

Ovulation

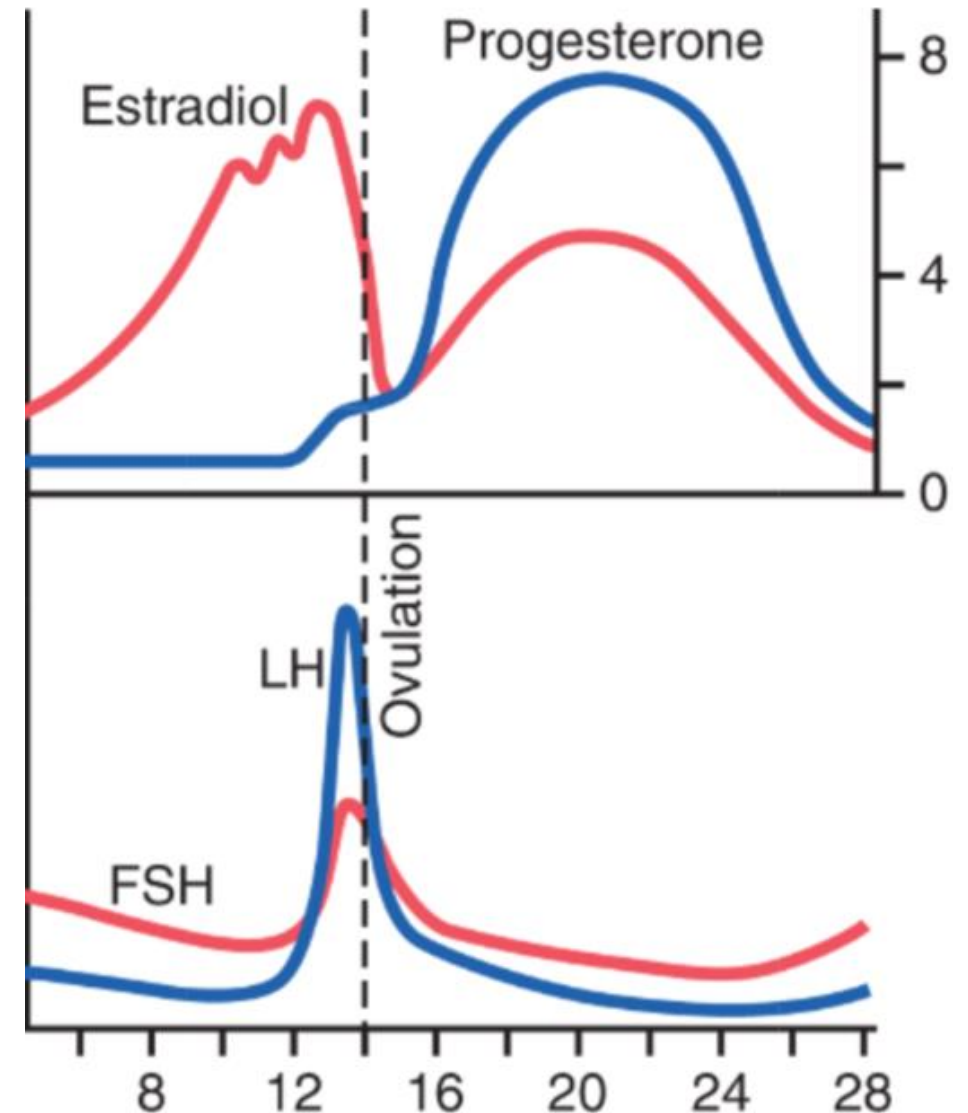
Alaa Bawaneh, MD. PhD

A Surge of Luteinizing Hormone Is Necessary for Ovulation

- LH is **necessary** for **final follicular growth** and **ovulation**.
- **Without** this hormone, even when large quantities of FSH are available, the **follicle will not progress to the ovulation** stage.
- FSH and LH act **synergistically** to cause **rapid swelling** of the follicle during the last few days before ovulation.
- The LH also has a specific effect on **the granulosa and theca cells**, converting them **mainly** to **progesterone-secreting cells**.
- Therefore, the rate of **estrogen** secretion begins to **fall** about 1 day before ovulation, while increasing amounts of **progesterone begin** to be secreted.

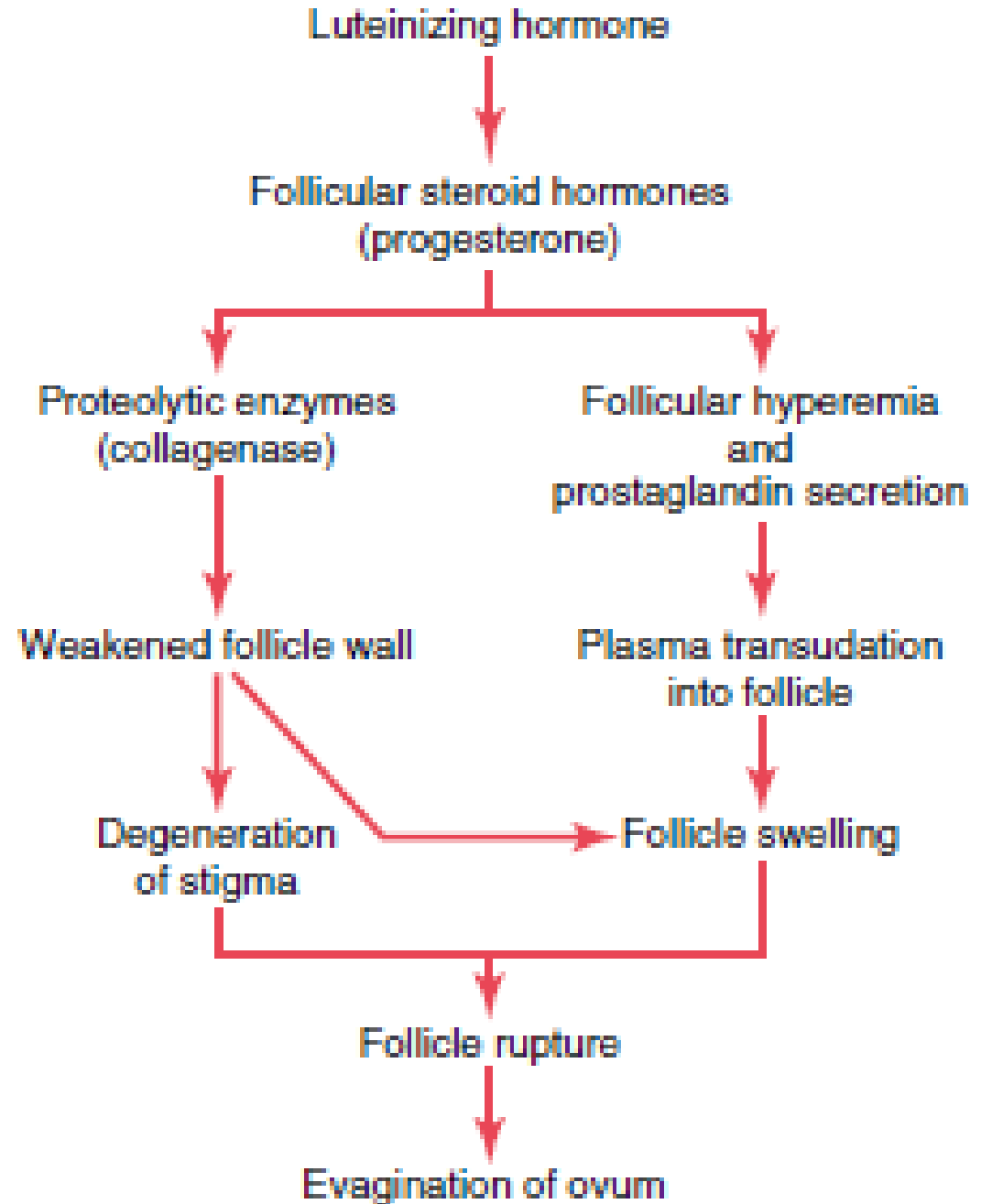
Surge of Luteinizing Hormone Is Necessary for Ovulation

- (1) rapid growth of the follicle
- (2) preovulatory surge of LH
- (3) initiation of secretion of progesterone.
- (4) diminishing estrogen secretion after a prolonged phase of excessive estrogen secretion.
- → ovulation occurs.



Mechanism of Ovulation

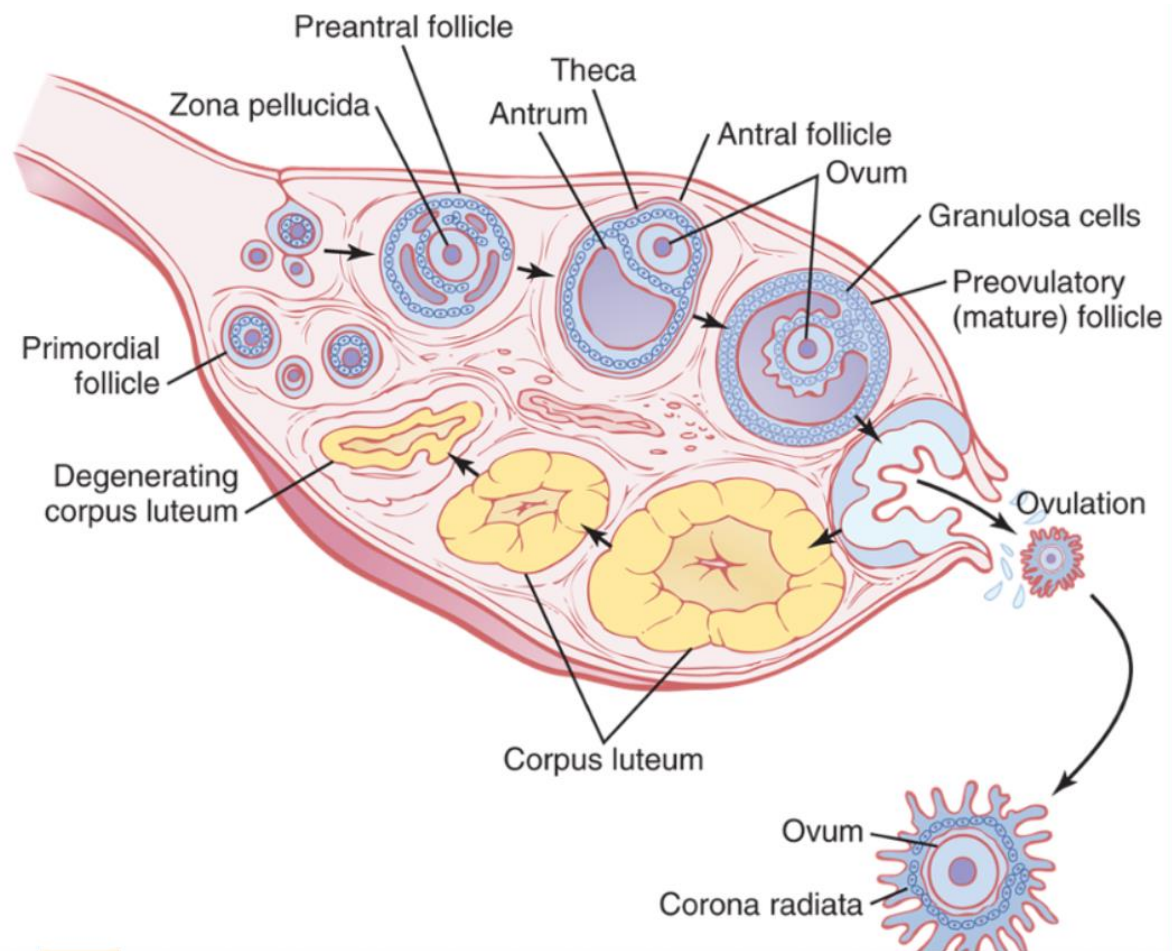
- LH surge
- Theca Externa release enzymes
- Rapid growth of new blood vessels into follicular wall
- Follicle swelling and degeneration of the stigma
- Follicle rupture
- Ovum discharge



- Shortly before ovulation the protruding outer wall of the follicle swells rapidly, and a small area in the center of the follicular capsule, called the *stigma*, protrudes like a nipple. In another 30 minutes or so, fluid begins to ooze from the follicle through the stigma, and about 2 minutes later, the stigma ruptures widely, allowing a more viscous fluid, which has occupied the central portion of the follicle, to evaginate outward. This LH causes rapid secretion of follicular steroid hormones that contain progesterone. Within a few hours, two events occur, both of which are necessary for ovulation:

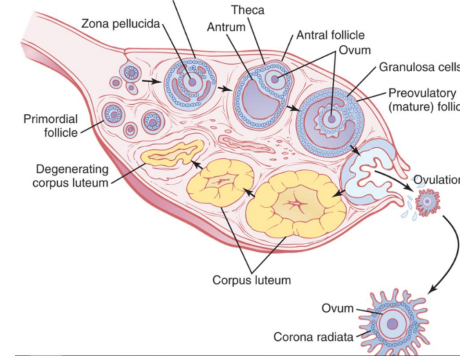
(1) The *theca externa* (the capsule of the follicle) begins to release proteolytic enzymes from lysosomes, and these cause dissolution of the follicular capsular wall and consequent weakening of the wall, resulting in further swelling of the entire follicle and degeneration of the stigma.

(2) Simultaneously there is rapid growth of new blood vessels into the follicle wall, and at the same time, prostaglandins (local hormones that cause vasodilation) are secreted into the follicular tissues. These two effects cause plasma transudation into the follicle, which contributes to follicle swelling. Finally, the combination of follicle swelling and simultaneous degeneration of the stigma causes follicle rupture, with discharge of the ovum.



Corpus Luteum—The Luteal Phase of the Ovarian Cycle

Corpus Luteum



- During the first few hours after expulsion of the ovum from the follicle, the **remaining granulosa and theca interna** cells change rapidly into **lutein cells**.
- They **enlarge** in diameter two or more times and become filled with **lipid inclusions** that give them a **yellowish appearance**.
- 12 days after ovulation → the corpus luteum begins to **involute** and eventually **loses its secretory function** and its **yellowish, lipid characteristic** about, becoming the corpus albicans; during the ensuing few weeks, the corpus albicans is **replaced by connective tissue** and over months is **absorbed**.

** Another hormone with almost exactly the same properties as LH, chorionic gonadotropin, which is secreted by the placenta, can act on the corpus luteum to prolong its life—usually maintaining it for at least the first 2 to 4 months of pregnancy.

Ovulation—The Preovulatory Luteinizing Hormone Surge

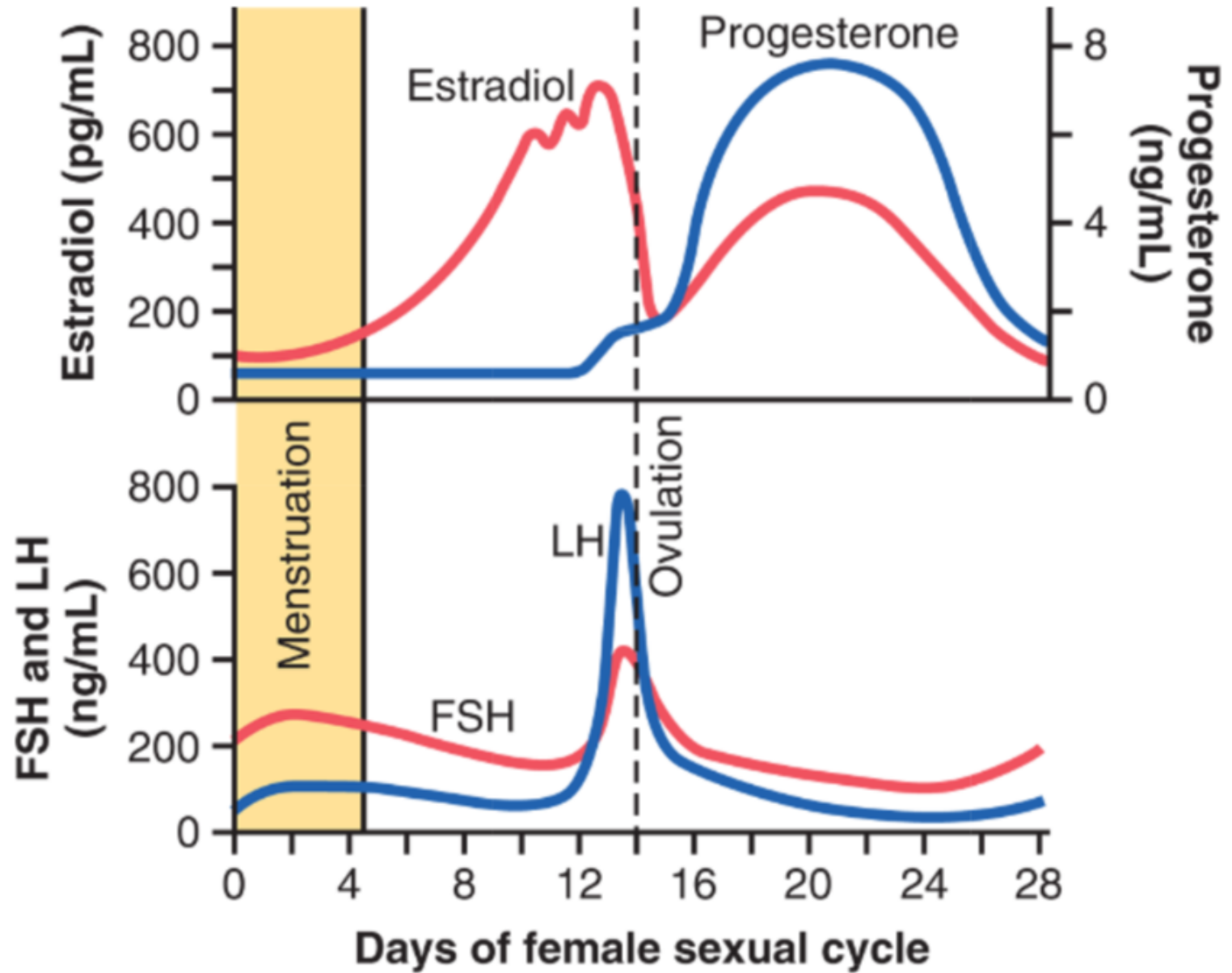
- Experiments have shown that estrogen infusion into a female **above a critical rate** for 2 to 3 days during **the latter part of the first half** of the ovarian cycle will cause rapidly accelerating growth of the ovarian follicles, as well as rapidly accelerating secretion of ovarian estrogens. During this period, secretions of FSH and LH by the anterior pituitary gland are at first **slightly suppressed**. Secretion of **LH** then **increases** abruptly 6-fold to 8-fold, and secretion of **FSH** increases about 2-fold.

Causes of LH surge

- The cause of this abrupt surge in LH secretion is not known. However, the following explanations are possible:
- 1. It has been suggested that at this point in the cycle, **estrogen (high level)** has a **peculiar positive feedback** effect of stimulating pituitary secretion of LH and, to a lesser extent, FSH. which is in sharp contrast to the normal negative feedback effect of estrogen that occurs during the remainder of the female monthly cycle.

Causes of LH surge

- 2. The granulosa cells of the follicles begin to secrete small but **increasing quantities of progesterone** a day or so before the preovulatory LH surge, and it has been suggested that this secretion might be the factor that stimulates the excess LH secretion.



Summary (Female hormones)

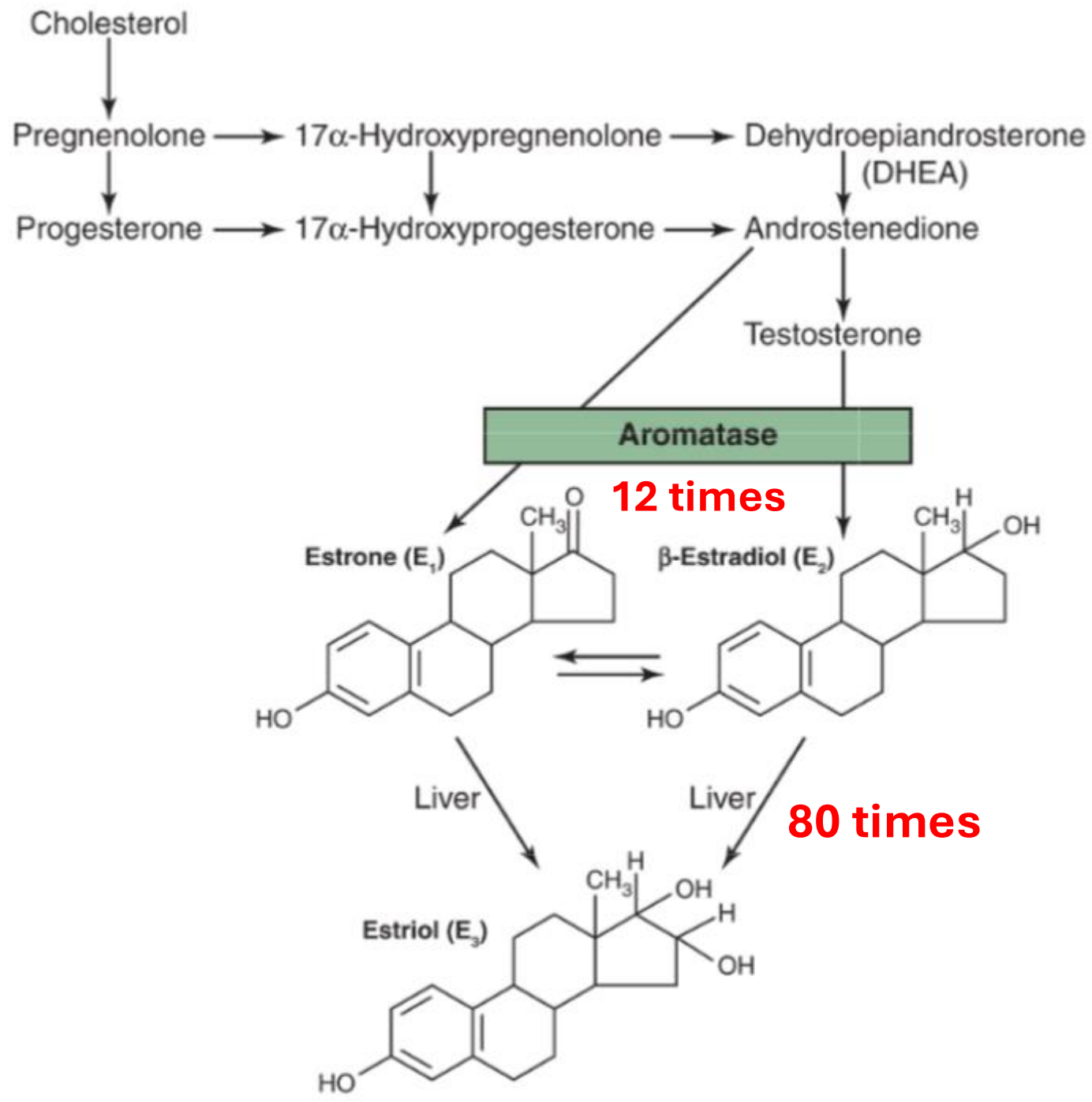
- The amount of GnRH released from the hypothalamus increases and decreases much less drastically during the monthly sexual cycle. It is secreted in short pulses averaging once every 90 minutes.
- During the first few days of each monthly female sexual cycle, the concentrations of FSH and LH increase slightly to moderately, with the increase in FSH slightly greater than that of LH and preceding it by a few days.
- FSH, cause accelerated growth of 6 to 12 primary follicles each month.
- During growth of the follicles, estrogen is mainly secreted.

Summary (Female hormones)

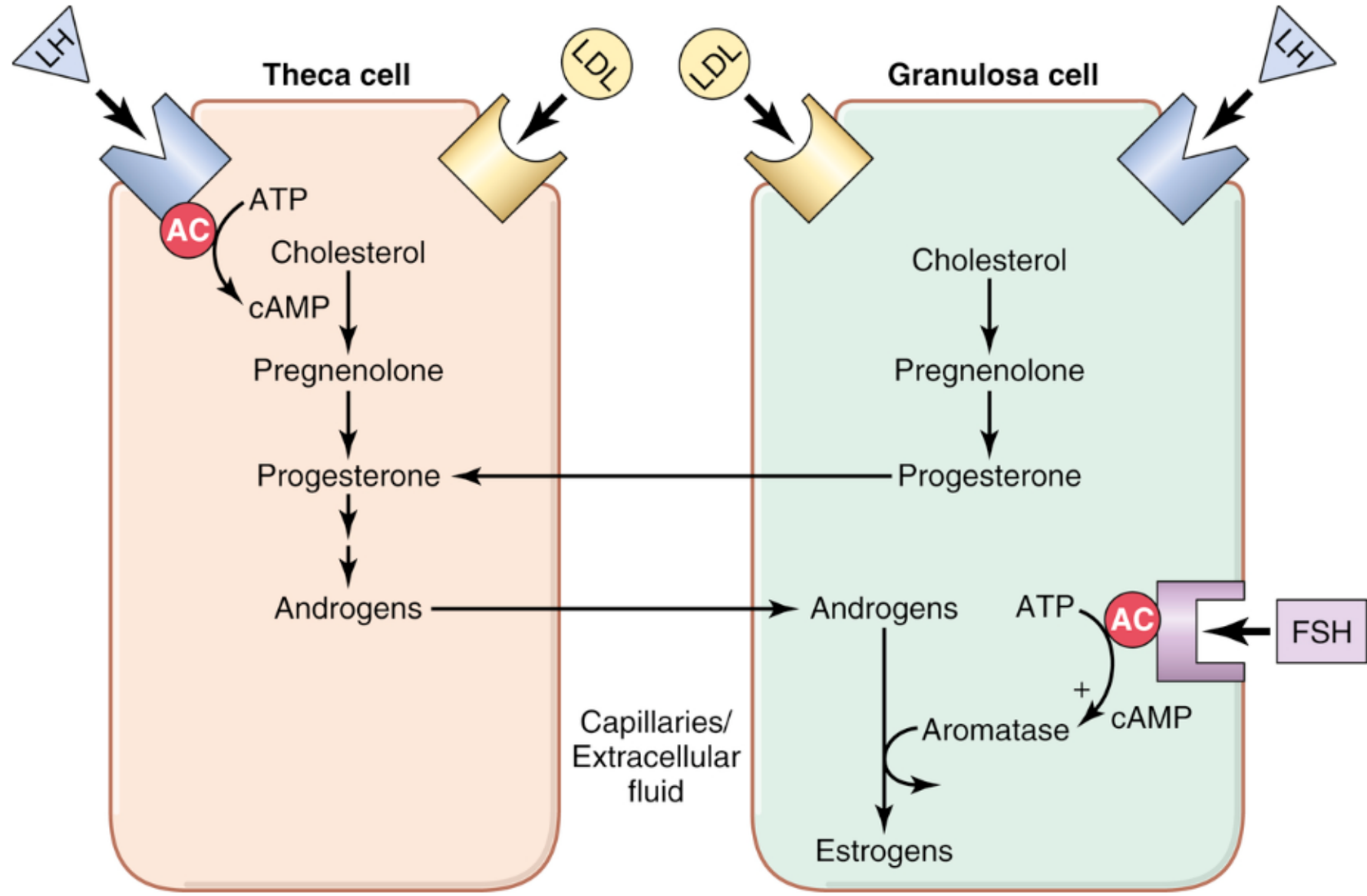
- ~2 days before ovulation there is a surge of LH, initiation of secretion of progesterone, and diminished estrogen secretion.
- Estrogen in particular and progesterone to a lesser extent, secreted by the corpus luteum during the luteal phase, have strong negative feedback effects on FSH and LH.
- In addition, the lutein cells secrete inhibin. This hormone inhibits FSH secretion.
- Low blood concentrations of FSH and LH result in corpus luteum involution.

Ovarian sex hormones

- Estrogens and the progestins.
- The most important of the estrogens → estradiol.
- The most important progestin → progesterone.
- The estrogens → mainly **promote proliferation** and **growth** of specific cells in the body that are responsible for development of most **secondary sexual characteristics** of females.
- The progestins → function mainly to **prepare the uterus for pregnancy** and the **breasts for lactation**.



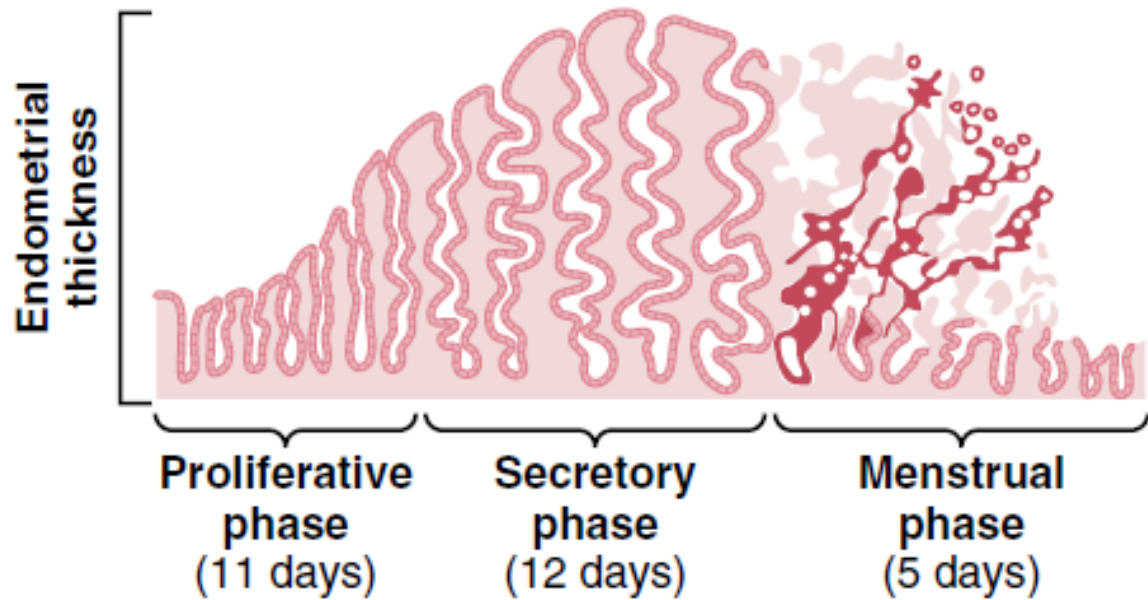
- ** nonpregnant women → ER (ovaries, less adrenal cortices). PR (in the latter half of each ovarian cycle, secreted by the corpus luteum).
- ** during pregnancy → ER (placenta). PR (placenta, especially after the fourth month of gestation)
- ** The principal estrogen secreted by the ovaries is β -estradiol.
- ** Small amounts of estrone are also secreted, but most of this is formed in peripheral tissues from androgens secreted by the adrenal cortices and by ovarian thecal cells.
- ** Estriol is a weak estrogen; it is an oxidative product derived from both estradiol and estrone (liver).
- ** Therefore, **diminished liver function** actually increases the activity of estrogens in the body, sometimes **causing hyperestrinism**.
- ** The major end product of progesterone degradation is **pregnanediol**. About 10% of the original progesterone is excreted in the urine in this form. Therefore, one can estimate the rate of progesterone formation in the body from the rate of this excretion.



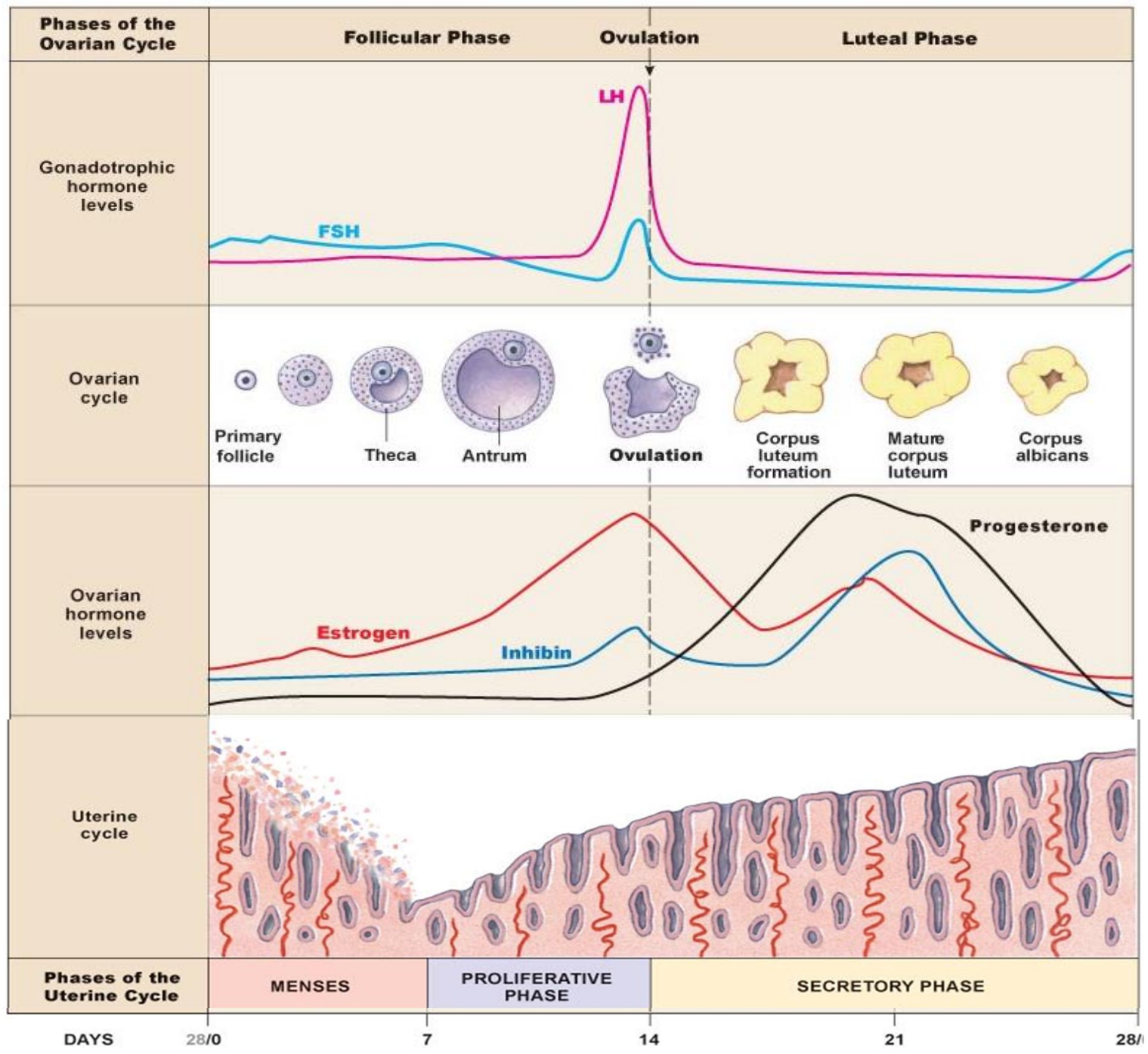
** Progesterone and androgens (testosterone and androstenedione) are synthesized first.

** During the **follicular phase** of the ovarian cycle, before these two initial hormones can leave the ovaries, **almost all** the androgens and much of the progesterone are converted into estrogens by the enzyme **aromatase in the granulosa cells**. Because the **theca cells lack aromatase**, they cannot convert androgens to estrogens. However, androgens diffuse out of the theca cells into the adjacent granulosa cells, where they are converted to estrogens by aromatase, **the activity of which is stimulated by FSH**

** During the **luteal phase** of the cycle, far too much progesterone is formed for all of it to be converted, which accounts for the large secretion of progesterone into the circulating blood at this time.



Monthly Endometrial Cycle and Menstruation



Menstruation

- If the ovum is not fertilized, about 2 days before the end of the monthly cycle, the corpus luteum in the ovary suddenly involutes, ovarian hormones (estrogens and progesterone) decrease to low levels of secretion.
- 24 hours preceding the onset of menstruation, vasospasm (increase release of prostaglandins), decrease in nutrients to the endometrium, and the loss of hormonal stimulation initiate necrosis in the endometrium.

- **Menstruation is caused by the reduction of estrogens and progesterone, especially progesterone, at the end of the monthly ovarian cycle.
- **During normal menstruation, approximately 40 milliliters of blood and an additional 35 milliliters of serous fluid are lost. The menstrual fluid is normally nonclotting because a fibrinolysin is released along with the necrotic endometrial material.
- **If heavy bleeding occurs from the uterine surface (first 2d), the quantity of fibrinolysin may be insufficient to prevent clotting, resulting in the passage of blood clots.

Menstruation

- Hormonal stimulation initiate necrosis in the endometrium.
- Hemorrhagic areas → superficial layers of the endometrium have desquamated → uterine contractions to expel the uterine contents (prostaglandins).
- Menstrual flow from the uterus consists of 50–150 mL of blood, tissue fluid, mucus, and epithelial cells shed from the endometrium.
- Tremendous numbers of leukocytes are released along with the necrotic material and blood (resistant to infection).

Proliferative Phase (Estrogen Phase)

- Under the influence of estrogens, the stromal cells and the epithelial cells proliferate rapidly.
- The endometrial surface is re-epithelialized within 4 to 7 days after the beginning of menstruation.
- During the next week and a half, the endometrium increases greatly in thickness, owing to **increasing numbers of stromal cells** and to progressive growth of the **endometrial glands** and **new blood vessels** into the endometrium.
- At the time of ovulation, the endometrium is 3 to 5 mm thick.

- **At the beginning of each monthly cycle, most of the endometrium has been desquamated by menstruation.
- **After menstruation, only a thin layer of endometrial stroma remains and the only epithelial cells that are left are those located in the remaining deeper portions of the glands and crypts of the endometrium.

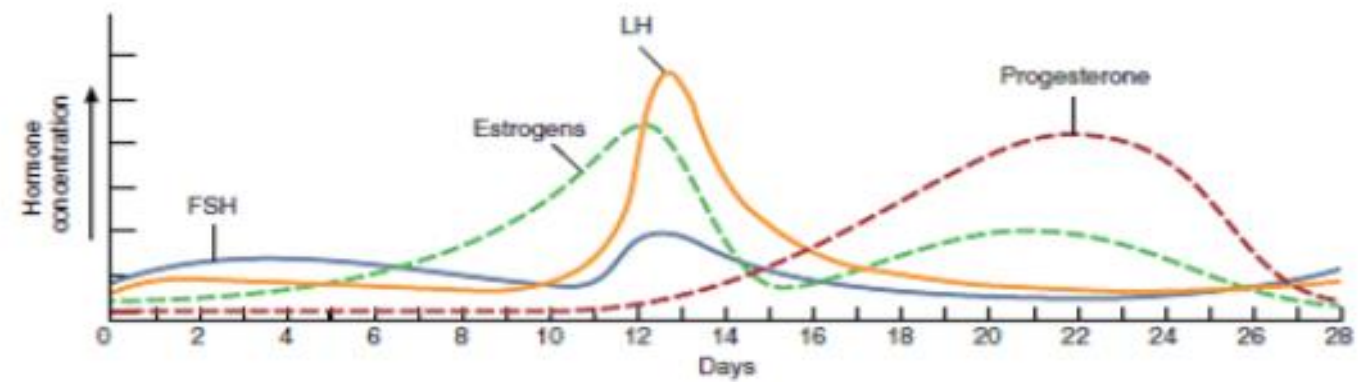
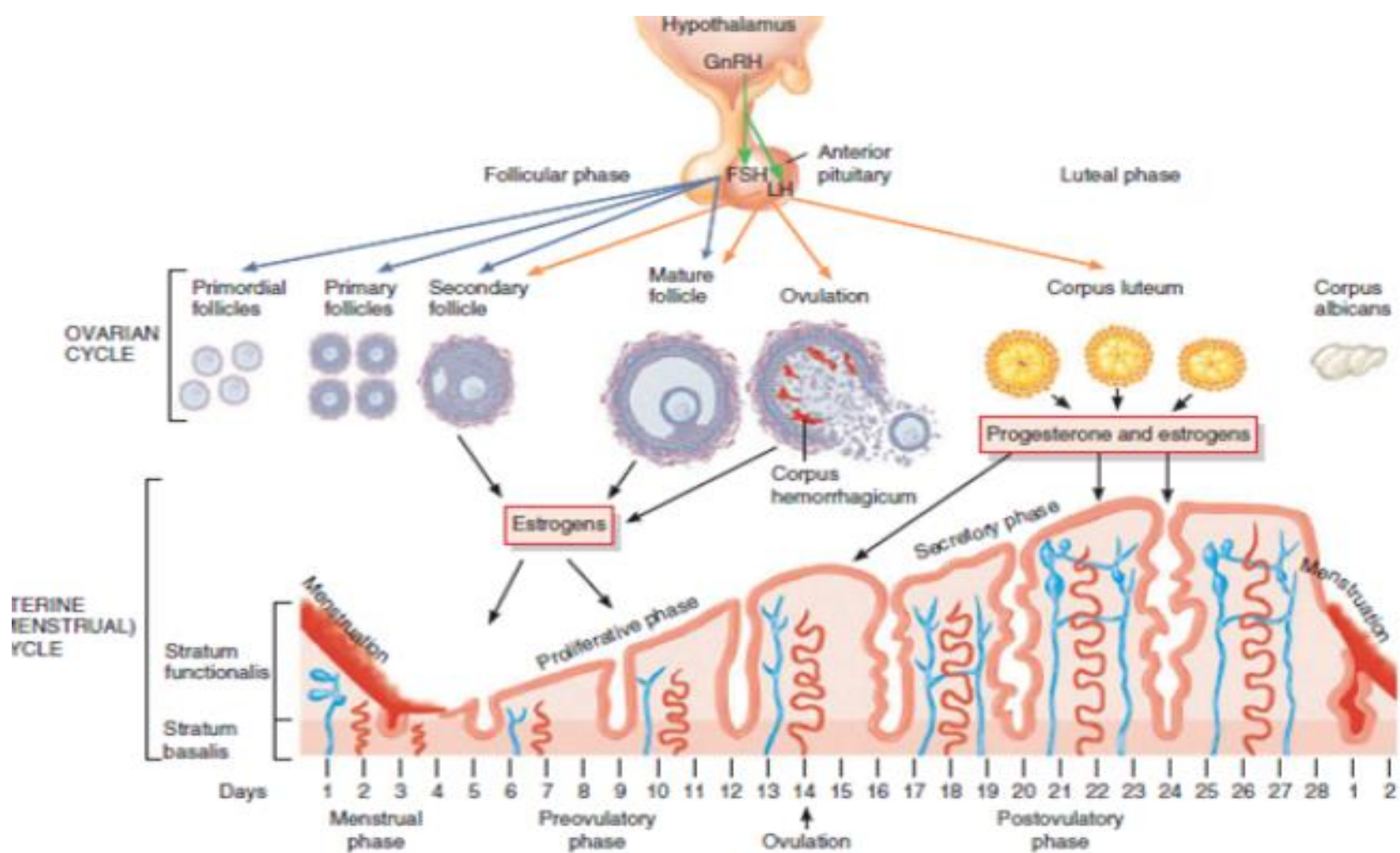
Secretory Phase (Progestational Phase)

- The estrogens cause slight additional cellular proliferation in the endometrium during this phase of the cycle.
 - Progesterone causes marked swelling and secretory development of the endometrium.
 - The glands increase in tortuosity; an excess of secretory substances accumulates in the glandular epithelial cells.
 - lipid and glycogen deposits increase greatly in the stromal cells.
 - Further Increase blood supply to the endometrium
- **At the peak of the secretory phase, about 1 week after ovulation, the endometrium has a thickness of 5 to 6 millimeters.

Secretory Phase (Proggestational Phase)

- From the time of fertilization (3-4d) until the time implantation (7-9d), the uterine secretions, called “uterine milk,” provide nutrition for the early dividing ovum.
- Then, once the ovum implants (7-9) in the endometrium, the trophoblastic cells on the surface of the implanting ovum (in the blastocyst stage) begin to digest the endometrium and absorb the endometrial stored substances, thus making great quantities of nutrients available to the early implanting embryo.

****The whole purpose of all these endometrial changes is to produce a highly secretory endometrium that contains large amounts of stored nutrients to provide appropriate conditions for implantation of a *fertilized* ovum during the latter half of the monthly cycle.



Function of sex hormones

Functions of Estrogens

- Effect of Estrogens on the Uterus and External Female Sex Organs
- Transform the female sex organs from those of a child → an adult.
- The ovaries, fallopian tubes, uterus, and vagina all increase several times in size.
- Deposition of fat and enlargement of external genitalia.
- Change the vaginal epithelium from a cuboidal into a stratified type, which is considerably more resistant to trauma and infection.
- Estrogens cause marked proliferation of the endometrial stroma and greatly increased development of the endometrial glands, which will later aid in providing nutrition to the implanted ovum.

Functions of Estrogens

- Effect of Estrogens on the Breast

- Development of the stromal tissues of the breasts.
- Growth of an extensive ductile system.
- Deposition of fat in the breasts.

** → estrogens initiate growth of the breasts and of the milk-producing apparatus. They are also responsible for the characteristic growth and external appearance of the mature female breast. However, they do not complete the job of converting the breasts into milk-producing organs.

Functions of Estrogens

- Effect of Estrogens on the Skeleton
- Estrogens inhibit osteoclastic activity in the bones and therefore stimulate bone growth.
- They cause uniting of the epiphyses with the shafts of the long bones.
- After menopause → increased osteoclastic activity, decreased bone matrix, and decreased deposition of bone calcium and phosphate → osteoporosis → fracture

**This effect of estrogen (uniting epiphyses) 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.

Functions of Estrogens

- Effect of Estrogens on metabolism
 - Estrogens **Slightly** Increase Protein Deposition.
 - Estrogens increase the whole-body metabolic rate **slightly**.
 - Increased deposition of fat in the subcutaneous tissues, breasts, buttocks and thighs.
- ** increase protein deposition → This effect mainly results from the growth-promoting effect of estrogen on the sexual organs, the bones, and a few other tissues of the body.

Functions of Progesterone

- Progesterone promotes **secretory changes** in the uterus.
- Progesterone decreases the frequency and intensity of uterine contractions, thereby helping to prevent expulsion of the implanted ovum.
- Progesterone promotes development of the lobules and alveoli of the breasts, causing the alveolar cells to proliferate, enlarge, and become secretory in nature.

**progesterone does not cause the alveoli to secrete milk; milk is secreted only after the prepared breast is further stimulated by *prolactin* from the anterior pituitary gland.

**Progesterone also causes the breasts to swell. Part of this swelling is due to the secretory development in the lobules and alveoli, but part also results from increased fluid in the tissue.