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Production of Courseware

e-Content for Post Graduate Courses

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Module : 24 Reproductive Hormones

ज्ञान-विज्ञान विमुक्तये

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7. Summary

1. Learning Outcomes

The module shall able to light on the different aspects of reproductive hormones such as

- The synthesis of all the steroid hormones takes place from the cholesterol or direct de - novo synthesis.
- The molecular mechanism of steroid hormone action is well studied. The module able to discuss both the Classical (genomic pathway) and Non-Classical (non-genomic) pathway of hormone action.
- Male sex hormone testosterone and female sex hormone estrogen and progesterone functions were well elaborately described.
- Able to know the regulation of hormone which is important part to maintain the body homeostasis.
- Disorders due to hypo and hyper secretion of hormones.

2. Introduction

Reproduction is fundamental property of life. Living organisms on earth get an opportunity to pass on the characters to next generation. There are two forms of reproduction are asexual and sexual. Sexual reproduction is complex phenomenon involving the formation of gametes, sexual interaction of two individuals of same species and fusion of gametes after the fertilization. After that development of zygote into individual takes place in the external or internal (inside the body) environment. The overall completion of process requires intricate interaction of number of reproductive hormones. Environmental cues such as temperature, photoperiod and the presence of suitable breeding sites stimulate the central nervous system and the hypothalamus -hypophysial axis to regulate the development and maturation of gonads by releasing several hormones.

There are many different reproductive hormones present both in males and females:

Male Hormones (Androgens)

- Testosterone

- 5α – Dihydrotestosterone (5α – DHT)
- 5α – Androstenediol
- Androstenedione
- Dehydroepiandrosterone
- Androsterone

Female Hormones:

- Estrogen
- Progesterone
- Relaxin
- Inhibin

3. Biosynthesis of Hormone

Cholesterol is the primary precursor of steroid hormones. In tissues large amount of steroids produced are derived primarily from acetate with cholesterol as an intermediate product. Direct synthesis of steroid from cholesterol also occurs. So both de novo synthesis and cholesterol present in plasma are utilized for biosynthesis of hormone.

3.1. Androgen Synthesis

Androgens are synthesized in the Leydig cells of the interstitial cells of testes. In addition, androgens are also produced in small amount in the ovary, placenta and in adrenal gland. The synthesis of androgen from acetate and cholesterol takes place in several steps.

1) The conversion of cholesterol (C-27) to pregnenolone (C-21) occurs in mitochondria of Leydig cells.

2) Transportation of pregnenolone to smooth endoplasmic reticulum where it undergoes any of the two pathways for the synthesis of testosterone. The two pathways are:

- Δ5 or dehydroepiandrosterone pathway
- Δ4 or progesterone pathway.

All the intermediates of Δ5 pathway converted into corresponding Δ4 intermediates by the enzyme 3β HSD (Hydroxy steroid Dehydrogenase) and Δ5, 4 isomerase.

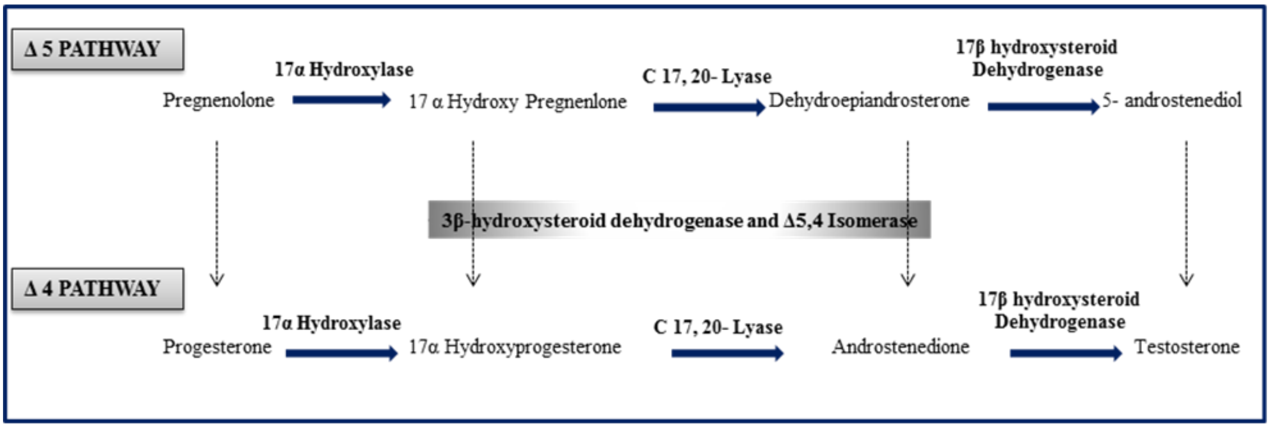

Fig. 1 Biosynthesis of Androgen. (Source Author)

In rat and mouse testes, the Δ4 pathway is preferably takes place while in man, rabbit, pig and dog Δ5 pathway is more important.

In seminal vesicles and prostate, testosterone gets converted into more active and potent form called DHT (dihydrotestosterone) with the help of enzyme 5α- reductase and exerts action similar to that of testosterone. Δ5 and Δ4 pathways for androgen synthesis also occur in the adrenal cortex and ovaries. Dehydroepiandrosterone sulphate synthesized (DHEA-SO4) in the adrenal cortex converted into DHEA by the enzyme sulphatase present in the testes. So, DHEA become the additional precursor of testosterone.

In normal male, daily approx 4-12mg testosterone and 10-15mg DHEA secreted. In adult female plasma level of testosterone is 10 times lower than in the adult male.

3.2. Estrogen Synthesis

Estrogens are C-18 compounds with aromatic character, synthesized in the ovary by the thecal and granulosa cells, corpus luteum, placenta, adrenal cortex, testes, and extragonadal tissues such as liver, muscle, adipose tissues, brain etc. In human three types of estrogen are found:

1) 17β- estradiol
2) Estrone
3) Estriol.

Among them 17β-estradiol is the most potent and active estrogen. Estriol is found in the urine of pregnant women and in the placenta. Estrone formed after the metabolic conversion of estradiol. The conversion of androgen to estrogen is completed in two steps.

i) Conversion of C-19 to C18 compound from the position C- 10.

ii) Aromatization of the ring.

In adult female, approx 0.1-0.2mg estrogen is secreted daily and it increases upto 0.5mg/day during the ovulation.

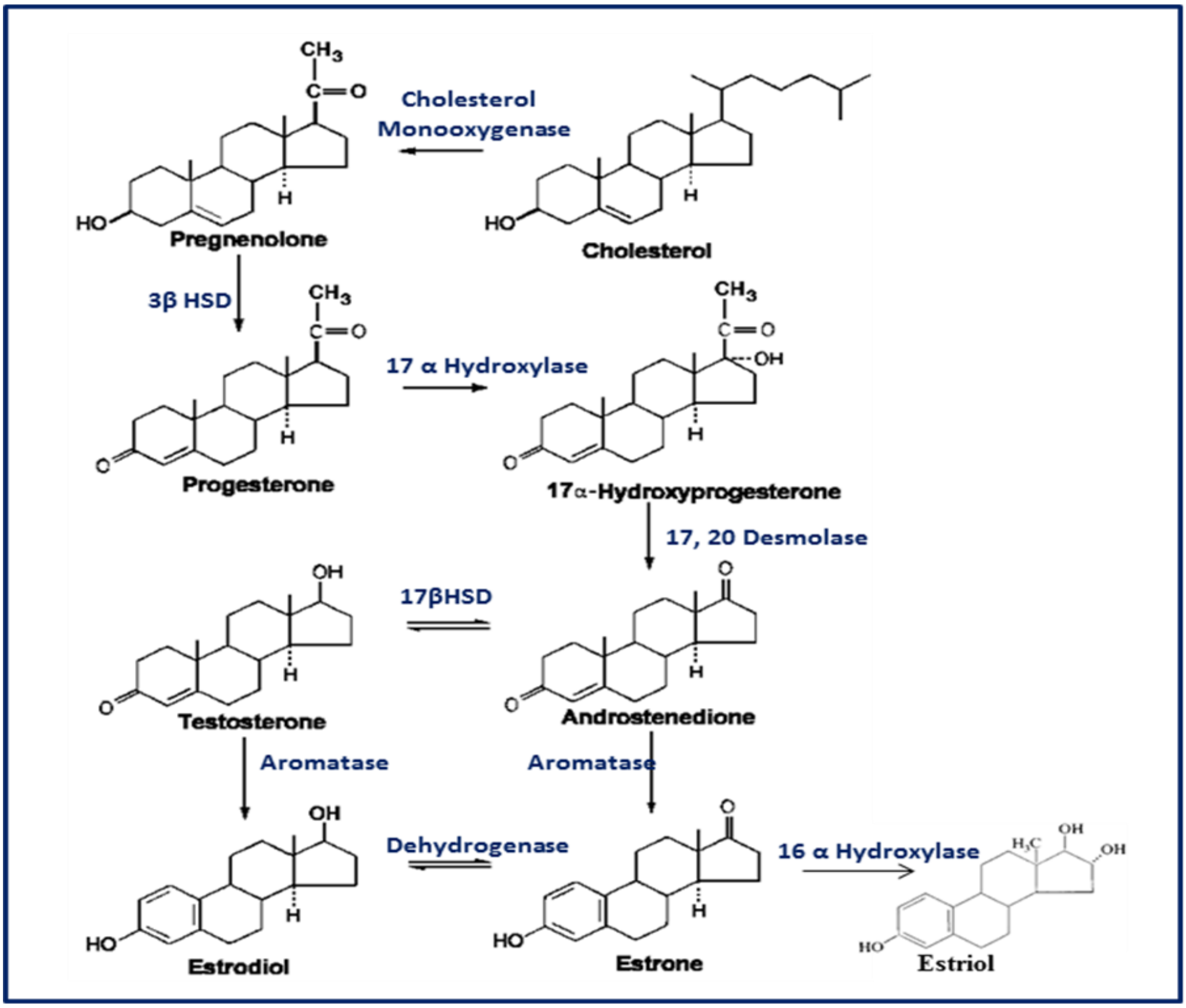

Fig. 2 Biosynthesis of Reproductive Hormones by Δ4 Pathway
Source - Author

3.3. Progesterone Synthesis

Progesterone is the other major ovarian hormone. It is a C-21 steroid also known as pregnancy or luteal hormone. It is synthesized in the ovary by the corpus luteum and by the placenta during the pregnancy. It is also formed in the adrenal cortex and testes as a precursor of both C-21 and C-19 steroid hormones.

Progesterone is also synthesized from acetate via cholesterol. Pregnenolone is the immediate precursor of steroid. It is an important intermediate of all the steroid synthesis in all the tissues. The relative potency of all the progesterone varies. Progesterone is 100% potent; 17α-hydroxyl progesterone has 40 – 70 % potency while 20α- hydroxyprogesterone is 5% potent.

Approx 2mg/day progesterone secreted daily during the follicular phase which increases upto 25mg/day after the ovulation during the luteal phase.

4. Mechanism of hormone action

On the basis of receptor localization, hormones are categorized into two parts

a) Hormones that binds to intracellular receptors (Genomic pathway).

b) Hormone that binds to cell surface receptors (Non-genomic pathway).

4.1. Genomic pathway

Hormone that binds to intracellular receptors is lipophilic in nature and their receptors present either in the cytosol or inside the nucleus. All steroids except thyroid hormones, estrogen, progesterone, glucocorticoids, mineralocorticoids once secreted diffuses through the plasma membrane of their target cells and encounter with their specific high affinity receptors shown in Fig.3.These receptors are oligomeric transport protein present in the cytosol or inside the nucleus also known as mobile receptors. Interaction of hormones with their receptors forms hormone receptor complex (HR). HR complex increases the solubility and stability of the hormone. The interaction leads to changes in size, conformation and surface charges to make it possible for interaction with specific region of DNA. The specificity involved in the control of transcription requires that regulatory protein bind with high affinity to the correct region of DNA called promoters. Analyses of these protein shows that structurally they have three unique supra secondary structural motifs that appears to be the characteristics of DNA binding protein. These are

1) Helix turns helix (helix loop helix)

2) Zinc (Zn finger)

3) Leucine zipper.

The binding affinity shows following characteristics features:

- Binding must be of high affinity to the specific site and of low affinity to another site.
- Small regions of proteins make direct contact with DNA. Rest of the protein provide the trans activation domain and may be involved in the dimerization of monomers of binding protein, or may provide contact surface for the formation of hetero-dimers or provide ligand binding site.
- Protein - DNA interaction maintained by the hydrogen bonds and Vander walls interaction.

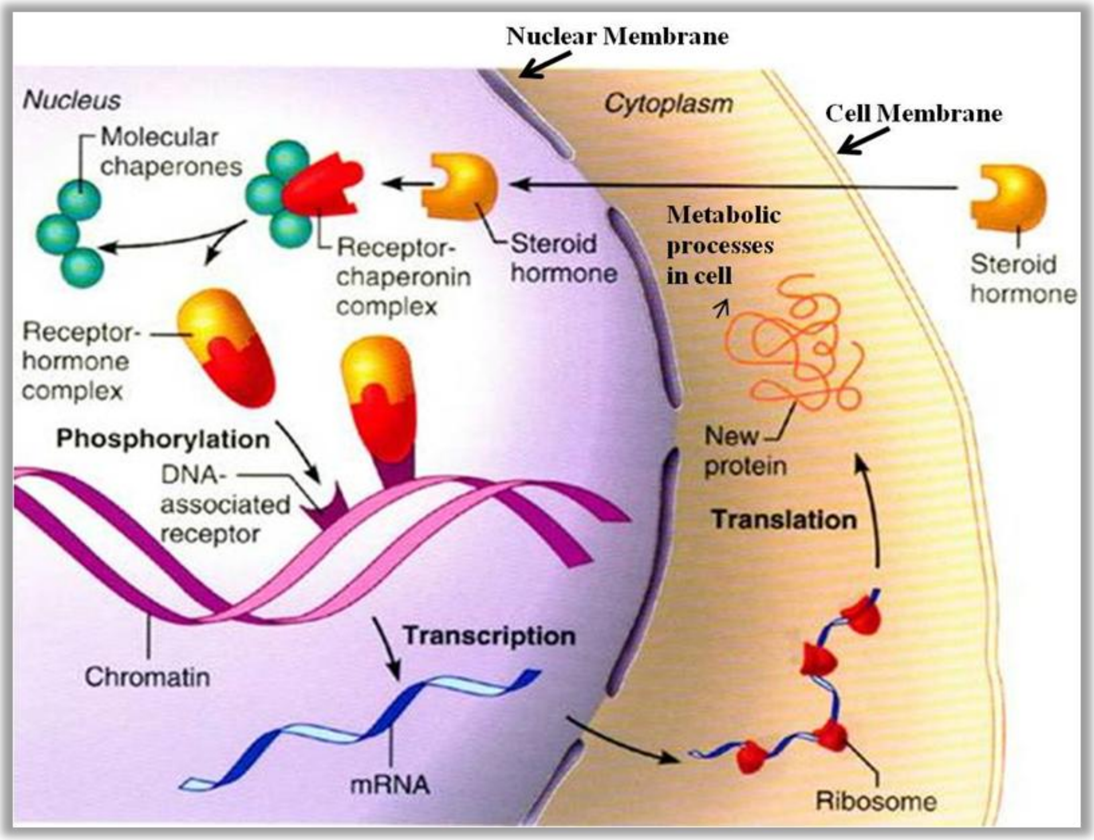

Fig. 3 Mechanism of Steroid Hormone Action through Classic Receptor

Once the steroid hormone enters the target cell and encounters specific receptors with affinity, makes HR complex. The complex diffuses or transported into the nucleus and interacts with chromatin at specific region called hormone response element (HRE). HR complex activates or inactivates concerned gene to affect the transcription process. HRE element is located slightly farther 5'than the promoter element (fig.4). It consists of several discrete elements and modulates the frequency of transcription initiation. HRE has been identified in many genes regulated by steroid hormones. Its exact location varies from gene to gene. The HR complex interacts with specific cis acting element called enhancers or silencers. This results in upregulation (enhanced) or down regulation (silenced) of the specific gene transcription. So, HR complex either activate or repress the specific gene transcription to form mRNA. mRNA diffuses into the cytoplasm for translation process to synthesize the proteins which affect the metabolic processes.

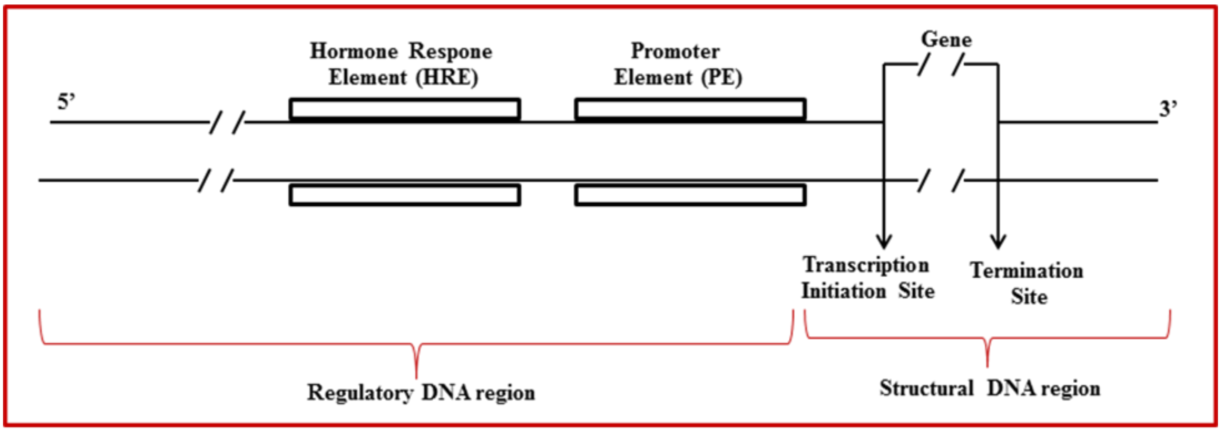

Fig. 4 Arrangement of Various Elements on Gene

4.2. Non-genomic Pathway

In contrast to genomic pathway, non-genomic pathway (which does not involve the nucleus and thus transcription) also occur with very short lag time. Recent studies discovered non-genomic pathway for the action of number of steroids such as thyroid, glucocorticoids, progesterone and estrogen also. Even the steroid effects also occur in cells without a functional nucleus, such as erythrocytes, platelets, or spermatozoa. All these cells rapidly respond to stimulation by various steroids. The physiological dose of E2 was reported to increase the uterine cAMP level in ovariectomized rats within 15 seconds. This effect is too rapid to be accounted for genomic action. Various signaling pathways are activated upon steroid binding to receptors. These signaling pathways involve second messenger as shown in fig.5. These rapid events may work through following signaling cascade:

- Phospholipase C (PLC)/protein kinase C (PKCs)
- Ras/Raf/MAPK
- Phosphatidyl inositol 3 kinase (PI3K)/AKT
- cAMP/ protein kinase A (PKA)

In contrast to the genomic pathway as discussed above, non-genomic pathway mediated phenomena often occur with very short lag time. As examples, progesterone induces a significant increase in intracellular calcium in spermatozoa within seconds and aldosterone activates the Na^+/H^+ antiporter within 1 min in colonic crypts.

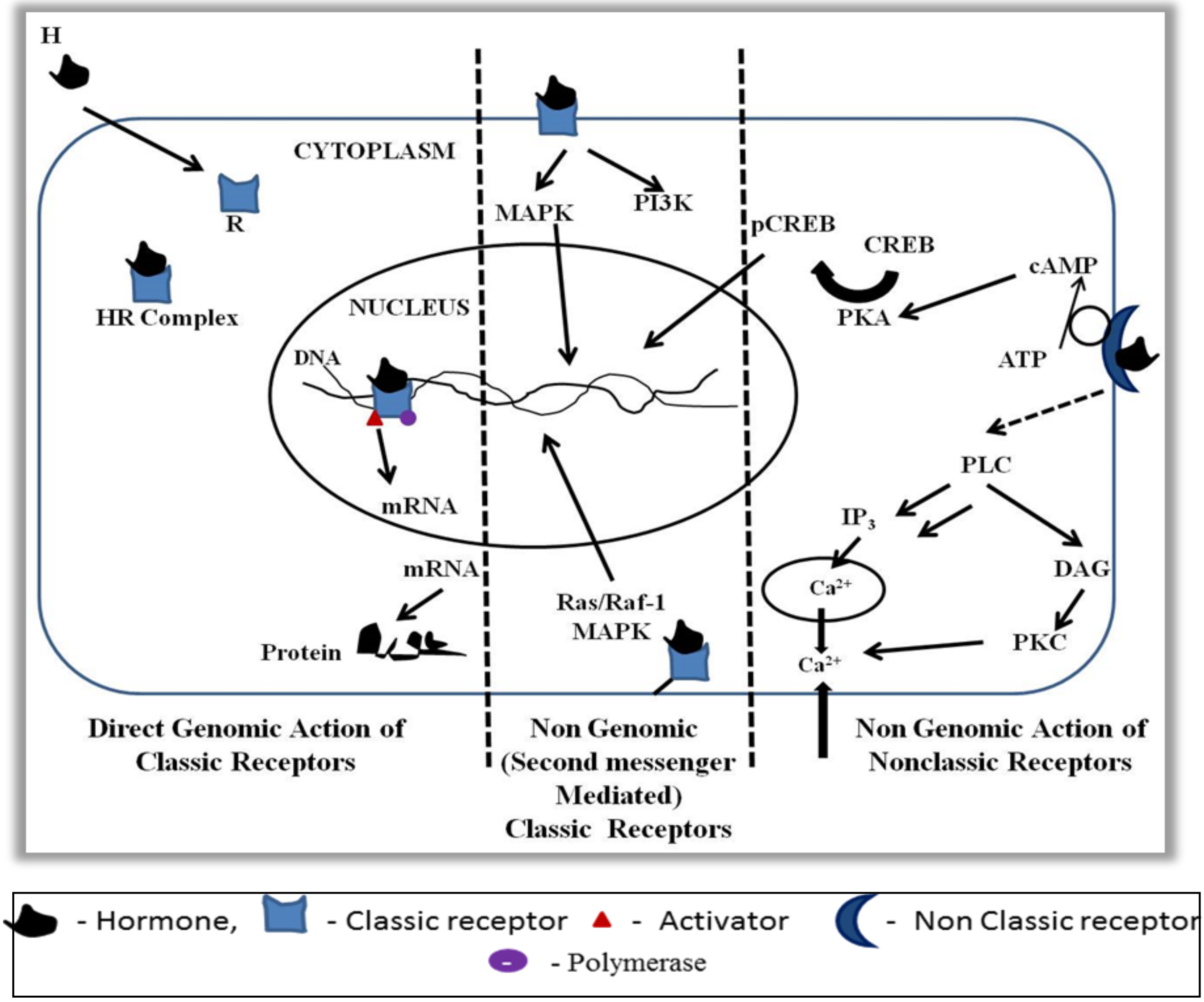

Fig. 5 Relationship Between Genomic and Non-Genomic Pathway for the Action of Steroid and Steroid like Molecules; Abbreviations, PLC (Phospholipase C), DAG(Diacylglycerol), PKC (Protein Kinase C), IP3(Inositol 3Phosphate), PI3K (Phosphoinositol 3Kinase) (Source – Author).

5. Male Sex Hormone

Androgens are male hormones of C19 steroid family. Naturally occurring androgens are testosterone, 5α – dihydrotestosterone (5α – DHT), 5α – androstenediol, androstenedione, dehydroepiandrosterone (DHEA) and androsterone. Testosterone is the principal masculinizing hormone secreted from the leydig cells present in the interstices of seminiferous tubules. Leydig cells constitute about 20% of the mass of testes. Testes secrete several male sex hormones like androstenedione, dihydrotestosterone but testosterone secretion is abundant.

Androgens	Relative Potency (%)
Testosterone	100
Dihydrotestosterone	90
5α – Androstenediol	60
Androstenedione	20
Dehydroepiandrosterone	10
Androsterone.	10

Table.1. Naturally Occurring Androgens and their Relative Potency

The male sex gonads testes are paired oval gland present outside the body in a bag like structure called scrotum. During the seventh month of fetal development testes descends through the inguinal canal. Scrotum provides 2- 3degree lower temperature as compare to that of body for spermatogenesis. In response to cold temperatures, the cremaster and dartos muscles contract. Contraction of the cremaster muscles moves the testes closer to the body, where they can absorb body heat. Contraction of the dartos muscle causes the scrotum to become tight (wrinkled in appearance), which reduces heat loss. Exposure to warmth reverses these actions.

Each testis divided into 200-300 lobules through the septa, which is the extension of tunica albuginea. Each lobule contains one to three tightly coiled tubules called seminiferous tubule.

These tubules contain two kinds of cells - spermatogenic cells and sertoli cells. Spermatogenic cells involved in the formation of sperms while sertoli cells responsible for the assistance of spermatogenesis process. During spermatogenesis, as the cells proliferate. They remain in contact via cytoplasmic bridges through their entire development (Fig. 6). This pattern of development accounts for the synchronized production of sperm in any given area of seminiferous tubule.

Sertoli cells nourish spermatocytes, spermatids, and sperm; phagocytize excess spermatid cytoplasm as development proceeds; and control movements of spermatogenic cells and the release of sperm into the lumen of the seminiferous tubule. In the space between the seminiferous tubules, clustered of cells are present called interstitial or Leydig cells. These cells synthesize and secrete testosterone.

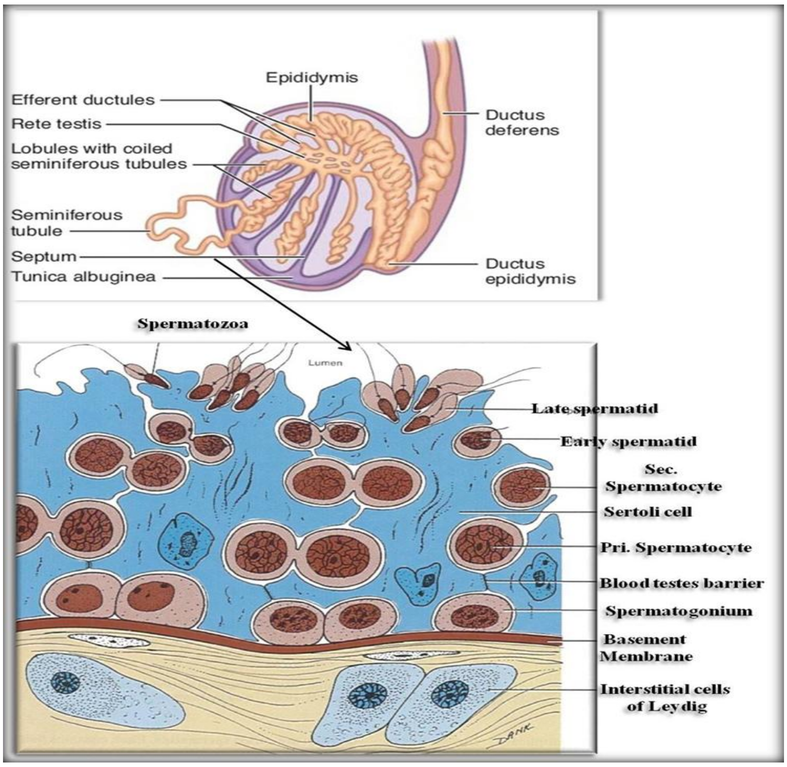

Fig.6 Structure of Testes and Cross Section of the Part of Seminiferous Tubule

5.1. Functions of testosterone

It is known for masculinizing character of male. Even in the fetal life testosterone secreted from the placenta under the influence of chorionic gonadotropin and it continues until the birth.

Development of primary and secondary sexual characteristics

Testosterone secretion causes development of the penis, scrotum, and testes and to enlarge about eightfold before the age of 20 years. The secondary sexual characteristics develop with the attainment of puberty and ending at the maturity under the influence of testosterone. The secondary sexual characteristics are

- *Distribution of body hair*: It causes growth of hair over the pubis, on the face, usually on the chest.
- *Baldness:* Testosterone decreases the growth of hair on the head and it assists the process of baldness which depends upon the genetic background of baldness.
- *Masculine voice:* Testosterone works on laryngeal mucosa and enlargement of the larynx which leads to first a relatively discordant, "cracking" voice, and gradually changes into the typical adult masculine voice.
- *Skin Pigmentation and thickening*: Skin pigmentation and tanning effect of ultraviolet light on skin is intensified by androgen. Secretion from sebaceous glands of skin and axillary gland enhances with androgen stimulation leading to an increased sebum production.

Protein Formation and Muscle Development

Increasing musculature after puberty, approx 50 per cent more muscle mass over that in the female is because of testosterone secretion. It also works on the non-muscle part of the body. Synthetic androgens are widely used by athletes and in old age to improve their muscular performance and vigor.

Effect on Bone

Testosterone increases the size and strength of bones, also used to treat osteoporosis in older age. The testosterone also causes the epiphyses of the long bones to unite with the shafts of the bones at an early age. Therefore, despite the rapidity of growth, this early uniting of the epiphyses prevents the person from growing as tall as he would have grown had testosterone not been secreted at all. Even in normal men, the final adult height is slightly less than that which occurs in males castrated before puberty.

Basal metabolism

Testosterone increases the rate of basal metabolism. It is an indirect result of the effect of testosterone on protein anabolism, the increased quantity of proteins, enzymes and in this way increasing the activities of all cells.

Red Blood Cells

The increased metabolic rate after the administration of testosterone leads to 10-15% increase in red blood cells count. The average man has about 700,000 more red blood cells per cubic millimeter than the average woman.

Effect on Electrolyte and Water Balance

Testosterone increases the reabsorption of sodium in the distal tubules of the kidneys but only to a minor degree in comparison with the adrenal mineralocorticoids. Nevertheless, after puberty, the blood and extracellular fluid volumes of the male in relation to body weight increase as much as 5 to 10 per cent.

Fetal Development

Male chromosome causes the newly developing genital ridge to secrete testosterone. So, testosterone secreted first by the genital ridges and later by the fetal testes is responsible for the development of the male body characteristics, including the formation of a penis and a scrotum rather than formation of a clitoris and a vagina. Also, it causes formation of the prostate gland, seminal vesicles, and male genital ducts, while at the same time suppressing the formation of female genital organs

Effect on descent of Testes

Descent of testes into the scrotum occurs during the last 2 to 3 months of gestation when the testes begin secreting reasonable quantities of testosterone. Testosterone acts as stimulus for the descent of testes into the scrotum. If a male child is born with undescended but otherwise normal testes and inguinal canal, the administration of testosterone or gonadotropin usually causes the testes to descend in the usual manner.

5.2. Regulation of testosterone secretion

Most of the endocrine hormones are regulated at the hypothalamic and to the pituitary level and the regulation works on feedback mechanism. It can be **long loop feedback**, where the pituitary ends the influence of hypothalamic factor by secreting a tropic hormone that stimulates target gland to release its hormone. Pituitary hormones exert positive or negative regulation of their own secretion, known as **short loop feedback**.

High level of testosterone in the blood regulated at the pituitary level by decreasing the secretion of luteinizing hormone (LH) and at hypothalamic level by decreasing the secretion of gonadotropin releasing hormone (GnRH). The decrease in LH and GnRH ultimately decreases the synthesis and secretion of testosterone by the Leydig cells. Both are the example of long negative feedback. In contrary, too little testosterone allows the hypothalamus to secrete large amounts of GnRH, with a corresponding increase in anterior pituitary LH and Follicle stimulating hormone (FSH) secretion and consequent increase in testicular testosterone secretion as shown in fig.7.

FSH controls the process of spermatogenesis by binding to the specific FSH receptors present on the sertoli cell and spermatogenic cells. These cells grow and secrete various spermatogenic substances. Testosterone diffusing into the seminiferous tubules from the Leydig cells in the interstitial spaces also has a strong tropic effect on spermatogenesis. So, for the spermatogenesis, both FSH and testosterone are necessary. Spermatogenesis process is regulated by inhibin secreted from the sertoli cells, which inhibited the secretion of FSH from the anterior pituitary. FSH also involved in the release of ABP (androgen binding protein) by binding specific receptor on sertoli cells. ABP binds to testosterone, keeping its concentration high in seminiferous tubule as compared to outside. Testosterone stimulates the final steps of spermatogenesis in the seminiferous tubules.

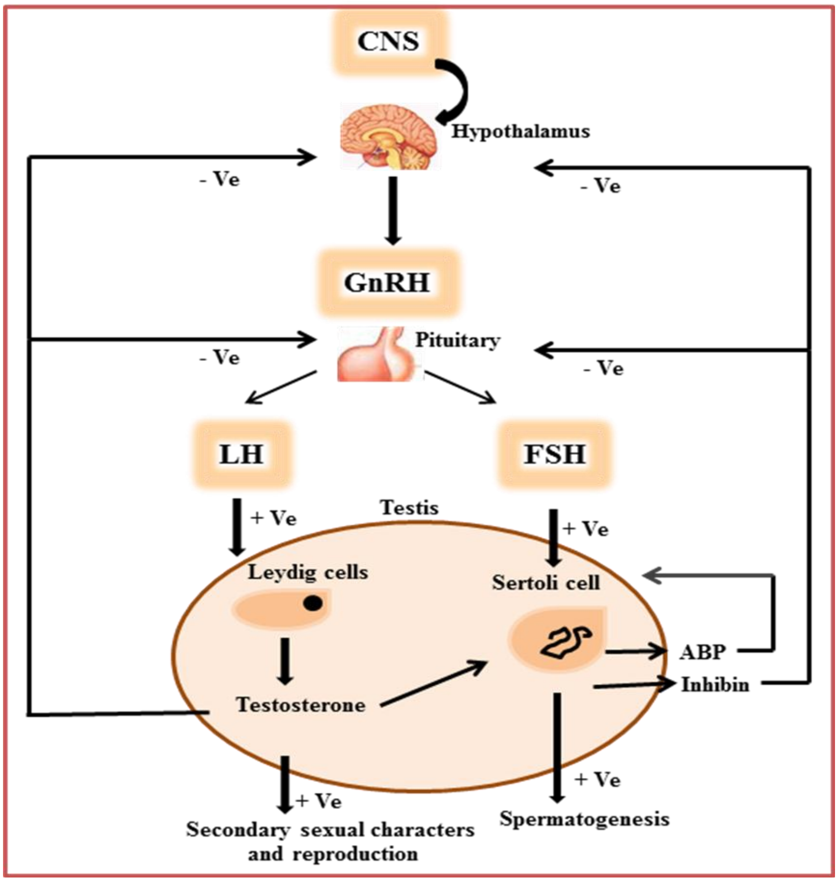

Fig. 7 Regulation of Testicular Function at Hypothalamic and Pituitary Level
Source -Author

5.3. Disorder associated with male sex hormone

5.3.1. Hypogonadism

The basic genetic characteristic of the fetus, whether male or female, is inclined to form female sexual organs if there are no sex hormones. The formation of female sexual organs is suppressed, and instead, male organs are induced in the presence of testosterone. So, before puberty, any abnormality of testes which cause testosterone decrease, leads to a state of eunuchism in which the person continues to have infantile sex organs and other infantile sexual characteristics throughout life. The height of an adult eunuch is slightly greater than that of a normal man because the bone epiphyses are slow to unite, although the bones are quite thin and muscles are weaker than of a normal man. The voice doesn't change (childlike), no loss of hair on the head, and the normal adult masculine hair distribution on the face and elsewhere does not occur.

After puberty, any loss of testosterone or testes, or castration leads to revert the male secondary sexual characteristics. The sexual organs regress slightly in size but not to a childlike state, and the voice regresses from the bass quality only slightly. Conversely, there is loss of masculine hair production, loss of the thick masculine bones, and loss of the musculature of the virile male. Also, in a castrated adult male, sexual desires are decreased but not lost.

5.3.2. Hypergonadism

The condition of the development of tumors in testes or tumors in the interstitial cells of leydig causes the hypersecretion of testosterone. If it occurs in young children, it causes rapid growth in musculature and bones. It also causes early uniting of the epiphyses so that the adult height is considerable less than that of the normal one.

The tumors also cause excessive development of the male sexual organs, all skeletal muscles, and other male sexual characteristics. However, in the adult male, small interstitial cell tumors are difficult to diagnose because masculine features are already present. But if the tumors are in germinal epithelium, the cells are capable to differentiate into any type of cell. It leads to development of multiple tissues, such as placental tissue, hair, teeth, bone, skin, and so forth, all found together in the same tumorous mass called a teratoma. These tumors often secrete few hormones. It may secrete large quantities of hCG with functions similar to those of LH or sometimes estrogenic hormones leads the condition called gynecomastia (overgrowth of the breasts).

6. Female Sex Hormones

The two most important female hormones are estrogen and progestins. These two hormones are responsible for the feminizing characters, sex cell development, and maintenance of reproductive cycle and for the development of embryo. The main estrogen is estradiol and the progestin is progesterone. In addition of these two hormones other hormones also involved in the female reproduction like GnRH, FSH, LH, inhibin, and relaxin etc. These hormones are polypeptides and not steroids but are associated with reproduction.

The human female reproductive cycle is complicated process, which is interplay of the coordinated regulation of these hormones. Ovary is very complex structure, containing ovarian follicles in the cortex region. The follicles consist of cells known as granulosa cells, enclosing oocytes in various stages of development. With the development, these follicles developed several layers of cells. The surrounding cells nourish the developing oocytes and begin to secrete estrogens as the follicle grows larger. A mature (graafian) follicle is a large, fluid-filled follicle that is ready to rupture and expel its secondary oocyte, a process known as ovulation.

Every month under the influence of GnRH, gonadotropic hormones (FSH, LH) cause 8 – 12 new follicles to grow in the ovaries. Among them only one follicle gets matured and goes for the ovulation once the LH peak level reached. Ovulation process release the ova from the ovary for the fertilization and the remaining follicles develop into the corpus luteum. Corpus luteum is one of the important sources of estrogen, progesterone, relaxin and inhibin. All these hormones are essential for the implantation of the fertilized ova and to maintain the pregnancy till the development of placenta. Later on, the placenta becomes the main source of these hormones and corpus luteum gets degenerated. If the fertilization does not take place, corpus luteum degenerated within 15 days. With the degeneration of corpus luteum, estrogen, progesterone level also goes down rapidly and menstruation begins. This leads to rise in GnRH to start new ovarian cycle i.e. recruitment of again new follicles.

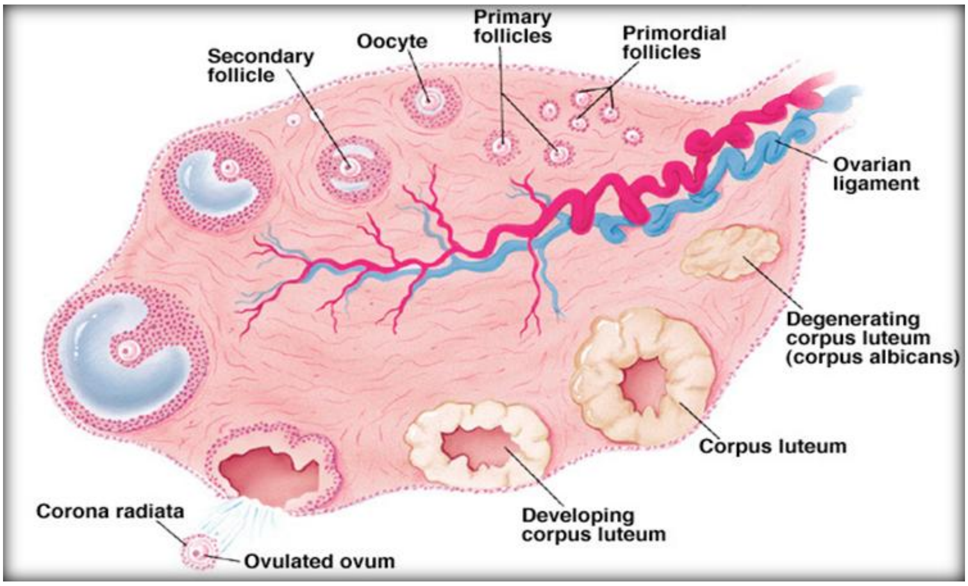

Fig 8: Histology of ovary, the female Gonad

6.1. Functions of female sex hormone

6.1.1. Estrogens

- ***Development of female sex organs***

  At the time of puberty under the influence of gonadotropic hormone, estrogen secretion increases approx 20 folds. Increased estrogen level works on all female sex organs like ovaries, fallopian tubes, uterus, and vagina to increase their size. Deposition of fats in the mons pubis and labia majora and enlargement of the labia minora also occurs under the influence of estrogen. The marked changes in uterus endometrium take place every month for the implantation under the influence of estrogen. It causes proliferation of the endometrial stroma and increased development of the endometrial glands, which later help in providing nutrition to the implanted ovum. The changes also occur in fallopian tubes glandular tissues and the ciliated epithelial cells. Increase in the number of cilia helps to propel the fertilized ovum.

- ***Development of Breast***

  Estrogens is involved in the structural development of mammary gland by the development of stromal tissues of the breasts, growth of an extensive ductile system, and deposition of fat in the breasts. The lobules and alveoli of the breast develop to a slight extent under the influence of estrogens alone, but it is progesterone and prolactin causes the ultimate growth and function of these structures. The male and female primordial breast are alike, the differences arises under the influence of appropriate hormones.

- ***Estrogen effect on the bone***

  Estrogens works on osteoclast cells, decreasing their activity in the bones and so stimulate bone growth. At puberty, the female height becomes rapid because of the influence of estrogen. However, estrogens also act on the epiphyses, causes to unite with the shafts of the long bones. This effect of estrogen in the female is much stronger than the similar effect of testosterone in the male. As a result, growth of the female usually ceases several years earlier than growth of the male. Deficiency of estrogen at older age leads to osteoporosis.

- ***Estrogen effect on body metabolism and fat deposition***

  Estrogens cause a slight increase in total body protein content, and it mainly results from the growth-promoting effect of estrogen on the sexual organs, bones and other tissues. It also increases the whole-body metabolic rate, comparatively very less as caused by the male sex hormone testosterone.

  Estrogen causes the deposition of fat in the buttocks and thighs, which is characteristic of the feminine figure. Because of this, the percentage of body fat in the female body is considerably greater than that in the male body, which contains more protein.

6.1.2. Progesterone

- ***Development of Breast***

  Progesterone mainly works on the lobules and alveoli of the breasts, causing the alveolar cells to proliferate, enlarge, and become secretory in nature. It prepares the breast for prolactin action which is mainly responsible for milk formation. Progesterone also causes the breasts to swell. The swelling also results from increased fluid in the subcutaneous tissue**.**

- ***Effect on the Uterus***

  The most important function of progesterone is to maintain the pregnancy and to prepare the uterus for successful implantation. During the entire reproductive cycle except during pregnancy every month the inner layer of uterus endometrium goes for the thickening process, endometrial glands development and proliferation takes place for implantation of the fertilized ovum. In addition to this effect on the endometrium, progesterone decreases the frequency and intensity of uterine contractions, thereby helping to prevent expulsion of the implanted ovum.

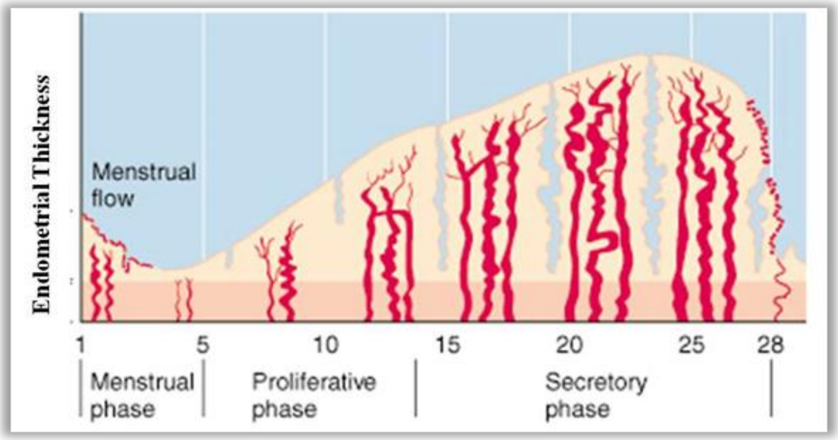

Fig 9: Phases of Endometrial growth during the Reproductive Cycle

6.1.3. Relaxin

In non-pregnant female, relaxin is secreted from the corpus luteum and in the pregnancy it is released from corpus luteum and placenta. In case of men it is secreted from the prostate gland. Relaxin is believed to inhibit myometrial contraction and during the parturition it increases the flexibility of pubic symphysis and dilates the uterine cervix. It also acts as stimulant of uterine and vaginal growth, uterine vascularization, mammary gland growth and maturation. In men it is found in semen and help to maintain sperm motility so helps in sperm fertilization.

6.1.4. Inhibin

It is secreted from the corpus luteum and mainly works in the regulation of hormone secretion. It inhibits the release of FSH and to lesser extent LH also. In case of male it is secreted from the sertoli cells and again inhibits the FSH to regulate spermatogenesis.

6.2. Regulation of female sex hormones

Hormones from the hypothalamus, anterior pituitary and gonadal axis regulate the periodic changes of the female reproductive system. These periodic changes follow a cyclic pattern which continues till the end of reproductive age, called as reproductive cycle.

The female reproductive cycle works on three hierarchies of hormones.

1) A hypothalamic hormone, gonadotropin-releasing hormone (GnRH) from the arcuate nuclei and the nuclei present in the preoptic area.

2) Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary both of which are secreted in response to the release of GnRH from the hypothalamus.

3) Estrogen and progesterone, which are secreted by the ovaries in response to the two female sex hormones from the anterior pituitary gland.

All these hormones are not secreted in constant amounts throughout the female cycle. Their secretions are in different rates during different phases of the cycle. The series of events associated with the maturation of an egg in a cycle is called ovarian cycle. Simultaneously the series of changes takes place in the endometrium of the uterus for the implantation process called as uterine cycle. The two significant results of the female sexual cycle are

- First, only a single ovum is normally released from the ovaries each month through the ovarian cycle, so that normally only a single fetus will begin to grow at a time.
- Second, the uterine endometrium is prepared in advance for implantation of the fertilized ovum at the required time of the month.

Both the ovarian and uterine cycle are regulated by GnRH at hypothalamic level and by FSH and LH at pituitary level. The level of estrogen and progesterone from the gonad exert negative feedback accordingly to maintain the titre or requirement of hormones in the blood as shown in fig.10. Overall the ovarian cycle is divided into four phases:

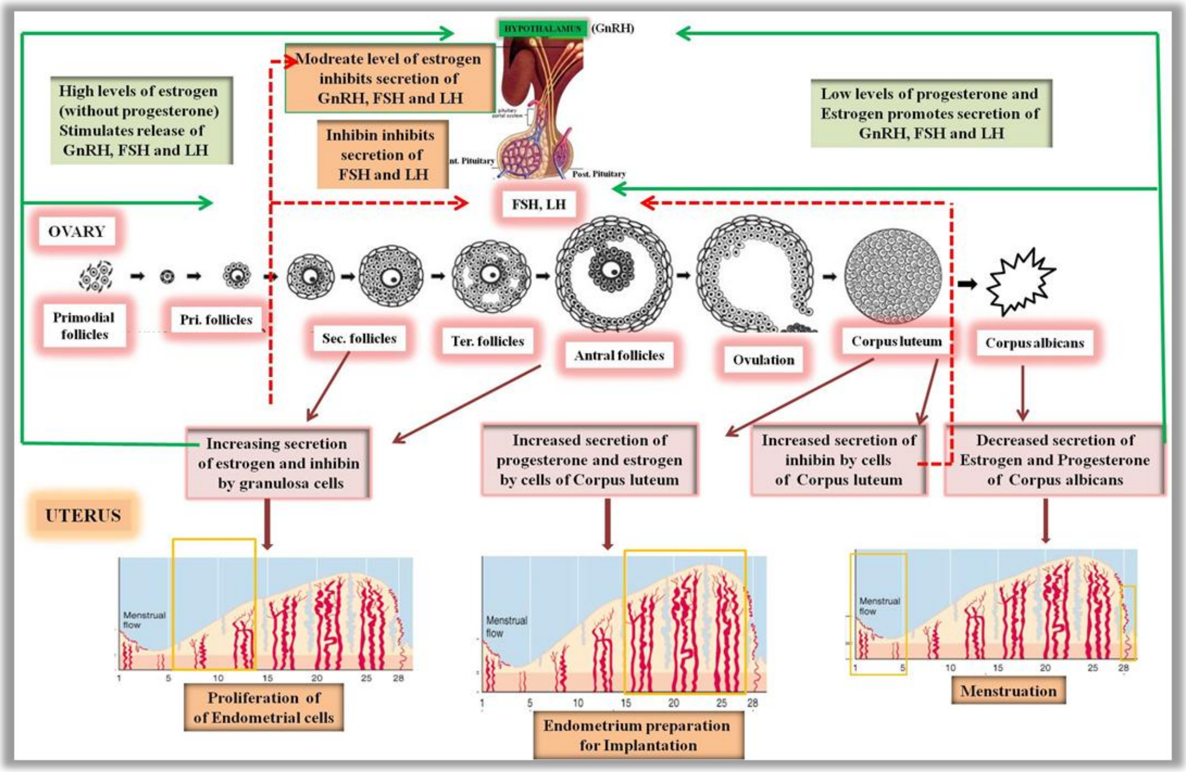

Fig. 10 Regulation of hormones in Ovarian and Uterine Cycle
Source - Author

The cycle is divided into 4 phases

1) **Proliferative phase or follicular phase:** The most variable phase of the cycle, characterized by a rise in serum level of FSH. The increased level of FSH responsible for secondary follicle of the ovary to grow and stimulates for the secretion of estrogen and inhibin. In the later phase, one of the secondary follicle become dominant and turned into mature or graafian follicle. Estradiol slowly increases in this period and reaches maximum on the day of LH surge. Rise in estradiol and inhibin level leads to decrease in FSH level (fig.11). In the uterus increased estrogen working on endometrial cells proliferation, vascularization and restores its glandular pattern.
2) **Ovulatory phase:** The rapid rise in plasma level on day 13, leads to rupture the mature follicle to release the ova. This is known as ovulation process. So, high level of estrogen acts as trigger for the LH surge for the ovulation process as discussed in fig.11.No major changes occur in the uterus during this period.

3) **Luteal Phase**: The most constant phase and it last from 15- 28 days. The remnants follicle changes into corpus luteum under the influence of LH. Now the corpus luteum becomes the source of estrogen, progesterone inhibin and relaxin. It alive for 15 days, after that it degenerated into corpus albicans. However, if fertilization takes place, corpus luteum remains alive and maintained by HCG till the first trimester of the pregnancy. Increased estrogen and progesterone promotes growth and coiling of endometrial glands, vascularisation and thickening of the endometrium and increase in the amount of tissue fluid. After completing the life span, if fertilization not happen corpus luteum converted into corpus albicans. Now the ovarian hormones starts declining, this leads to start increasing the GnRH, FSH and LH via negative feedback. This resumes the new follicles recruitment and growth.

4) **Menstrual Phase:** Because of the withdrawal of ovarian hormones, uterine epithelium undergoes degenerative changes. The spiral arteries constrict and then dilate and rupture producing hemorrhage or bleeding. This is accompanied with sloughing of uterine mucosa. The declining level of progesterone increases the prostaglandin causes the spiral arteriole to constrict as a result the cells they supply oxygen die. This phase last for 5 days. In the ovary, the growth the follicle continues to form secondary follicles.

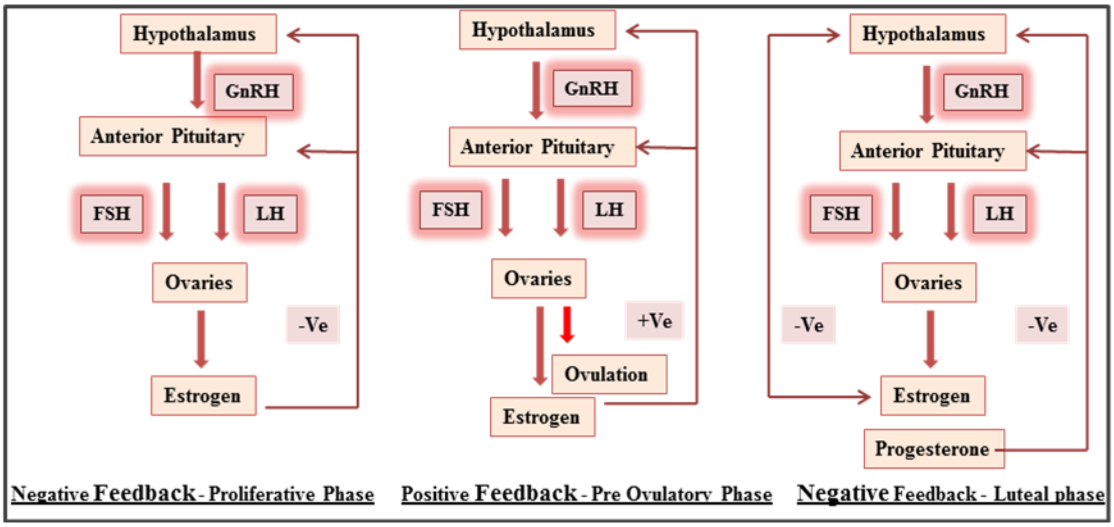

Fig. 11 Regulation of female sex hormones at Various Phases
Source - Author

6.3. Abnormalities associated with female sex hormone

6.3.1. Hypogonadism

Hypogonadism can occur because of poorly formed ovaries, lack of ovaries, or genetically abnormal ovaries which synthesize and secrete dysfunctional hormones. Before puberty, hypogonadism causes eunuchism in females. The usual secondary sexual characteristics do not appear, and the sexual organs remain infantile. It often leads to prolonged growth of the long bones because the epiphyses do not unite with the shafts as early as they do in a normal woman. Consequently, the female eunuch is essentially as tall as or perhaps even slightly taller than her male counterpart of similar genetic background.

After puberty hypogonadism leads the regression of sexual organs. The uterus becomes almost infantile in size, the vagina becomes smaller, the vaginal epithelium becomes thin and easily damaged and the breasts become atrophy. The same changes occur in women after menopause. In old age osteoporosis is one of the common disease associated with the deficiency of estrogen. After menopause, almost no estrogens are secreted by the ovaries. It leads to (1) increased osteoclastic activity in the bones, (2) decreased bone matrix, and (3) decreased deposition of bone calcium and phosphate. This can greatly weaken the bones and lead to bone fracture, especially fracture of the vertebrae large share of postmenopausal women are treated prophylactically with estrogen replacement to prevent the osteoporotic effects.

6.3.2. Hypergonadism

Hypersecretion of ovarian hormones is a rare phenomenon because it is regulated at the hypothalamic as well as pituitary level. So, hypersecretion can only happen with the development of tumor. Granulosa cells tumor can develop in an ovary, occurring more often after menopause than before. It causes the secretions of large quantities of estrogens, which exert the estrogenic effects, like hypertrophy of the uterine endometrium and irregular bleeding from the endometrium.

7. Summary

- Reproduction is universal phenomenon in organism, which accomplished with the interplay of reproductive hormones.

- Majority of reproductive hormones are steroids and few are of peptide in nature.
- Synthesis of steroid hormone occurs in the tissues by the cholesterol directly or from the acetate with cholesterol as an intermediate.
- The molecular mechanism of steroid action takes place through both classical and non-classical pathway.
- Non-genomic pathway (which does not involve the nucleus and thus transcription) occur with very short lag time as compared to genomic pathway.
- Testosterone is the main male sex hormone while in case of female estrogen and the progesterone is the dominant hormone.
- Testosterone is the sole hormone for masculine features and for the development of secondary sexual characters. However, some other androgens are also secreted but testosterone is the most potent one.
- The two hormones estradiol and progesterone are responsible for the feminizing characters, sex cell development, and maintenance of reproductive cycle and for the development of embryo.
- Estradiol has the major role in the development of secondary sexual character and for the feminine features while progesterone has major role during the pregnancy.
- Regulation of both the male and female hormone takes place through hypothalamic pituitary axis. Increase or decrease level of gonadal hormones is regulated at both the hypothalamic and pituitary level.
- Hyper or hypo secretion of hormones are regulated to maintain the homeostasis, even though abnormalities occurs because of the development of tumors or with some genetic changes.