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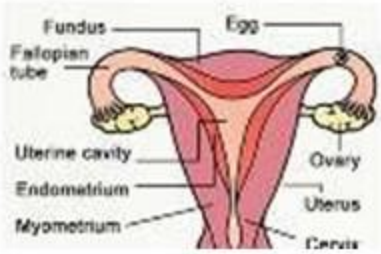
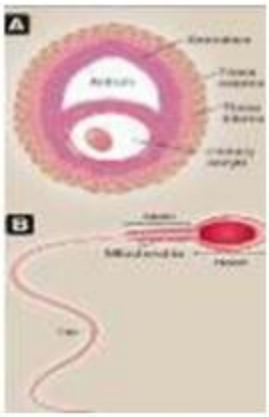
HYPOTHALAMIC–PITUITARY–OVARIAN AXIS



The female gonads are the ovaries, secrete estrogens and progestins. The ovaries are subject to multi-tiered endocrine axis feedback, which allows for precise regulation of function.

Hypothalamus:

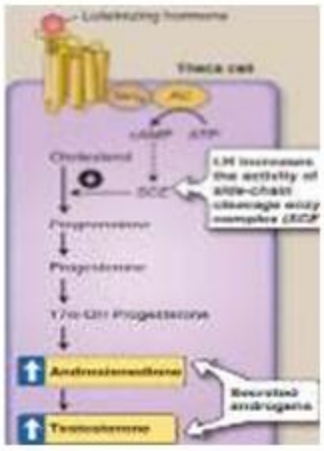
The principal hypothalamic areas involved in ovarian control called Parvocellular neurons in these areas synthesize and secrete GnRH. GnRH is a peptide hormone that is produced and secreted into the hypophyseal portal system. The release of GnRH is pulsatile, meaning that there is not a constant release from the hypothalamus. The perception of stress and other inputs from the higher brain centers as well as from the brain's rhythm centers help influence the pulsatile secretion of GnRH. Frequency of GnRH bursts is increased by estrogens and decreased by progesterone and testosterone. The frequency increases late in the follicular phase of the cycle, culminating in the LH surge. During the luteal phase, the frequency decreases as a result of the action of progesterone, but when estrogen and progesterone secretion decrease at the end of the cycle, the frequency once again increases.



Pituitary gland:

The hypophyseal portal circulation delivers GnRH to anterior pituitary gonadotropes, which subsequently secrete LH and FSH. GnRH receptors are part of the G protein–coupled receptor (GPCR).

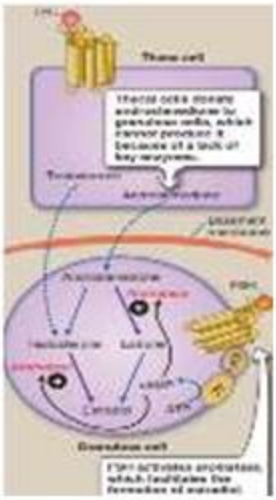
Ovaries:



The ovaries house female germ cells (oocytes) containing follicles in various stages of development: primordial, primary, secondary, tertiary, and Graafian follicles. The endocrine portion of the ovaries is primarily related to the latter follicles and involves theca and granulosa cells. These cells work cooperatively to synthesize and secrete estradiol.

1. Theca cells: Theca cells are a superficial layer of the follicle that transports low-density lipoprotein (LDL) into the cells via cell membrane LDL receptors in clathrin-coated pits. Cholesterol is the initial substrate of the first reaction of steroid hormone synthesis as it is in the adrenal gland. LH receptors are in the GPCR family, which activates a side-

chain cleavage enzyme complex that facilitates the conversion of cholesterol into pregnenolone. Steroid hormone synthesis continues in the theca cell, producing androstenedione and testosterone. The majority of these androgens exits the theca cell and enters nearby granulosa cells, because there are insufficient quantities of aromatase in theca cells to facilitate the conversion of either androstenedione or testosterone into estrogens.

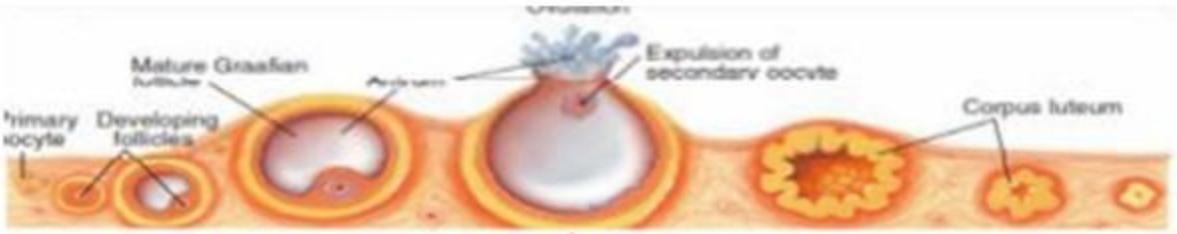


2. Granulosa cells: The granulosa cell is deep compared to theca cells in follicles. The granulosa cell layer dramatically increases during the development from primary to secondary follicles. Granulosa cells express both LH and FSH receptors. Therefore, not only is the conversion of cholesterol to pregnenolone facilitated as in theca cells, but, in addition, the enzyme aromatase is also activated. FSH receptors are in the GPCR induced cAMP second messenger system to activate aromatase. Thus, products such as estradiol can be synthesized and then secreted into the bloodstream. Granulosa cells do not contain sufficient quantities of 17α -hydroxylase or 17,20-desmolase and, thus, rely on androstenedione and testosterone to be secreted from the theca cell to complete sex steroid synthesis.

Oogenesis:

Primary oocyte: From the time of birth, there are many primordial follicles under the ovarian capsule. Each contains an immature ovum that is stopped in prophase of the first meiosis. At the start of each cycle, several of these follicles enlarge, and a cavity forms around the ovum (antrum formation). This cavity is filled with follicular fluid.

Graafian follicle: One of the follicles in one ovary starts to grow rapidly and becomes the dominant follicle, while the others regress, forming atretic follicles. The primary source of circulating estrogen is the granulosa cells of the ovaries.



Ovulation: At about the 14th day of the cycle, the distended follicle ruptures, and the ovum is extruded into the abdominal cavity. The ovum is picked up by the fimbriated, transported to the ends of the fallopian tubes (oviducts), transported to the uterus, and, if it is fertilized, is implanted into the endometrium. If fertilization does not occur, the ovum moves out through the vagina.

Corpus luteum: The follicle that ruptures at the time of ovulation promptly fills with blood. The granulosa and theca cells of the follicle lining promptly begin to proliferate, and the clotted blood is rapidly replaced with yellowish, lipid-rich luteal cells, forming the corpus luteum. This initiates the luteal phase of the menstrual cycle, during which the luteal cells secrete estrogen and progesterone. If occurs, the corpus luteum persists as a source of progesterone to maintain the early pregnancy until chorionic gonadotropin is made. If pregnancy does not occur, the corpus luteum begins to degenerate about 4 days before the next menses and is eventually replaced by scar tissue, the corpus albicans. No new ova are formed after birth.

Tissue	Effect
Bone	↑ Growth via osteoblasts
Endocrine	↑ Progesterone responses
Liver	↑ Clotting factors
	↑ Steroid-binding proteins
	↓ Total and LDL
	↑ HDL
Reproductive organs	↑ Uterine growth
	↑ Vaginal and fallopian tube growth
	↑ Breast growth
	↑ Cervical mucus secretion
	↑ LH receptors on granulosa cells

ESTROGENS

There are three main estrogens. The most potent is estradiol, although estrone, which is also formed in peripheral tissues, and estriol, which is secreted in higher concentrations during pregnancy, also have functional effects. Estradiol has a high binding affinity to sex steroid–binding globulin (SSBG) and a moderate binding affinity to albumin, which keeps the amount in the active free form low in the blood. The liver processes estrogens, and these products are secreted in the urine.

Function Estrogens: have a number of functional effects, both genomic and nongenomic. The nongenomic effects are mediated by cell membrane receptors and do not directly induce transcription, translation, and protein synthesis. Most of estrogens' effects are genomic and utilize a similar mechanism to that of other steroid hormones.

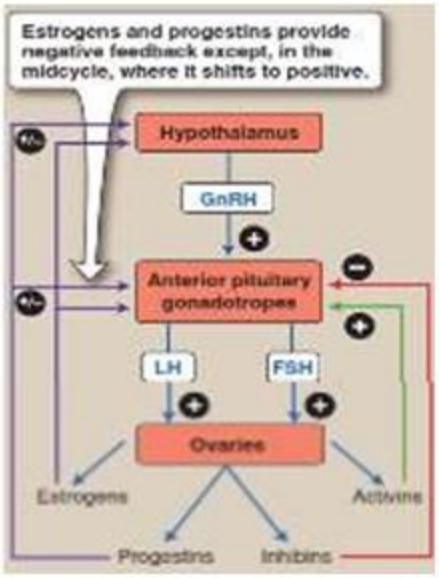
There are two classes of estrogen receptors (ERs): ERα and ERβ. ERα is primarily expressed in the reproductive organs. Whereas ERβ is primarily expressed in granulosa cells and in the nonreproductive organs. ERα and ERβ are cytosolic and nuclear. The nature of the proteins synthesised and their effect is dependent on the tissue.

Secretion: The regulation of estrogens comprises an interrelated set of feedback loops at each level of the hypothalamic–pituitary–ovarian axis. Estrogens, progestins, inhibins, and activins provide axis feedback. These multiple layers of control allow for precise timing of hormona signaling, despite the two main hormone classes (estrogens and progestins) using the same control system axis.

Table 36.2: Effect of Progestins

Tissue	Effect
Breast	↑ Lobular development ↓ Milk production
Reproductive organs	↓ Endometrial growth ↑ Endometrial secretions Mucosal secretions become thicker
Temperature	↑ Internal temperature

1. **Estrogens:** secreted from the granulosa cells negatively feedback to both the anterior pituitary and hypothalamus, and some evidence suggests that there may be additional feedback to higher brain centers that can stimulate or inhibit the axis. Estrogens normally exert negative feedback, but this feedback shifts to positive feedback midcycle. This shift is caused by the upregulation of receptors, such as GnRH in the anterior pituitary, when circulating estrogen levels are elevated. The functional result of the shift is a surge in LH and FSH just prior to ovulation.
2. **Progestins:** also provide negative feedback to the anterior pituitary and hypothalamus.
3. **Inhibins:** Granulosa cells synthesize and secrete peptide hormones called inhibins that feed back to the anterior pituitary. There are two inhibins, A and B, both of which appear to be functional in females. Inhibins decrease secretion of FSH. FSH is the primary stimulus for the production of inhibins, and, thus, inhibin increase lags slightly behind FSH in the menstrual cycle but does provide negative feedback for FSH regulation.



4. **Activins:** are peptide hormones secreted by the granulosa cells that stimulate secretion of FSH from the anterior pituitary as well as local FSH receptor up regulation. Activin levels are highest during follicle development.

Progestins

Progesterone is the most common and biologically active progestin. A second, less potent but measureable, progestin is 17α-hydroxyprogesterone. Progesterone is produced in both theca and granulosa cells. Progesterone binds to albumin with low affinity, and therefore has a fairly short half-life of about 5 min in the circulation. The liver processes progesterone similarly to other steroid hormones, and these products are secreted in the urine.

Function Progesterone:

Functions are more limited compared to those of estrogens, primarily initiating and maintaining pregnancy. The effects of progestins are mediated by progesterone receptors that have A and B half-sites.

The principal target organs of progesterone are the uterus, the breasts, and the brain. Progesterone is responsible for the luteal changes in the endometrium and the cyclical changes in the cervix and vagina. It has an antiestrogenic effect on the myometrial cells,

decreasing their excitability, their sensitivity to oxytocin, and their spontaneous electrical activity while increasing their membrane potential. It also decreases the number of estrogen receptors in the endometrium and increases the rate of conversion of 17β-estradiol to less active estrogens.

In the breast, progesterone stimulates the development of lobules and alveoli. It induces differentiation of estrogen-prepared ductal tissue and supports the secretory function of the breast during lactation.

The feedback effects of progesterone are complex and are exerted at both the hypothalamic and pituitary levels. Large doses of progesterone inhibit LH secretion and potentiate the inhibitory effect of estrogens, preventing ovulation.

Progesterone is thermogenic and is probably responsible for the rise in basal body temperature at the time of ovulation. It stimulates respiration in women during the luteal phase of the menstrual cycle is lower than that in men. In pregnancy, the PCO 2 falls as progesterone secretion rises.

B. Secretion The control of progestin secretion is intricately linked to those of estrogens and thus was discussed above.

OVARIAN AND ENDOMETRIAL CYCLES

The menstrual cycle is actually two distinct cycles: The ovarian cycle deals with follicle development and the endometrial cycle with changes associated in the endometrial lining. Both are controlled and regulated by the hypothalamic pituitary–ovarian axis. The mean duration of these cycles is approximately 28 days, but normal menstrual cycles can vary by a number of days. The most variability in cycle duration occurs earlier and later in the reproductive years.

A.Regulation by the hypothalamic pituitary–ovarian axis:

Changes in plasma LH, FSH, sex steroids, and inhibin during the menstrual cycle. During the early part of the follicular phase, inhibin B is low and FSH is modestly elevated, fostering follicular growth. LH secretion is held in check by the negative feedback effect of the rising plasma estrogen level. At 36–48 h before ovulation, the estrogen feedback effect becomes positive, and this initiates the burst of LH secretion (LH surge) that produces ovulation. Ovulation occurs about 9 h after the LH peak. FSH secretion also peaks, despite a small rise in inhibin. During the luteal phase, the secretion of LH and FSH is low because of the elevated levels of estrogen, progesterone, and inhibin. Once regression of the corpus luteum (luteolysis) begins, estrogen and progesterone levels fall and the secretion of FSH and LH increases. A new crop of follicles develops, and a single dominant follicle matures as a result of the action of FSH and LH. Near midcycle, estrogen secretion from the follicle rises augmenting GnRH-mediated LH surge.

B. Ovarian cycle

The ovarian cycle is divided into follicular and luteal phases. Each phase lasts for half of the duration of the cycle. The events that divide these phases are ovulation and the beginning of menses.

1. Follicular phase: The primary result of the follicular phase is the development of a mature Graafian follicle and secondary oocyte. Follicular phase duration is variable. Estrogens gradually increase, causing FSH and LH to peak, whereas progesterone remains low throughout.

2. Ovulatory phase is 1–3 days and culminates with ovulation

3. Luteal phase: The luteal phase is dominated by the actions of the corpus luteum (residual theca and granulosa cells of the follicle after oocyte release), which synthesizes and secretes estrogen and progesterone. These hormones are necessary for implantation and maintenance of any fertilized oocytes. If fertilization does not occur, the corpus luteum regresses and eventually forms a nonfunctional scar like structure (corpus albicans). The corpus albicans slowly migrates deeper into the ovary and is slowly degraded. The regression of the corpus luteum occurs about 10–12 days after ovulation in the absence of human chorionic gonadotropin (hCG). Thus, the 14 days of the luteal phase is fairly constant. Progestins gradually rise, and estrogens first fall but then increase again. Body temperature increases.

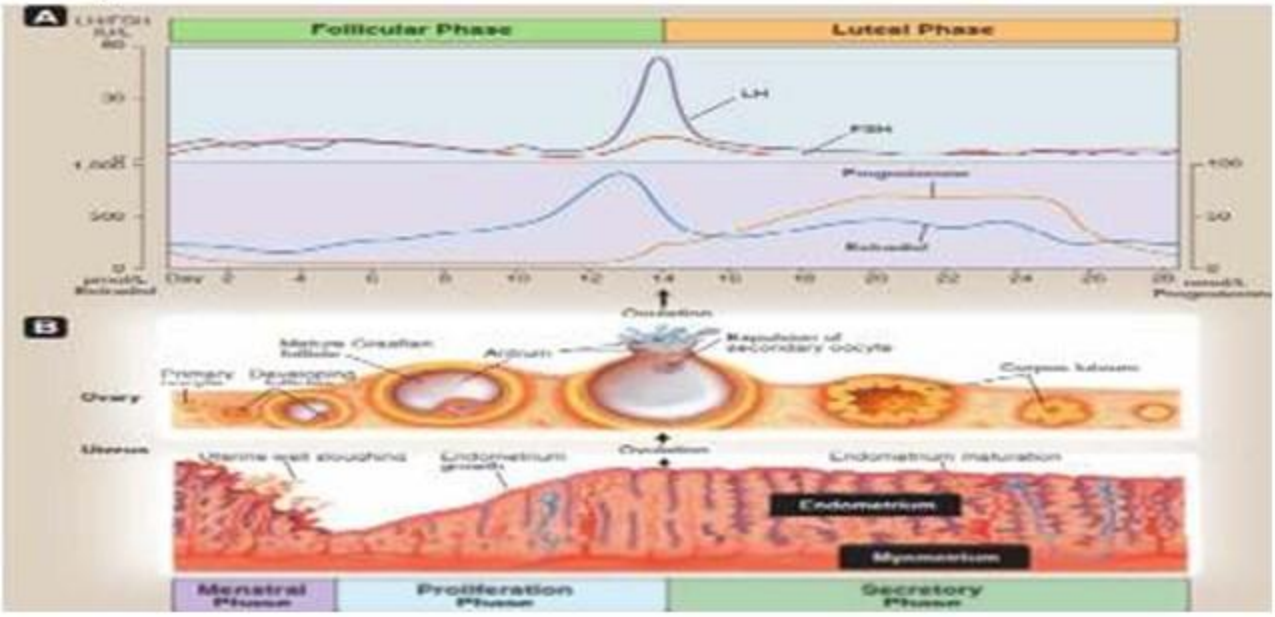
C. **Endometrial cycle:** The uterine inner wall lining (endometrium) undergoes many changes during a typical month in a woman in her childbearing years. The endometrial cycle is divided into a proliferative phase, a secretory phase, and menstruation.

1. Proliferative phase: Endometral growth is the primary outcome of this phase and is mediated by increases in estrogens. Growth is pronounced, with endometrial thickness increasing from 1–2 mm to 8–10 mm by the end of the phase, which is marked by ovulation. Blood vessels and gland growth occur within the expanding stratum functionalis of the endometrium.

2. Secretory phase: The primary outcome of this phase is the maturation of the endometrium. Decreasing levels of estrogens halt endometrial lining growth. Meanwhile, mucous glands more fully develop, and both the glands and blood vessels in this area increase surface area and coil.

3. Menstruation: If conception does not occur, the endometrial lining is replaced to prepare for the next cycle. Menstruation begins with a pronounced prostaglandin-mediated vasoconstriction of spiral arteries, which causes local ischemic injury. Inflammatory cells infiltrate the area and cause further breakdown of the lining. During

this time, factors that break down clots are activated to maintain bleeding until the lining is sloughed off the uterine wall.

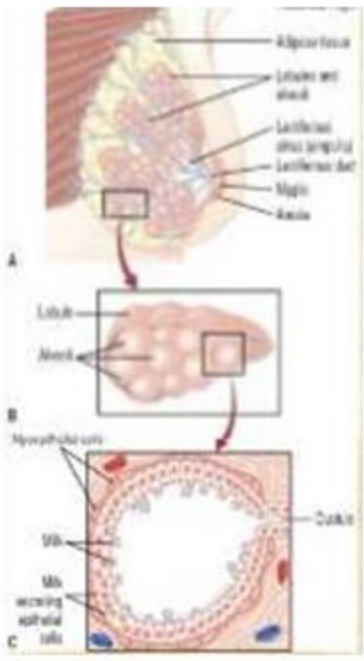


Cyclical Changes in the Uterine:

Estrogen makes the mucus thinner and more alkaline, changes that promote the survival and transport of sperm. The mucus is thinnest at the time of ovulation. Progesterone makes it thick, tenacious, and cellular.

Cyclical Changes in the Breasts

Estrogens cause proliferation of mammary ducts, whereas progesterone causes growth of lobules and alveoli. The breast swelling, tenderness, and pain experienced by many women during the 10 days preceding menstruation are probably due to distension of the ducts, hyperemia, and edema of the interstitial tissue of the breast. All these changes regress, along with the symptoms, during menstruation.



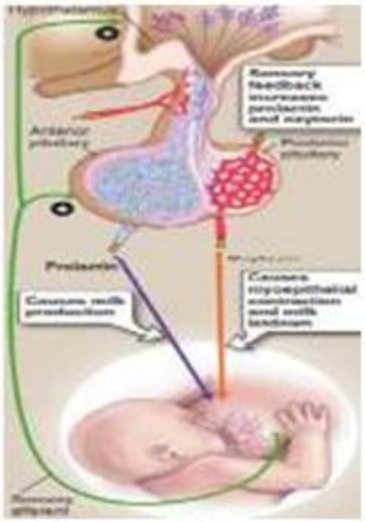
MAMMARY GLANDS

The breast and mammary glands provide optimal nourishment for infants. Although lactation (the period during which milk is produced and secreted) occurs just after birth, the development of breast tissue and preparation for this act occurs during puberty. This growth and development is mediated by female gonadal hormones as part of secondary sex characteristics. The breast develops more fully via high levels of estrogens, progestins, hCG from the fetus, and prolactin. Besides

beginning milk production and sustaining it, which is primarily mediated by prolactin, milk must be "let down" and ejected to allow for suckling, a process mediated by the posterior pituitary hormone oxytocin.

Prolactin: is a peptide hormone produced and secreted from lactotropes in the anterior pituitary gland. Unlike the other anterior pituitary hormones, it is not associated with a hormone axis and is produced and secreted in both males and females. In females, lactotropes hypertrophy, and prolactin secretion increases during pregnancy. Prolactin is not associated with a hormone-binding protein and has a half-life of about 20 min.

Function: Prolactin causes mammary glandular tissue growth and development, ductal proliferation, synthesis of breast milk, and preparation of the breast for lactation. The effects of prolactin on the breast and mammary gland are mediated by a cytokine cell membrane receptor.



Secretion: Prolactin secretion by lactotropes is normally suppressed by tonic dopamine secretion from the hypothalamus. Prolactin has a negative feedback loop to the hypothalamus to adjust the release of dopamine. Nursing and breast manipulation as well as estrogen, oxytocin, thyroid-releasing hormone, sleep, and stress all increase prolactin secretion. Somatostatin and growth hormone decrease prolactin secretion. These alterations in prolactin secretion occur either directly at the level of the lactotrope or via inhibition of the hypothalamic dopaminergic neurons.