menstrual symptoms are the unpleasant symptoms with discomfort, which appear in many women during menstruation. These symptoms are due to hormonal withdrawal, leading to cramps in uterine muscle before or during menstruation.

Common Menstrual Symptoms

1. Abdominal pain
2. Dysmenorrhea (menstrual pain)
3. Headache

4. Occasional nausea and vomiting
5. Irritability
6. Depression
7. **Migraine** (neurological disorder, characterized by intense headache causing disability).

■ PREMENSTRUAL SYNDROME

Premenstrual syndrome (PMS) is the symptom of stress that appears before the onset of menstruation. It is also called **premenstrual stress syndrome, premenstrual stress** or **premenstrual tension.** It lasts for about 4 to 5 days prior to menstruation. Symptoms appear due to salt and water retention caused by estrogen.

Common Features

1. Mood swings
2. Anxiety
3. Irritability
4. Emotional instability
5. Headache
6. Depression
7. Constipation
8. Abdominal cramping
9. Bloating (abdominal swelling).

■ ABNORMAL MENSTRUATION

1. **Amenorrhea:** Absence of menstruation
2. **Hypomenorrhea:** Decreased menstrual bleeding
3. **Menorrhagia:** Excess menstrual bleeding
4. **Oligomenorrhea:** Decreased frequency of menstrual bleeding
5. **Polymenorrhea:** Increased frequency of menstruation
6. **Dysmenorrhea:** Menstruation with pain
7. **Metrorrhagia:** Uterine bleeding in between menstruations.

■ ANOVULATORY CYCLE

Anovulatory cycle is the menstrual cycle in which ovulation does not occur. The menstrual bleeding occurs but the release of ovum does not occur. It is common during puberty and few years before menopause. When it occurs before menopause, it is called **perimenopause.** If it occurs very often during childbearing years, it leads to infertility.

Common Causes

1. Hormonal imbalance
2. Prolonged strenuous exercise program
3. Eating disorders
4. Hypothalamic dysfunctions
5. Tumors in pituitary gland, ovary or adrenal gland
6. Long-term use of drugs like steroidal oral contraceptives.

Ovulation

Chapter 81

INTRODUCTION

Ovulation is the process by which the **graafian follicle** in the ovary ruptures and the **ovum** is released into the abdominal cavity. Ovulation occurs on the 14th day of menstrual cycle in a normal cycle of 28 days.

The ovum, which is released into the abdominal cavity, enters the fallopian tube through the fimbriated end of the tube. Usually, only one ovum is released from any one of the ovaries. LH is responsible for ovulation.

PROCESS OF OVULATION

Prior to ovulation, large amount of LH is secreted (luteal surge). This causes changes in the graafian follicle leading to ovulation.

Stages of Ovulation

1. Graafian follicle moves towards the periphery of ovary
2. New blood vessels are formed in the ovary by actions of LH and progesterone
3. These blood vessels protrude into the wall of the follicle
4. This increases the blood flow to the follicle
5. Now, prostaglandin is released from granulosa cells of the follicle
6. It causes leakage of plasma into the follicle
7. Just before ovulation the follicle swells and protrudes against the capsule of the ovary. This protrusion is called **stigma**
8. Then, progesterone activates the proteolytic enzymes present in the cells of theca interna
9. These enzymes weaken the follicular capsule and cause degeneration of the stigma
10. After about 30 minutes, fluid begins to ooze from the follicle through the stigma
11. It decreases the size of the follicle causing rupture of stigma
12. Now, ovum is released from the follicle along with fluid and plenty of small granulosa cells into the abdominal cavity (Fig. 81.1).

HORMONAL REGULATION OF OVULATION

Hormonal regulation of ovulation is discussed in the previous chapter.

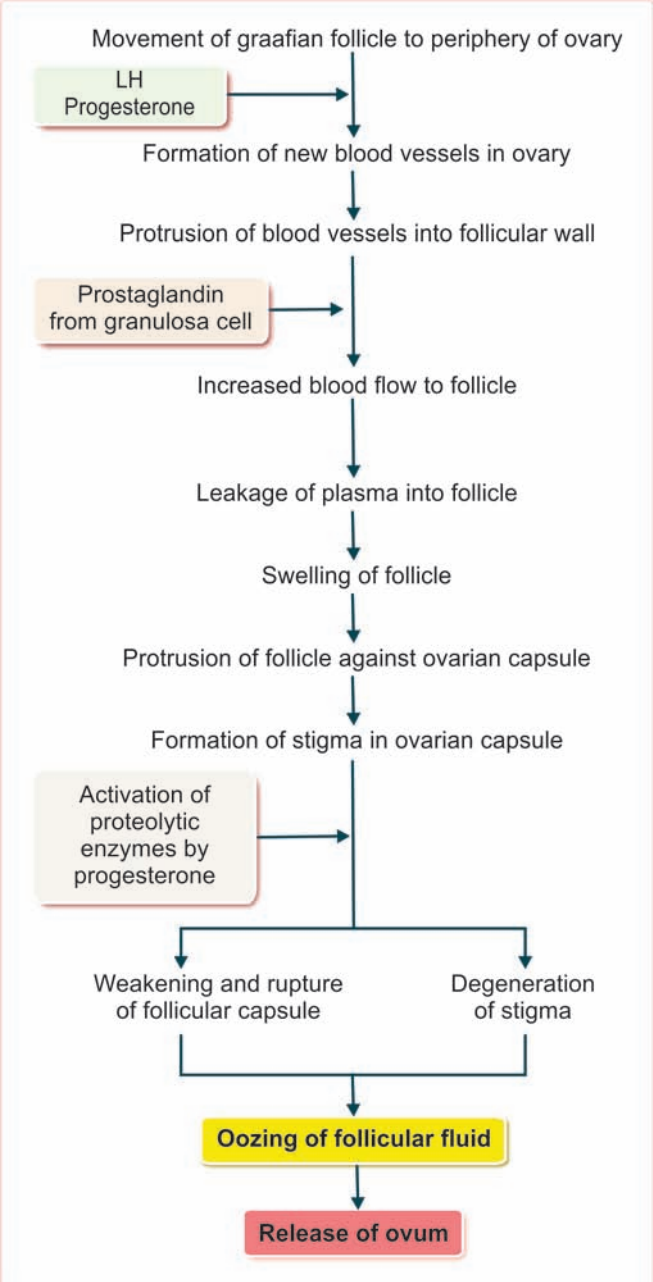


FIGURE 81.1: Process of ovulation

DETERMINATION OF OVULATION TIME

Various methods are available to determine the ovulation time. In human beings, usually indirect methods are adopted such as:

1. Determination of basal body temperature
2. Determination of hormonal excretion in urine
3. Determination of hormonal level in plasma
4. Ultrasound scanning
5. Cervical mucus pattern.

DETERMINATION OF BASAL BODY TEMPERATURE

Body temperature is measured for few days during the mid period of menstrual cycle. Temperature is measured in the morning by placing the thermometer in rectum or vagina. There is a slight fall in the basal temperature just prior to ovulation. And the temperature increases after ovulation. The alteration in the temperature is very mild and it is about ± 0.3°C to 0.5°C. The increase in temperature is due to the **thermogenic effect** of **progesterone** (Chapter 79).

DETERMINATION OF HORMONAL EXCRETION IN URINE

At the time of ovulation, there is an increase in the urinary excretion of metabolic end products of estrogen and progesterone. The end products of estrogen metabolism are estrone, estriol and 17-β-estradiol. The end product of progesterone metabolism is **pregnanediol.**

DETERMINATION OF HORMONAL LEVEL IN PLASMA

Plasma level of FSH, LH, estrogen and progesterone is measured. Hormone level is altered at the time of ovulation and after ovulation.

At the time of ovulation:

i. FSH level decreases
ii. LH level increases
iii. Estrogen level increases.

After ovulation:

Progesterone level increases.

ULTRASOUND SCANNING

Process of ovulation can be observed in ultrasound scanning.

CERVICAL MUCUS PATTERN

When the cervical mucus spread on a slide is examined under microscope, it shows a **fern pattern.** This pattern disappears after ovulation.

SIGNIFICANCE OF DETERMINING OVULATION TIME

Determination of ovulation time is helpful for family planning by **rhythm method** (Chapter 88).

Chapter 82

Menopause

- CLIMACTERIC AND MENOPAUSE
- CAUSE FOR MENOPAUSE
- CHANGES DURING MENOPAUSE
  - CAUSE
  - SYMPTOMS
  - TREATMENT – HORMONE REPLACEMENT THERAPY (HRT)

CLIMACTERIC AND MENOPAUSE

Climacteric is the period in old age when reproductive system undergoes changes due to the decreased secretion of sex hormones, estrogen and progesterone. It occurs at the age of 45 to 55. In females, climacteric is accompanied by menopause.

Menopause is defined as the period when permanent cessation of menstruation takes place. Normally, it occurs at the age of 45 to 55 years.

In some women, the menstruation stops suddenly. In others, the menstrual flow decreases gradually during every cycle and finally it stops. Sometimes irregular menstruation occurs with lengthening or shortening of the period with less or more flow.

Early menopause may occur because of surgical removal of ovaries **(ovariectomy)** or uterus **(hysterectomy)** as a part of treatment for abnormal menstruation. Usually, females with short menstrual cycle attain menopause earlier than the females with longer cycle. Cigarette smoking causes earlier onset of menopause.

CAUSE FOR MENOPAUSE

Due to advancement of age, the atrophy of ovaries occurs. It leads to the cessation of menstrual cycle causing menopause. Throughout a woman's sexual life, about 450 of the primordial follicles grow into graafian follicles and ovulate, while thousands of the follicles degenerate.

At the age of 45 years, only few primordial follicles remain in the ovary to be stimulated by FSH and LH. Now, the production of estrogen by ovary decreases due to the decrease in the number of primordial follicles. When estrogen secretion becomes almost zero, FSH and LH are continuously secreted. When all the primordial follicles are atrophied, estrogen secretion stops completely.

CHANGES DURING MENOPAUSE – POSTMENOPAUSAL SYNDROME

Postmenopausal syndrome is the group of symptoms that appear in women immediately after menopause. It is characterized by certain physical, physiological and psychological changes. The symptoms start appearing soon after the ovaries stop functioning.

CAUSE

Major cause for the symptoms is the lack of estrogen and progesterone. Symptoms may persist till the body gets acclimatized to the absence of estrogen and progesterone.

SYMPTOMS

Symptoms do not appear in all women. Some women develop mild symptoms and some women develop severe symptoms, which last for few months to few years.

Symptoms of postmenopausal syndrome:

1. *Hot flashes characterized by extreme flushing of the skin:* Hot flashes start with **discomfort** in the abdomen and **chill** followed by the feeling of heat spreading towards the head. Then the face becomes red followed by sweating and exhaustion.
2. *Vasomotor instability:* Wide fluctuation in blood pressure may be present. Blood pressure increases suddenly and it comes back to normal automatically.
3. Fatigue
4. Nervousness
5. Emotional outburst like crying and anger
6. Mental depression
7. Insomnia
8. Palpitation
9. Vertigo
10. Headache
11. Numbness or tingling sensation
12. Urinary disturbances such as increased frequency of micturition
13. *Long-term effects of estrogen lack such as osteoporosis and atherosclerosis:* **Osteoporosis** is the bone disease resulting in reduction in bone mass. And the bones become susceptible for fracture. **Atherosclerosis** is the condition characterized by deposition of cholesterol on the wall of the blood vessels.

■ TREATMENT – HORMONE REPLACEMENT THERAPY

Most of the women manage it very well. But, about 15% of the women need treatment. In many cases, psychotherapy works very well. If it fails, hormone replacement therapy (HRT) is given. Daily administration of estrogen in small quantities will reverse the symptoms. The combination of estrogen and progesterone is considered to be more advantageous because progesterone prevents the **estrogen-induced cancer** and **hyperplasia of myometrium.** Dose of the hormones should be gradually reduced to prevent the reoccurrence of **postmenopausal symptoms.**

Chapter 83

Infertility

DEFINITION

Infertility is the inability to produce the offspring. In females, it is the inability to conceive a child by natural process or inability to carry pregnancy till the completion of term. Infertility occurs due to various factors such as immature reproductive system, defective reproductive system, endocrine disorders, etc.

INFERTILITY IN MALES

CAUSES

1. *Decreased Sperm Count – Oligozoospermia*

Normal sperm count in a male is about 100 to 150 millions/mL of semen. Infertility occurs when the sperm count decreases below 20 millions/mL of semen. Sperm count decreases because of disruption of seminiferous tubules or acute infection in testis. In some males, there is possibility of sterility (permanent inability to produce offspring) because of absence of spermatogenesis as in the case of cryptorchidism or underdeveloped testis (Chapter 74).

2. *Abnormal Sperms*

Sometimes, the sperm count may be normal, but the structure of the sperm may be abnormal. The sperms may be without tail and nonmotile or with two heads or with abnormal head. When a large number of abnormal sperms are produced infertility occurs (Chapter 77).

3. *Obstruction of Reproductive Ducts*

Obstruction of reproductive ducts like vas deferens leads to infertility.

4. *Other Disorders*

i. Cryptorchidism
ii. Trauma
iii. Mumps
iv. Long-term use of drugs
v. Alcoholism
vi. Genetic disorders
vii. Hypothalamic disorders
viii. Disorders of pituitary, thyroid and pancreas.

INFERTILITY IN FEMALES

CAUSES

1. *Abnormalities of Ovary*

Sometimes, a thick capsule develops around the ovaries and prevents ovulation. In some women, ovaries develop cysts (membranous sac containing fluid) or become fibrotic (hardened tissues resulting from lymphedema).

In these conditions, maturation and release of ovum does not occur.

2. *Abnormalities of Uterus*

A type of endometrial tissue similar to uterine endometrium grows in the pelvic cavity surrounding

the uterus, fallopian tubes and ovaries. It is called endometriosis. And, pregnancy does not occur in this condition.

In some cases, there is low grade infection or inflammation or abnormal hormonal stimulation in the cervix. It leads to the abnormal secretion of thick mucus in cervix, which prevents entry of sperm and fertilization of ovum.

3. *Absence of Ovulation*

Ovulation does not occur in some females, because of hyposecretion of gonadotropic hormones. Quantities of these hormones are not sufficient enough to cause maturation of ovum or release of ovum. The cycle without ovulation is known as anovulatory cycle.

4. *Other Disorders*

i. Diabetes mellitus
ii. Renal diseases
iii. Liver diseases
iv. Hypothalamic disorders
v. Disorders of pituitary gland, thyroid and adrenal glands.

Chapter 84

Pregnancy and Parturition

INTRODUCTION

Ovum is released from graafian follicle of ovary into the abdominal cavity at the time of ovulation.

From abdominal cavity, ovum enters fallopian tube through the **fimbriated end.** Entry of ovum is facilitated by movement of cilia present in the inner surface of fimbriated end.

Ovum of matured follicle in the ovary is in **primary oocyte** stage with **diploid number** (23 pairs) of chromosomes. Just before ovulation, meiotic division takes place in the ovum. Primary oocyte divides into a **secondary oocyte** and a **first polar body.** First polar body is expelled out. **Secondary oocyte** contains only 23 chromosomes **(haploid).** Remaining 23 chromosomes are lost in the expelled first polar body.

Thus, when the ovum is released into abdominal cavity during ovulation, it is in the secondary oocyte stage with haploid number of chromosomes.

FERTILIZATION OF THE OVUM

Fertilization refers to **fusion** (union) of male and female gamates (sperm and ovum) to form a new offspring.

If sexual intercourse occurs at ovulation time and semen is ejaculated in the vagina, the sperms travel through the vagina and uterus to reach the fallopian tube. Sperms reach the ovarian end of fallopian tube within 30 to 60 minutes.

Movement of the sperm through uterus is facilitated by the **antiperistaltic contractions** of uterine muscles. Uterine contractions are induced by oxytocin, which

is secreted from posterior pituitary by neuroendocrine reflex during sexual intercourse (Chapter 66). Uterine contractions are also facilitated by **prostaglandin** (PGE_2) present in male seminal fluid.

Among 200 to 300 millions of sperms entering female genital tract, only a few thousand sperms reach the spot near the ovum. Among these few thousand sperms, only one succeeds in fertilizing the ovum.

During fertilization, the sperm enters the ovum by penetrating the multiple layers of granulosa cells known as **corona radiata** present around the ovum. It is facilitated by **hyaluronidase** and **proteolytic enzymes** present in acrosome of sperm. Proteolytic enzymes from acrosome of the successful sperm diffuse through the structures of zona pellucida and inactivate the other sperms entering the ovum.

Penetrating movement of sperm is enabled by a protein called **CatSper** present in the tail portion of the sperm. It is a tunnel-shaped protein and forms the ion channel for entry of calcium into sperm cell.

Immediately after fertilization, ovum, which is in secondary oocyte stage, divides into a matured ovum and a **second polar body.** Second polar body is expelled. Nucleus of matured ovum becomes female pronucleus with 23 chromosomes, which include **22 autosomes** and one sex chromosome called **X chromosome.**

Simultaneously, head of sperm swells and becomes male pronucleus. Then 23 chromosomes of the sperm and 23 chromosomes of ovum arrange themselves to reform the 23 pairs of chromosomes in the fertilized ovum.

SEX CHROMOSOMES AND SEX DETERMINATION

SEX CHROMOSOMES

All the dividing cells in the body have 23 pairs of chromosomes. Among the 23 pairs, 22 pairs are called **somatic chromosomes** or **autosomes.** Remaining one pair of chromosomes is called **sex chromosomes.** Sex chromosomes are X and Y chromosomes.

SEX DETERMINATION

Sex chromosomes are responsible for sex determination. During fertilization of ovum, 23 chromosomes from ovum and 23 chromosomes from the sperm unite together to form the 23 pairs (46) of chromosomes in the fertilized ovum. Now, sex determination occurs. Ovum contains the X chromosome. Sperm has either X chromosome or Y chromosome. When the ovum is fertilized by a sperm with X chromosome, the child will be female with XX chromosome. And, if the ovum is fertilized by a sperm with Y chromosome, the sex of the child will be male with XY chromosome. So, the sex of the child depends upon the male partner.

Role of testosterone in **sex differentiation** is explained in Chapter 74.

IMPLANTATION

Implantation is the process by which the fertilized ovum called **zygote** implants (fixes itself or gets attached) in the endometrial lining of uterus.

After the fertilization, the ovum is known as zygote. Zygote takes 3 to 5 days to reach the uterine cavity from fallopian tube. While travelling through the fallopian tube, the zygote receives its nutrition from the secretions of fallopian tube.

After reaching the uterus, the developing zygote remains freely in the uterine cavity for 2 to 4 days before it is implanted. Thus, it takes about 1 week for implantation after the day of fertilization. During the stay in uterine cavity before implantation, the zygote receives its nutrition from the secretions of endometrium, which is known as **uterine milk.**

Just before implantation, the zygote develops into **morula** and then the implantation starts. A layer of spherical cells called trophoblast cells is formed around morula. Trophoblast cells release proteolytic enzymes over the surface of endometrium. These enzymes digest the cells of the endometrium. Now, morula moves through the digested part of endometrium and implants itself.

DEVELOPMENT OF PLACENTA AND EMBRYO

Already uterus is prepared by progesterone secreted from the corpus luteum during secretory phase of menstrual cycle. After implantation, placenta develops between morula and endometrium.

When implantation occurs, there is further increase in the thickness of endometrium because of continuous secretion of progesterone from corpus luteum. At this stage, the endometrial stromal cells are called **decidual cells** and the endometrium at the implanted area is called **decidua.**

Now the **trophoblastic cells** of morula develop into cords, which are attached with decidual portion of endometrium. Blood capillaries grow into these cords from the blood vessels of the newly formed embryo. At about 16th day after fertilization, heart of embryo starts pumping the blood into the **trophoblastic cords.**

At the same time, blood sinusoids develop around the trophoblastic cords. These sinusoids receive blood from the mother.

Trophoblastic cells form some vascular projections into which fetal capillaries grow. These vascular projections become **placental villi.**

Thus, the final form of **placenta** has got the fetal part and the maternal part.

Fetal part of placenta contains the two umbilical arteries, which carry fetal blood to the placental villi through the capillaries. The blood returns back to fetus through umbilical vein. Maternal part of placenta is formed by uterine arteries through which blood flows into sinusoids that surround the villi. The blood returns back to mother's body through uterine vein.

Functions of placenta are described in detail in Chapter 85.

MATERNAL CHANGES DURING PREGNANCY

During pregnancy, the changes are noticed in various organs, body weight, the metabolic activities and functional status of different physiological systems in the mother.

STRUCTURAL CHANGES

Various structural changes are noticed in the primary sex organs, accessory sex organs and in the mammary glands during pregnancy.

1. *Ovaries*

Follicular changes do not appear in ovary and ovulation does not occur because the secretion of FSH and LH from anterior pituitary is inhibited. Corpus luteum enlarges and secretes a large quantity of progesterone and little estrogen, which are essential for maintaining the pregnancy. It continues for 3 months and then, corpus luteum degenerates. By this time placenta develops fully and takes over the function of secreting estrogen and progesterone. It continues throughout the period of pregnancy thus inhibiting the secretion of FSH and LH.

2. *Uterus*

When the fetus grows, uterus undergoes changes in volume, size, shape and weight.

i. *Volume*

Volume of uterus increases gradually due to fetal growth. From almost zero volume, uterus reaches about 5 to 7 liters at the end of pregnancy. Out of this, 50% of the volume is due to the fetus and rest is due to the placenta, amniotic fluid, etc.

ii. *Size*

Size of the uterus also increases due to:

a. **Hyperplasia** (increase in number of cells) of myometrium
b. **Hypertrophy** (increase in size of the cells) of myometrium
c. Growth of fetus.

iii. *Shape*

The shape of non-pregnant uterus is **pyriform.** As the fetus grows, at the 12th week of pregnancy, it becomes **globular.** Then, once again it becomes pyriform gradually.

iv. *Weight*

Non-pregnant uterus weighs about 30 to 50 g. The weight increases as the pregnancy advances. At the end of pregnancy, the uterine weight increases to about 1,000 to 1,200 g.

v. *Histological changes*

Endometrium shows formation of decidua, which is the bed for the fertilized ovum during the initial stages of pregnancy. Later, by the end of 3 months, three layers of decidua are formed:

a. Decidua basalis, which is the maternal part
b. Decidua capsularis that surrounds fetal sac
c. Decidua parietalis, which lines rest of uterine wall.

After the 3rd month, the decidua capsularis and parietalis fuse together.

3. *Vagina*

Vagina increases in size and its color changes to violet due to increased blood supply. There is deposition of **glycogen** in the epithelial cells.

4. *Cervix*

In cervix, the number of glands, blood supply and mucus secretion increase. The tough cervix becomes soft and it is closed by **mucus plug.**

5. *Fallopian Tube*

The number of epithelial cells and blood supply increase in fallopian tubes.

6. *Mammary Glands*

Size of the mammary glands increases because of development of new ducts and alveoli, deposition of fat and increased vascularization. Pigmentation of nipple and areola occurs.

■ INCREASE IN BODY WEIGHT

Average weight gained by the body during pregnancy is about 12 kg. Approximate weight of various structures, which adds to the weight gain:

1. Fetus : 3.5 kg
2. Amniotic fluid : 2.0 kg
3. Placenta : 1.5 kg
4. Increase in maternal body weight : 5.0 kg

If proper **prenatal care** is not taken, the body weight increases greatly by about 20 to 30 kg.

■ METABOLIC CHANGES

The metabolic activities are accelerated in the body due to increased secretion of various hormones like thyroxine, cortisol and sex hormones.

1. *Basal Metabolic Rate*

Increase in the secretion of various hormones especially thyroxine increases the basal metabolic rate by about 15% in the later stages of pregnancy.

2. *Protein Metabolism*

The anabolism of proteins increases during pregnancy. Positive nitrogen balance occurs. The deposition of proteins increases in the uterus.

3. *Carbohydrate Metabolism*

Blood glucose level increases leading to **glucosuria. Ketosis** develops either due to less food or more vomiting. Because of all these reasons, there is **hyperplasia** of beta cells of islets of Langerhans in pancreas leading to increase in secretion of insulin. Inspite of this, there is possibility of developing **diabetes in pregnancy** or **latent diabetes** after delivery.

4. *Lipid Metabolism*

During pregnancy, there is deposition of about 3 to 4 kg of fat in the maternal body. It also increases the blood cholesterol level and ketosis.

5. *Water and Mineral Metabolism*

Estrogen and progesterone are secreted by corpus luteum in the first trimester and by placenta later. These hormones increase the retention of sodium and water. Secretion of aldosterone increases during pregnancy. Aldosterone in turn increases the reabsorption of sodium from renal tubules. Apart from water and sodium retention, there is retention of calcium and phosphorus as well. Calcium and phosphorus are necessary for the growing fetus.

■ CHANGES IN PHYSIOLOGICAL SYSTEMS

1. *Blood*

The blood volume increases by about 20% or about 1 L. This increase is mainly because of increase in plasma volume. It causes hemodilution. Because of great demand for iron by the fetus, the mother usually develops anemia. It can be rectified by proper prenatal care and iron replacement.

2. *Cardiovascular System*

Cardiac output

Generally, cardiac output increases by about 30% in the first trimester. After the 3rd month, cardiac output starts decreasing and reaches almost the normal level in the later stages of pregnancy.

Blood pressure

Arterial blood pressure remains unchanged during the first trimester. During the second trimester, there is a slight decrease in blood pressure. It is due to the diversion of blood to uterine sinuses. And, hypertension develops if proper prenatal care is not taken.

Pre-eclampsia

Pre-eclampsia is the **hypertensive** disorder of pregnancy. It is otherwise known as **toxemia of pregnancy.** About 3% to 4% of the pregnant women suffer from this. It usually occurs during last trimester of pregnancy.

Cause for hypertension

1. Release of vasoconstrictor substances from placenta
2. Hypersecretion of adrenal hormones and other hormones, which cause vasoconstriction
3. Development of autoimmune processes induced by the presence of placenta or fetus.

Other symptoms associated with hypertension

1. Decreased blood flow to kidney and thickening of glomerular capillary membrane, leading to reduction in GFR and urinary output
2. Retention of sodium and water
3. Decreased urinary output along with retention of sodium and water results in increased extracellular fluid volume and edema
4. Excretion of proteins through urine.

Eclampsia

Eclampsia is the serious condition of pre-ecclampsia characterized by severe **vascular spasm,** dangerous **hypertension** and **convulsive muscular contractions** almost like **seizures.** It occurs just before, during or immediately after delivery. It leads to **death,** if timely treatment is not given.

Features of eclampsia

1. Spasm of blood vessels
2. Very severe hypertension
3. Renal failure
4. Liver failure
5. Heart failure
6. Convulsions
7. Coma.

Treatment for eclampsia

Treatment should be immediate. It includes administration of quick acting vasodilator drugs or termination of pregnancy.

3. *Respiratory System*

Overall activity of respiratory system increases slightly. Tidal volume, pulmonary ventilation and oxygen utilization are increased.

4. *Excretory System*

Renal blood flow and GFR increase resulting in increase in urine formation. It is because of increase in fluid intake and the increased excretory products from fetus. The urine becomes diluted with the specific gravity of 1,025. In the first trimester, the frequency of micturition increases because of the pressure exerted by the uterus on bladder.

5. *Digestive System*

During the initial stages of pregnancy, the **morning sickness** occurs in mother. It involves **nausea, vomiting** and **giddiness.** This is because of the hormonal imbalance. The motility of GI tract decreases by progesterone and constipation is common. **Indigestion** and **hypochlorhydria** (decrease in the amount of hydrochloric acid in gastric juice) also occur.

6. *Endocrine System*

i. *Anterior pituitary*

During pregnancy, the size of anterior pituitary increases by about 50%. And secretion of corticotropin, thyrotropin and prolactin increases. However, the secretion of FSH and LH decreases very much. It is because of negative feedback control by estrogen and progesterone, which are continuously secreted from corpus luteum initially and placenta later on.

ii. *Adrenal cortex*

There is moderate increase in secretion of cortisol, which helps in the mobilization of amino acids from the mother's tissues to the fetus. Aldosterone secretion also increases. It reaches the maximum at the end of pregnancy. Along with estrogen and progesterone, aldosterone is responsible for the retention of water and sodium.

iii. *Thyroid gland*

The size and the secretory activity of thyroid gland increase during pregnancy. The increased secretion of thyroxine helps in the preparation of mammary glands for lactation. It is also responsible for increase in basal metabolic rate.

iv. *Parathyroid glands*

Parathyroid glands also show an increase in the size and secretory activity. Parathormone is responsible for maintenance of calcium level in mother's blood in spite of loss of large amount of calcium to fetus.

7. *Nervous System*

There is general excitement of nervous system during pregnancy. It leads to the **psychological imbalance** such as change in the moods, excitement or depression in the early stages of pregnancy. During the later months of pregnancy, the woman becomes very much excited because of anticipation of delivery of the baby, labor pain, etc.

■ GESTATION PERIOD

Gestation period refers to the pregnancy period. The average gestation period is about 280 days or 40 weeks from the date of last menstrual period (LMP). Traditionally, it is calculated as 10 lunar months. However, in terms of modern calendar it is calculated as 9 months and 7 days. If the menstrual cycle is normal 28 day cycle, the fertilization of ovum by the sperm occurs on 14th day after LMP. Thus the actual duration of human pregnancy is 280 – 14 = 266 days. If the pregnancy ends before 28th week, it is referred as miscarriage. If the pregnancy ends before 37th week, then it is considered as premature labor.

PARTURITION

Parturition is the expulsion or delivery of the fetus from the mother's body. It occurs at the end of pregnancy. The process by which the delivery of fetus occurs is called **labor.** It involves various activities such as contraction of uterus, dilatation of cervix and opening of vaginal canal.

BRAXTON HICKS CONTRACTIONS

Braxton Hicks contractions are the weak, irregular, short and usually painless uterine contractions, which start after 6th week of pregnancy. These contractions are named after the British doctor, **John Braxton Hicks** who discovered them in 1872. It is suggested that these contractions do not induce cervical dilatation but may cause softening of cervix. Often called the **practice contractions,** Braxton Hicks contractions help the uterus practice for upcoming labor. Sometimes these contractions cause discomfort.

Braxton Hicks contractions are triggered by several factors such as:

1. Touching the abdomen
2. Movement of fetus in uterus
3. Physical activity
4. Sexual intercourse
5. Dehydration.

FALSE LABOR CONTRACTIONS

While nearing the time of delivery, the Braxton Hicks contractions become intense and are called **false labor contractions.** The false labor contractions are believed to help cervical dilatation.

STAGES OF PARTURITION

Parturition occurs in three stages:

First Stage

First, the strong uterine contractions called **labor contractions** commence. Labor contractions arise from fundus of uterus and move downwards so that the head of fetus is pushed against cervix. It results in dilatation of cervix and opening of vaginal canal. Exact cause for the onset of labor is not known. This stage extends for a variable period of time.

Second Stage

In this stage, the fetus is delivered out from uterus through cervix and vaginal canal. This stage lasts for about 1 hour.

Third Stage

During this stage, the placenta is detached from the decidua and is expelled out from uterus. It occurs within 10 to 15 minutes after the delivery of the child.

MECHANISM OF LABOR

The slow and weak contractions of uterus commence at about a month before parturition. Later, the contractions gradually obtain strength and finally are converted into labor contractions at the time of labor. Exact cause for the onset of labor contractions is not known. It is strongly believed that the labor contractions are induced by the signal from fetus. And during labor, reflexes from uterus and cervix produce the powerful uterine contractions. Thus, uterus and cervix play an important role in labor. Many hormones are also involved during parturition.

ROLE OF UTERUS

Once started, the uterine contractions cause the development of more and more strong contractions. That is, the irritation of uterine muscle during initial contraction leads to further reflex contractions. It is called **positive feedback** mechanism. It plays an important role, not only in producing more number of uterine contractions but also the contractions to become more and more powerful.

ROLE OF CERVIX

Cervix also plays an important role in increasing the strength of uterine contractions. When the head of fetus is forced against the cervix during the first stage of labor, the cervix stretches. It causes stimulation of muscles of cervix, which in turn results in reflex contractions of uterus.

ROLE OF HORMONES

Hormones involved in the process of parturition:

Maternal Hormones

1. Oxytocin
2. Prostaglandins
3. Cortisol
4. Catecholamines
5. Relaxin.

Fetal Hormones

1. Oxytocin
2. Cortisol
3. Prostaglandins.

Placental Hormones

1. Estrogen
2. Progesterone
3. Prostaglandins.

Estrogen

Estrogen is continuously secreted along with progesterone throughout the gestation period. However, in the later period, the quantity of estrogen released is much greater than that of progesterone.

Estrogen:

i. Increases the force of uterine contractions
ii. Increases the number of oxytocin receptors in uterine wall
iii. Accelerates the synthesis of prostaglandin from uterus.

Progesterone

Progesterone plays an important role in labor indirectly by its sudden withdrawal at the end of pregnancy.

Throughout the period of gestation, progesterone suppresses uterine contractions. It also inhibits the synthesis of prostaglandin (PGE_2), which is necessary for uterine contraction. Progesterone inhibits prostaglandin synthesis by inhibiting the release of the enzyme phospholipase A, which is essential for prostaglandin synthesis.

Sudden decrease in progesterone secretion at the end of gestation period increases the uterine contractions and PGE_2 synthesis.

Oxytocin

Oxytocin:

i. Causes contraction of smooth muscle of uterus and enhances labor. During the later stages of pregnancy, the number of receptors for oxytocin increases in the wall of uterus by the influence of estrogen. Because of this, the uterus becomes more sensitive to oxytocin.
ii. Stimulates the release of prostaglandins in the decidua.

Oxytocin is released in large quantity during labor. It is due to **neuroendocrine reflex.** During the movement of fetus through cervix, the receptors on the cervix are stimulated and start discharging a large number of impulses. Impulses are carried to hypothalamus by the somatic nerve fibers and result in the release of a large quantity of oxytocin, which enhances labor. The release of more amount of oxytocin occurs due to **positive feedback** (Chapter 66).

Relaxin

Relaxin is secreted from maternal ovary (corpus luteum) during the initial period of pregnancy. It is secreted in large quantity at the time of labor by placenta and mammary glands (Chapter 87).

Relaxin:

i. Helps labor by softening the cervix and loosening the ligaments of symphysis pubis, so that the dilatation of cervix occurs
ii. Increases the number of receptors for oxytocin in the myometrium
iii. Simultaneously suppresses the inhibitory action of progesterone on uterine contraction so that the uterus starts contracting
iv. Facilitates the development of mammary glands.

Prostaglandins

In recent times, prostaglandins are considered to play a vital role in labor. Prostaglandins particularly PGE_2 facilitate labor by increasing the force of uterine contractions. The prostaglandins are secreted from uterine tissues, fetal membranes and placenta. Their concentration is increased in maternal blood and amniotic fluid at the time of labor.

Prostaglandins increase the force of uterine contractions by elevating the intracellular concentration of calcium ions in the uterine muscles.

Catecholamines

It is believed that the circulating adrenaline and noradrenaline also might increase the uterine contraction through alpha adrenergic receptors.

Cortisol

At the time of labor, hypothalamus releases large quantity of corticotropin-releasing hormone, which increases the release of cortisol from the adrenal cortex. Cortisol enhances the uterine contraction and plays an important role in helping the mother to withstand the stress during labor.

Chapter 85

Placenta

INTRODUCTION

Placenta is a temporary membranous vascular organ that develops in females during pregnancy. It is expelled after childbirth. Placenta forms a link between the fetus and mother. It is considered as an anchor for the growing fetus. It is not only the physical attachment between the fetus and mother, but also forms the physiological connection between the two.

Placenta is implanted in the wall of the uterus. It is formed from both embryonic and maternal tissues. So, it consists of two parts namely the fetal part and the mother's part. It is connected to the fetus by umbilical cord, which contains blood vessels and connective tissue. Development of placenta is explained in Chapter 84.

The delivery of fetus is followed by the expulsion of placenta. After expulsion of the placenta, the umbilical cord is cut. The site of attachment of placenta in the center of anterior abdomen of fetus is called navel or umbilicus.

FUNCTIONS OF PLACENTA

NUTRITIVE FUNCTION

Nutritive substances, electrolytes and hormones necessary for the development of fetus diffuse from mother's blood into fetal blood through placenta.

EXCRETORY FUNCTION

Metabolic end products and other waste products from the fetal body are excreted into the mother's blood through placenta.

RESPIRATORY FUNCTION

Fetal lungs are non-functioning and placenta forms the respiratory organ for fetus. Oxygen necessary for fetus is received by diffusion from the maternal blood and carbon dioxide from fetal blood diffuses into the mother's blood through placenta.

Exchange of Respiratory Gases between Fetal Blood and Maternal Blood

Exchange of respiratory gases between fetal blood and maternal blood occurs mainly because of pressure gradient. Partial pressure of oxygen in the maternal blood is 50 mm Hg. In fetal blood, the partial pressure of oxygen is 30 mm Hg. This pressure gradient of 20 mm Hg causes the diffusion of oxygen into the fetal blood.

This pressure gradient is very low, compared to the gradient existing between partial pressure of oxygen in arterial blood and alveoli in adults. Still, an adequate quantity of oxygen is available for fetus.

It is because of two reasons:

1. The hemoglobin in fetal blood has 20 times more affinity for oxygen than the adult hemoglobin

2. The concentration of hemoglobin is about 50% more in fetal blood than in adult blood.

Bohr effect and Double Bohr effect

Bohr effect is the decrease in the affinity of hemoglobin for oxygen due to increased carbon dioxide tension. When carbon dioxide tension decreases, the affinity of hemoglobin for oxygen is increased. All the metabolic end products including carbon dioxide are completely excreted from fetus into the maternal blood. This develops low partial pressure of carbon dioxide in fetal blood. So, the affinity of fetal hemoglobin for oxygen increases resulting in diffusion of more amount of oxygen from mother's blood into fetal blood.

At the same time, because of entrance of fetal carbon dioxide into maternal blood, partial pressure of carbon dioxide is very high in mother's blood. It decreases the affinity of mother's hemoglobin for oxygen resulting in diffusion of more amount of oxygen into the fetal blood.

Double Bohr effect is the operation of Bohr effect in both fetal blood and maternal blood.

■ ENDOCRINE FUNCTION

Hormones secreted by placenta are:

1. Human chorionic gonadotropin
2. Estrogen
3. Progesterone
4. Human chorionic somatomammotropin
5. Relaxin.

1. *Human Chorionic Gonadotropin*

Human chorionic gonadotropin (hCG) is a glycoprotein. Its chemical structure is similar to that of LH.

Actions of hCG

i. *On corpus luteum:* hCG is responsible for the preservation and the secretory activity of corpus luteum. Progesterone and estrogen secreted by corpus luteum are essential for the maintenance of pregnancy. Deficiency or absence of hCG during the first 2 months of pregnancy leads to termination of pregnancy (abortion), because of involution of corpus luteum.

ii. *On fetal testes:* Action of hCG on fetal testes is similar to that of LH in adults. It stimulates the interstitial cells of Leydig and causes secretion of testosterone. The testosterone is necessary for the development of sex organs in male fetus.

2. *Estrogen*

Placental estrogen is similar to ovarian estrogen in structure and function.

Actions of placental estrogen

i. *On uterus:* Causes enlargement of the uterus so that, the growing fetus can be accommodated.

ii. *On breasts:* Responsible for the enlargement of the breasts and growth of the duct system in the breasts.

iii. *On external genitalia:* Causes enlargement of the female external genitalia.

iv. *On pelvis:* Relaxes pelvic ligaments. It facilitates the passage of the fetus through the birth canal at the time of labor.

3. *Progesterone*

Placental progesterone is similar to ovarian progesterone in structure and function.

Actions of placental progesterone

i. *On endometrium of uterus:* Accelerates the proliferation and development of decidual cells in the endometrium of uterus. The decidual cells are responsible for the supply of nutrition to the embryo in the early stage.

ii. *On the movements of uterus:* Inhibits the contraction of muscles in the pregnant uterus. It is an important function of progesterone as it prevents expulsion of fetus during pregnancy.

iii. *On breasts:* Causes enlargement of breasts and growth of duct system of the breasts.

Progesterone is responsible for further development and preparation of mammary glands for lactation.

4. *Human Chorionic Somatomammotropin*

Human chorionic somatomammotropin (HCS) is a protein hormone secreted from placenta. It is often called placental lactogen. It acts like prolactin and growth hormone secreted from pituitary. So, it is believed to act on mammary glands and to enhance the growth of fetus by influencing the metabolic activities. It increases the amount of glucose and lipids in the maternal blood, which are transferred to fetus.

Actions of HCS

i. *On breasts:* In experimental animals, administration of HCS causes enlargement of mammary glands and induces lactation. That is why, it is

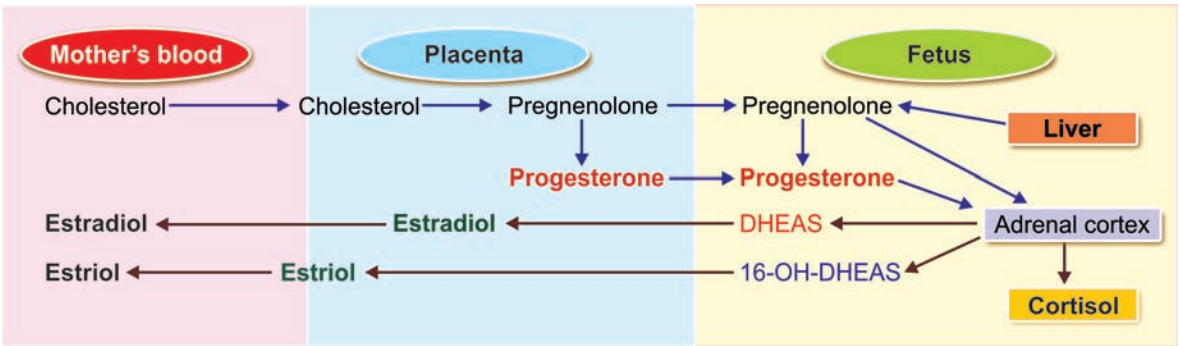


FIGURE 85.1: Fetoplacental unit. DHEAS = Dehydroepiandrosterone sulfate, 16-OH-DHEAS = 16-hydoxy-dehydroepiandrosterone sulfate.

named as mammotropin. However, the action of this hormone on the breasts of pregnant women is not known.

ii. *On protein metabolism:* HCS acts like GH on protein metabolism. It causes anabolism of proteins and accumulation of proteins in the fetal tissues. Thus, the growth of fetus is enhanced.

iii. *On carbohydrate metabolism:* It reduces the peripheral utilization of glucose in the mother leading to availability of large quantity of glucose to the growing fetus.

iv. *On lipid metabolism:* It mobilizes fat from the adipose tissue of the mother. A large amount of free fatty acid is made available as the source of energy in the mother's body. It compensates the loss of glucose from the mother's blood to fetus.

5. *Relaxin*

Relaxin is a polypeptide, which is secreted by corpus luteum. It is also secreted in large quantity by placenta and mammary glands at the time of labor (Refer Chapter 84).

■ FETOPLACENTAL UNIT

Fetoplacental unit refers to the interaction between fetus and placenta in the formation of steroid hormones. The interaction between fetus and placenta occurs because some of the enzymes involved in steroid synthesis present in fetus are absent in placenta and those enzymes, which are absent in fetus are present in placenta.

Due to this interaction during synthesis of steroid hormones, fetus and placenta are together called fetoplacental unit (Fig. 85.1).

■ FUNCTIONS OF FETOPLACENTAL UNIT

Placenta and fetus interact with each other in the synthesis of steroid hormones in the following manner:

1. Cholesterol, which is the precursor for steroid hormones, is obtained by placenta from mother's blood
2. Placenta synthesizes pregnenolone from cholesterol
3. From pregnenolone, progesterone is formed
4. Some amount of the pregnenolone from placenta enters fetus. Fetal liver also produces a small quantity of pregnenolone
5. Pregnenolone from placenta and fetal liver forms the substrate for the formation of two substances in the adrenal gland of the fetus:
   i. Dehydroepiandrosterone sulfate (DHEAS)
   ii. 16-hydroxy-dehydroepiandrosterone sulfate (16-OH-DHEAS).

   Some of the DHEAS is also hydroxylated into 16-OH-DHEAS in fetal liver
6. DHEAS and 16-OH-DHEAS are transported back into the placenta to form estrogen
7. Estradiol is synthesized from DHEAS and estriol from 16-OH-DHEAS. These two forms of estrogen enter mother's blood
8. Some amount of the progesterone enters the fetus from placenta
9. From this progesterone, cortisol and corticosterone are synthesized in fetal adrenal glands.

Chapter 86

Pregnancy Tests

- INTRODUCTION
- BIOLOGICAL TEST
- IMMUNOLOGICAL TESTS

INTRODUCTION

Pregnancy test is the test used to detect or confirm pregnancy. The basis of pregnancy tests is to determine the presence of the **human chorionic gonadotropin (hCG)** in the urine of woman suspected for pregnancy. Both biological and immunological tests are available to determine the presence of hCG in the urine of the pregnant woman.

BIOLOGICAL TESTS

These tests are performed by using experimental animals. The biological tests for pregnancy can be performed only after 2 or 3 weeks of conception so that, the concentration of hCG in urine is sufficient to show the result.

ASCHHEIM-ZONDEK TEST

Aschheim-Zondek test was the first test invented for confirming the pregnancy. It depends upon the ovarian changes in immature mice caused by hCG. The immature mice do not ovulate naturally.

Ovulation occurs only if hCG is injected. 2 mL of urine from the woman suspected for pregnancy is injected daily for 2 days into the immature mice. 5 days after injection of urine, the mice are killed. The ovaries are examined for the presence of corpora lutea (plural for corpus luteum) and hemorrhages, which indicates ovulation. Ovulation is due to the presence of hCG in urine.

KUPPERMAN TEST

Kupperaman test is the modification of Aschheim-Zondek test, in order to save time. In this, an immature rat is used instead of immature mice. About 2 mL of urine is injected subcutaneously into immature rat and ovarian changes are observed after 6 hours. If the urine is injected intraperitoneally, the ovarian changes can be observed within 2 hours.

FRIEDMAN TEST

In this test, 10 to 15 mL of urine is injected intravenously into rabbit and ovulation is observed by examining the ovaries after 48 hours.

HOGBEN TEST

In this test, about 20 to 30 ml of urine is concentrated and injected into the dorsal lymph sac of South African toad, *Xenopus levis*. If hCG is present in the urine, it causes ovulation after 12 hours.

GALLI-MAININI TEST

In this test, 2 mL of urine is injected into the male amphibian (toad or frog). hCG in urine causes expulsion of spermatozoa within 2 hours.

Biological tests are outdated after the development of immunological tests.

Disadvantages of Biological Tests

Biological tests for pregnancy are replaced by immunological tests because of several disadvantages:

1. The biological test require animals
2. Tests can be performed only after 2 to 3 weeks of pregnancy so that sufficient quantity of hCG is excreted in urine
3. Results are not obtained quickly; one has to wait for 2 to 48 hours
4. Tests involve tedious procedures such as sacrificing the animals.

IMMUNOLOGICAL TESTS

Presence of hCG is also determined by using immunological techniques. Immunological tests are based on **double antigen-antibody reactions.** Commonly performed immunological test is known as **Gravindex test.**

PRINCIPLE

Principle is to determine the agglutination of sheep RBCs coated with hCG. Latex particles could also be used instead of sheep RBCs.

REQUISITES

1. *Antiserum from Rabbit*

Urine from a pregnant woman is collected and hCG is isolated. This hCG is injected into a rabbit.

The rabbit develops **antibodies against hCG.** The antibodies are called **hCG antibody or anti-hCG.** The rabbit's blood is obtained and serum is separated. The serum containing hCG antibody is called **rabbit antiserum** or **hCG antiserum.** It is readily available in the market.

2. *Red Blood Cells from Sheep*

RBCs are obtained from sheep blood and are coated with pure hCG obtained from urine of the pregnant women. Nowadays, instead of sheep RBCs, the rubberized synthetic particles called the **latex particles** are used.

3. *Urine*

Fresh urine sample of the woman, who needs to confirm pregnancy is used for Gravindex test.

PROCEDURE

1. One drop of hCG antiserum is taken on a glass slide. One drop of urine from the woman who wants to confirm pregnancy is added to this and both are mixed well.
2. Now, one drop of latex particles is added to this and mixed.

OBSERVATION AND RESULT

Result is determined by observing the agglutination of latex particles added to mixer of hCG antiserum and woman's urine.

Absence of Agglutination of Latex Particles

If hCG is present in urine, it is agglutinated by antibodies of antiserum and all the antibodies are fully used up. No free antibody is available. Agglutination of hCG molecules by antibodies is not visible because it is colorless.

Later when latex particles are added, these particles are not agglutinated because, free antibody is not available. Thus, absence of agglutination of latex particles indicates that the woman is pregnant.

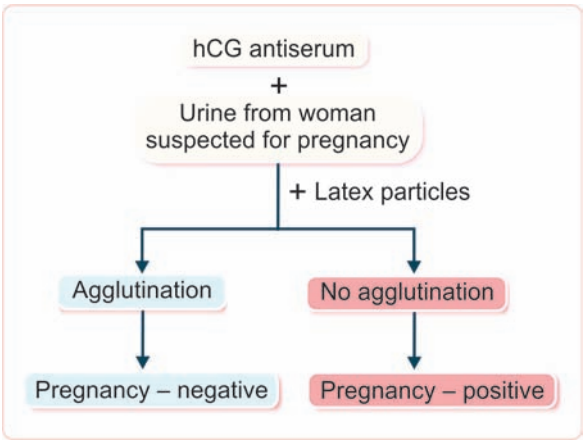


FIGURE 86.1: Immunological test for pregnancy

Presence of Agglutination of Latex Particles

If urine without hCG is mixed with antiserum, the antibodies are freely available. When latex particles are added, the antibodies cause agglutination of these latex particles. Agglutination of latex particles can be seen clearly even with naked eye. Thus, presence of agglutination of latex particles indicates that, the woman is not pregnant (Fig. 86.1).

ADVANTAGES OF IMMUNOLOGICAL TESTS FOR PREGNANCY

1. Immunological tests are more accurate
2. Result is obtained quickly within few minutes
3. These tests can be carried out very easily. The procedure is not cumbersome, as in the case of biological tests
4. Immunological tests can be performed on 5th day of conception. By biological methods, the tests can be performed only after 2 or 3 weeks of conception. It is because, the concentration of hCG required for producing changes in the animals is excreted in urine only after 2 or 3 weeks of pregnancy
5. Recently available immunological tests are more sensitive and involve single step method. Test kit is available in the form of cards. These **pregnancy test** cards can be used even in the first few days of conception. Most sensitive test can detect hCG level as low as 20 mIU/mL.

Mammary Glands and Lactation

Chapter 87

- DEVELOPMENT OF MAMMARY GLANDS
- ROLE OF HORMONES IN GROWTH OF MAMMARY GLANDS
- LACTATION
- BREAST MILK

DEVELOPMENT OF MAMMARY GLANDS

AT BIRTH

At the time of birth, mammary gland is **rudimentary** and consists of only a tiny nipple and few radiating ducts from it.

AT CHILDHOOD

Till puberty, there is no difference in the structure of mammary gland between male and female.

AT PUBERTY

At the time of puberty and afterwards there is a vast change in the structure of female mammary gland due to hormonal influence. The beginning of changes in mammary gland is called **thelarche.** It occurs at the time of puberty, just before **menarche** (Chapter 80). At puberty, there is growth of duct system and formation of glandular tissue. During every sexual cycle, at the time of menstruation there is slight regression and in between the phases of menstruation, proliferative changes occur. On the whole, progressive enlargement occurs, which is also due to the deposition of fat.

DURING PREGNANCY

During pregnancy, the mammary glands enlarge to a great extent accompanied by marked changes in structure. During first half of pregnancy, the duct system develops further with appearance of many new alveoli. No milk is secreted by the gland now.

During the second half, there is enormous growth of glandular tissues and the development is completed for the production of milk just before the end of gestation period.

ROLE OF HORMONES IN GROWTH OF MAMMARY GLANDS

Various hormones are involved in the development and growth of breasts at different stages:

1. Estrogen
2. Progesterone
3. Prolactin
4. Placental hormones
5. Other hormones.

1. ESTROGEN

Growth of Ductile System

Estrogen causes growth and branching of **duct system;** so the normal development of duct system in breasts at puberty depends upon estrogen. Estrogen is also responsible for the accumulation of fat in breasts.

2. PROGESTERONE

Growth of Glandular Tissue

The development of stroma of the mammary glands depends upon progesterone activity. Progesterone also stimulates the development of **glandular tissues.**

■ 3. PROLACTIN

Prolactin is necessary for **milk secretion.** However, it also plays an important role in growth of mammary glands during pregnancy.

Normally, prolactin is inhibited by prolactin-inhibiting hormone secreted from hypothalamus. However, prolactin secretion starts increasing from 5th month of pregnancy. At that time, it acts directly on the mammary glands and causes proliferation of epithelial cells of alveoli.

■ 4. PLACENTAL HORMONES

Estrogen and progesterone secreted from placenta are essential for further development of mammary glands during pregnancy. Both the hormones stimulate the proliferation of ducts and glandular cells during pregnancy.

■ 5. OTHER HORMONES

Growth hormone, thyroxine and cortisol enhance the overall growth and development of mammary glands in all stages. Relaxin also facilitates the development of mammary glands. It is secreted by corpus luteum, mammary glands and placenta. Its major function is to facilitate dilatation of cervix during labor (Chapter 84).

■ LACTATION

Lactation means synthesis, secretion and ejection of milk.

Lactation involves two processes:

A. Milk secretion
B. Milk ejection.

■ MILK SECRETION

Synthesis of milk by alveolar epithelium and its passage through the duct system is called milk secretion.

Milk secretion occurs in two phases:

1. Initiation of milk secretion or lactogenesis
2. Maintenance of milk secretion or galactopoiesis.

1. *Initiation of Milk Secretion or Lactogenesis*

Although small amount of milk secretion occurs at later months of pregnancy, a free flow of milk occurs only after the delivery of the child. The milk, which is secreted initially before parturition is called **colostrum.**

Colostrum is lemon yellow in color and it is rich in protein (particularly globulins) and salts. But its sugar content is low. It contains almost all the components of milk except fat.

Role of hormones in lactogenesis

Prolactin is responsible for lactogenesis. During pregnancy, particularly in later months, large quantity of prolactin is secreted. But the activity of this hormone is suppressed by estrogen and progesterone secreted by placenta. Because of this, lactation is prevented during pregnancy.

Immediately after the delivery of the baby and expulsion of placenta, there is sudden loss of estrogen and progesterone. Now, the prolactin is free to exert its action on breasts and to promote lactogenesis.

2. *Maintenance of Milk Secretion or Galactopoiesis*

Galactopoiesis depends upon the hormones like growth hormone, thyroxine and cortisol, which are essential for continuous supply of glucose, amino acids, fatty acids, calcium and other substances necessary for the milk production (Fig. 87.1).

Role of hypothalamus in galactopoiesis

Galactopoiesis occurs till 7 to 9 months after delivery of child provided feeding the baby with mother's milk is continued till then. In fact, the milk production is continued only if feeding the baby is continued. Suckling of nipple by the baby is responsible for continuous milk production.

When the baby suckles, the impulses from touch receptors around the nipple stimulate hypothalamus. It is suggested that hypothalamus releases some prolactin-releasing factors, which cause the prolactin secretion from anterior pituitary. Prolactin acts on glandular tissues and maintains the functional activity of breast for subsequent nursing.

■ MILK EJECTION

Milk ejection is the discharge of milk from mammary gland. It depends upon suckling exerted by the baby and on contractile mechanism in breast, which expels milk from alveoli into the ducts.

Milk ejection is a reflex phenomenon. It is called **milk ejection reflex** or **milk let-down reflex.** It is a **neuroendocrine reflex.**

Milk Ejection Reflex

Milk ejection reflex is explained in Chapter 66.

■ EFFECT OF LACTATION ON MENSTRUAL CYCLE

Woman who nurses her child regularly does not have menstrual cycle for about 24 to 30 weeks after delivery.

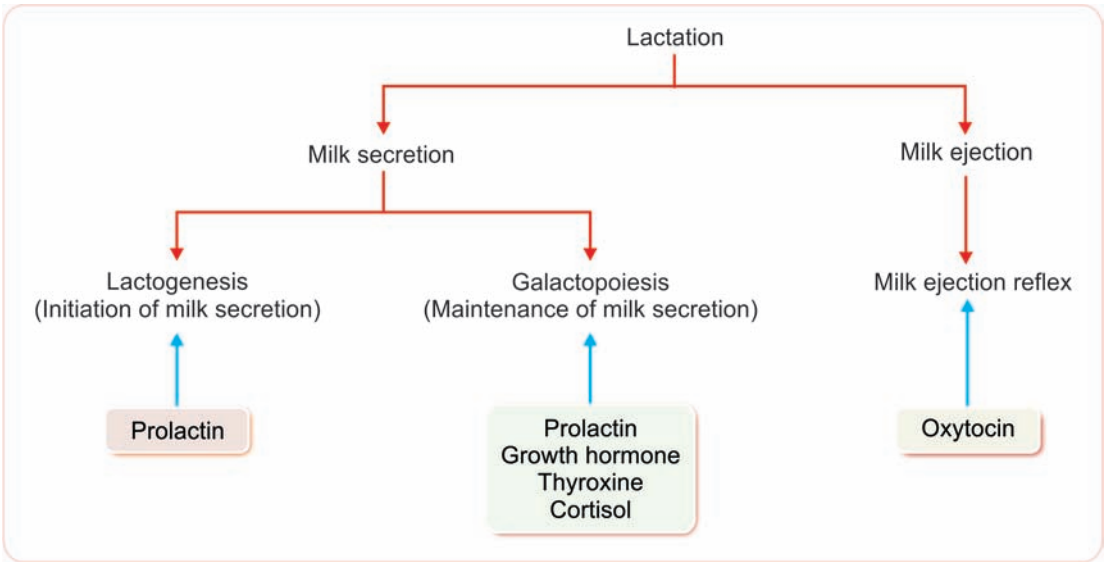


FIGURE 87.1: Process of lactation and role of hormones

It is because, regular nursing the baby stimulates prolactin secretion continuously. Prolactin inhibits GnRH secretion resulting in suppression of gonadotropin secretion. In the absence of gonadotropin, the ovaries become inactive and ovulation does not occur.

When the frequency of nursing the baby decreases (after about 24 weeks) the secretion of GnRH and gonadotropins starts slowly. When sufficient quantity of gonadotropins is secreted, the menstrual cycle starts.

BREAST MILK

Breast or human milk forms the primary source of nutrition for infants.

COMPOSITION

Breast milk contains about 88.5% of water and 11.5% of solids. Important solids are lactose, lactalbumin, iron, vitamins A and D and minerals.

ADVANTAGES OF BREAST MILK

Breast milk is always considered superior to animal milk (cow milk or goat milk) because it consists of sufficient quantity of all the substances necessary for infants like iron, vitamins and minerals.

Besides nourishment of infant, the breast milk also provides several antibodies, which help the infant resist the infection by lethal bacteria. Even some neutrophils and macrophages are secreted in milk. These phagocytic cells protect the infant by destroying microbes in the infant's body.

DISADVANTAGES OF ANIMAL MILK

1. It causes irritation of GI tract and anemia
2. Excess proteins and fats in animal milk are difficult to digest and absorb by the infants
3. High content of casein is harder to digest resulting in GI bleeding and anemia
4. High concentrations of sodium and potassium in animal milk causes overstraining of immature kidneys in infants
5. Low iron content in animal milk develops iron deficiency anemia
6. It has low content of vitamins and essential fatty acids.

Chapter 88

Fertility Control

INTRODUCTION

Fertility control is the use of any method or device to prevent pregnancy. It is also called **birth control, family planning** or **contraception.** Fertility control techniques may be temporary or permanent. Several methods are available for fertility control.

RHYTHM METHOD (SAFE PERIOD)

Rhythm method of fertility control is based on the time of ovulation. After ovulation, i.e. on the 14th day of menstrual cycle, the ovum is fertilized during its passage through fallopian tubes. Its viability is only for 2 days after ovulation and should be fertilized within this period.

Sperms survive only for about 24 to 48 hours after ejaculation in the female genital tract. If sexual intercourse occurs during this period, i.e. between few days before and few days after ovulation, there is chance of pregnancy. This period is called the **dangerous period.** Pregnancy can be avoided if there is no sexual intercourse during this period. The prevention of pregnancy by avoiding sexual mating during this period is called rhythm method.

The periods, when pregnancy does not occur are 4 to 5 days after menstrual bleeding and 5 to 6 days before the onset of next cycle. These periods are together called **safe period.**

Advantages and Disadvantages

It is one of the most successful methods of fertility control provided the woman knows the exact day of ovulation. However, it is not a successful method because of various reasons. Basic knowledge about

the menstrual cycle is necessary to determine the day of ovulation. Self-restraint is essential to avoid sexual intercourse. Because of the practical difficulties, this method is not popular.

MECHANICAL BARRIERS – PREVENTION OF ENTRY OF SPERM INTO UTERUS

Mechanical barriers are used to prevent the entry of sperm into uterine cavity. These barriers are called **condoms.** The **male condom** is a leak proof sheath, made of latex. It covers the penis and does not allow entrance of semen into the female genital tract during coitus.

In females, the commonly used condom is **cervical cap** or **diaphragm.** It covers the cervix and prevents entry of sperm into uterus.

CHEMICAL METHODS

Chemical substances, which destroy the sperms, are applied in female genital tract before coitus. Destruction of sperms is called **spermicidal action.** The spermicidal substances are available in the form of foam tablet, jelly, cream and paste.

ORAL CONTRACEPTIVES (PILL METHOD)

Oral contraceptives are the drugs taken by mouth (pills) to prevent pregnancy. These pills prevent pregnancy by inhibiting maturation of follicles and ovulation. This leads to alteration of normal menstrual cycle. The menstrual cycle becomes the anovulatory cycle.

This method of fertility control is called **pill method** and pills are called **contraceptive pills** or **birth control pills.** These pills contain synthetic estrogen and progesterone.

Contraceptive pills are of three types:

1. Classical or combined pills
2. Sequential pills
3. Minipills or micropills.

1. CLASSICAL OR COMBINED PILLS

Classical or combined pills contain a moderate dose of synthetic estrogen like ethinyl estradiol or mestranol and a mild dose of synthetic progesterone like nor-ethindrone or norgestrol.

Pills are taken daily from 5th to 25th day of menstrual cycle. The withdrawal of the pills after 25th day causes menstrual bleeding. The intake of pills is resumed again after 5th day of the next cycle.

Mechanism of Action

During the continuous intake of the pills, there is relatively large amount of estrogen and progesterone in the blood. It suppresses the release of gonadotropins, FSH and LH from pituitary by means of feedback mechanism. Lack of FSH and LH prevents the maturation of follicle, and ovulation. In addition, progesterone increases the thickness of mucosa in cervix, which is not favorable for transport of sperm. When the pills are withdrawn after 21 days the menstrual flow starts.

2. SEQUENTIAL PILLS

Sequential pills contain a high dose of estrogen along with moderate dose of progesterone. These pills also prevent ovulation.

Sequential pills are taken in two courses:

i. Daily for 15 days from 5th to 20th day of the menstrual cycle and then
ii. During the last 5 days, i.e. 23rd to 28th day.

3. MINIPILLS OR MICROPILLS

Minipills contain a low dose of only progesterone and are taken throughout the menstrual cycle. It prevents pregnancy without affecting ovulation. The progesterone increases the thickness of cervical mucosa, so that the transport of sperms is inhibited. It also prevents implantation of ovum.

DISADVANTAGES AND ADVERSE EFFECTS OF ORAL CONTRACEPTIVES

About 40% of women who use contraceptive pills may have minor transient side effects. However, long term use of oral contraceptives causes some serious side effects. Some of the side effects are rare, but may be dangerous.

Following are the disadvantages and adverse effects of oral contraceptives:

1. Major practical difficulty is the regular intake of the pills
2. May not be suitable for women having disorders such as diabetes, cardiovascular diseases or liver diseases
3. Clotting tendency of blood due to suppressed production of anticoagulants in liver
4. Hypertension and heart attack
5. Increases the risk of stroke
6. Tenderness of breast and risk of breast cancer (but may decrease the risk of ovarian and uterine cancer).

LONG-TERM CONTRACEPTIVES

To avoid taking pills daily, the long-term contraceptives are used. These contraceptives are in the form of implants containing mainly progesterone. The implants,

which are inserted beneath the skin release the drug slowly and prevent fertility for 4 to 5 years. Though it seems to be effective, it may produce amenorrhea.

INTRAUTERINE CONTRACEPTIVE DEVICE (IUCD) – PREVENTION OF FERTILIZATION AND IMPLANTATION OF OVUM

Fertilization and the implantation of ovum are prevented by inserting some object made from metal or plastic into uterine cavity. Such object is called intrauterine contraceptive device (IUCD).

MECHANISM OF ACTION OF IUCD

Intrauterine contraceptive device prevents fertilization and **implantation of the ovum.** The IUCD with copper content has **spermicidal action** also. The IUCD which is loaded with synthetic progesterone slowly releases progesterone. Progesterone causes thickening of cervical mucus and prevents entry of sperm into uterus.

The common IUCDs are **Lippes loop,** which is 'S' shaped and made of plastic and copper T, which is made up of copper. It is inserted into the uterine cavity by using some special applicator.

DISADVANTAGES OF IUCD

IUCD has some disadvantages. It has the tendency to:

1. Cause heavy bleeding in some women
2. Promote infection
3. Come out of uterus accidentally.

MEDICAL TERMINATION OF PREGNANCY (MTP) – ABORTION

Abortion is done during first few months of pregnancy. This method is called medical termination of pregnancy (MTP). There are three ways of doing MTP (Table 88.1).

DILATATION AND CURETTAGE (D AND C)

In this method, the cervix is dilated and the implanted ovum or zygote is removed.

VACUUM ASPIRATION

The implanted ovum is removed by vacuum aspiration method. This is done up to 12 weeks of pregnancy.

ADMINISTRATION OF PROSTAGLANDIN

Administration of prostaglandin like PGE_2 and PGF_2 intravaginally increases uterine contractions resulting in abortion.

TABLE 88.1: Contraceptive methods in males and females

	Males	Females
Rhythm method		Safe period
Condom	Male condom	Cervical cap Diaphragm
Chemical methods		Chemical substances applied in genital tract
Oral contraceptives		Classical pills Sequential pills Mini pills
Implants		Intrauterine contraceptive device: Lippe loop Copper T
Medical termination of pregnancy (MTP)		Dilation and curettage Vacuum aspiration Prostaglandin administration
Surgical method (sterilization)	Vasectomy	Tubectomy

SURGICAL METHOD (STERILIZATION) – PERMANENT METHOD

Permanent sterility is obtained by surgical methods. It is also called sterilization.

TUBECTOMY

In tubectomy, the fallopian tubes are cut and both the cut ends are ligated. It prevents entry of ovum into uterus. The operation is done through vaginal orifice in the postpartum period. During other periods, it is done by abdominal incision. Tubectomy is done quickly (in few minutes) by using a **laparoscope.**

Though tubectomy causes permanent sterility, if necessary **recanalization** of fallopian tube can be done using plastic tube by another surgical procedure.

VASECTOMY

In vasectomy, the vas deferens is cut and the cut ends are ligated. So the sperms cannot enter the ejaculatory duct and the semen is devoid of sperms. It is done by surgical procedure with **local anesthesia.** If necessary, the **recanalization** of vas deferens can be done with plastic tube.

QUESTIONS IN REPRODUCTIVE SYSTEM

LONG QUESTIONS

1. Describe the functions of testis and regulation of testicular functions.
2. Describe the actions and regulation of secretion of testosterone.
3. What are the female sex hormones? Explain their actions.
4. What is menstrual cycle? Explain the ovarian changes taking place during menstrual cycle.
5. Describe the uterine changes during menstrual cycle.
6. Give an account of menstrual cycle and explain the hormonal regulation of menstrual cycle.
7. Give an account of lactation. And, add a note on the role of various hormones in the development of mammary glands and lactation.

SHORT QUESTIONS

1. Gametogenic function of testis or spermatogenesis.
2. Endocrine functions of testis.
3. Sertoli cells.
4. Testosterone.
5. Cryptorchidism.
6. Secondary sexual characters in males.
7. Puberty in males.
8. Seminal vesicles.
9. Prostate gland.
10. Semen.
11. Spermatozoa.
12. Effects of removal of testes.
13. Hyper and hypogonadism in males.
14. Estrogen.
15. Progesterone.
16. Follicle-stimulating hormone.
17. Luteinizing hormone.
18. Gonadotropins.
19. Secondary sexual characters in females.
20. Puberty in females.
21. Ovarian follicles.
22. Graafian follicle.
23. Ovulation.
24. Corpus luteum.
25. Hormonal regulation of menstrual cycle.
26. Menopause.
27. Infertility in females.
28. Infertility in males.
29. Maternal changes during pregnancy.
30. Functions of placenta.
31. Placental hormones.
32. Fetoplacental unit.
33. Parturition.
34. Pregnancy tests.
35. Role of hormones in lactation.
36. Prolactin.
37. Lactation.
38. Milk ejection reflex.
39. Oxytocin.
40. Safe period/Rhythm method.
41. Condoms.
42. Oral contraceptives.
43. IUCD.
44. MTP.
45. Vasectomy.
46. Tubectomy.
47. Contraceptive methods in females.
48. Contraceptive methods in males.