PHYSIOLOGY OF OVARIAN CYCLE

GUYTON & HALL, CHAPTER 82

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ASSOCITAE PROF.

By the end of this lecture, you should be able to:

- List the hormones of female reproduction and describe their physiological functions
- Describe the changes that occur in the **ovaries** during the menstrual cycle
- Describe the hormonal control of the development of ovarian follicles, mature oocytes and corpus luteum
- Recognize the *pituitary-ovarian-axis* and the changes that occur in the ovaries leading to ovulation

OBJECTIVES

Physiologic Anatomy of the Female Sexual Organs

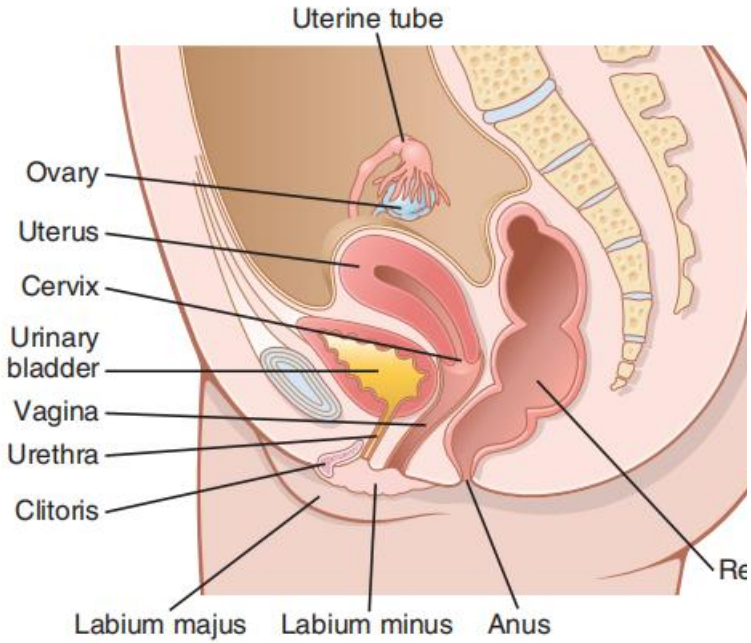
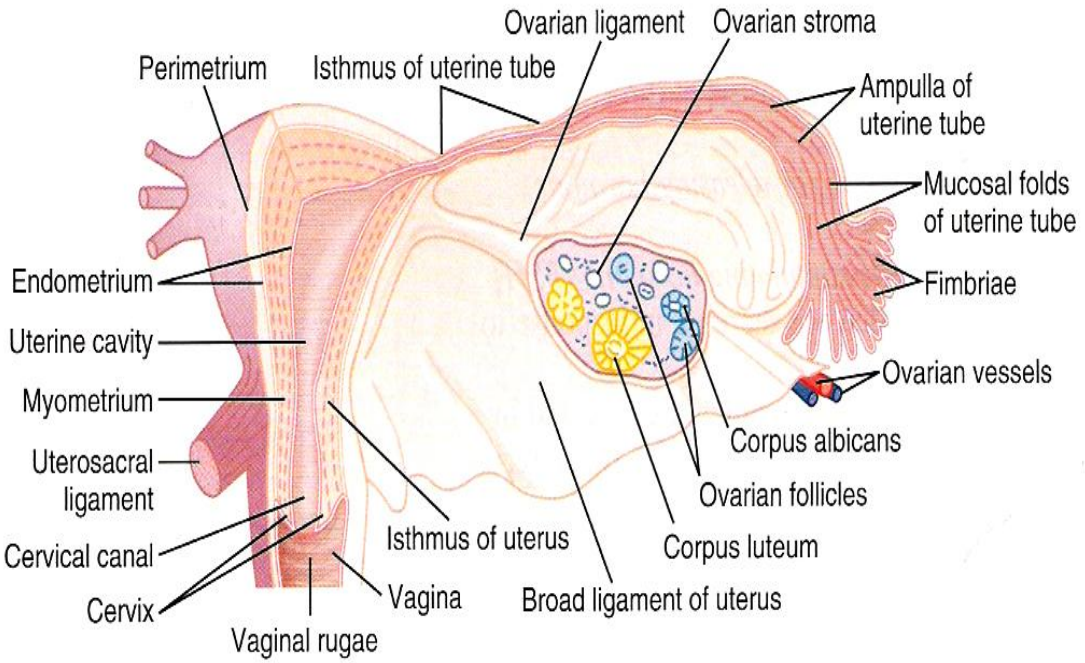


Figure 82-1. The female reproductive organs.



Monthly Reproductive "Menstrual" Cycle

Normal reproductive age of female → Monthly rhythmical changes in the rates of secretion of female hormones & corresponding physical changes in the ovaries & other sexual organs.

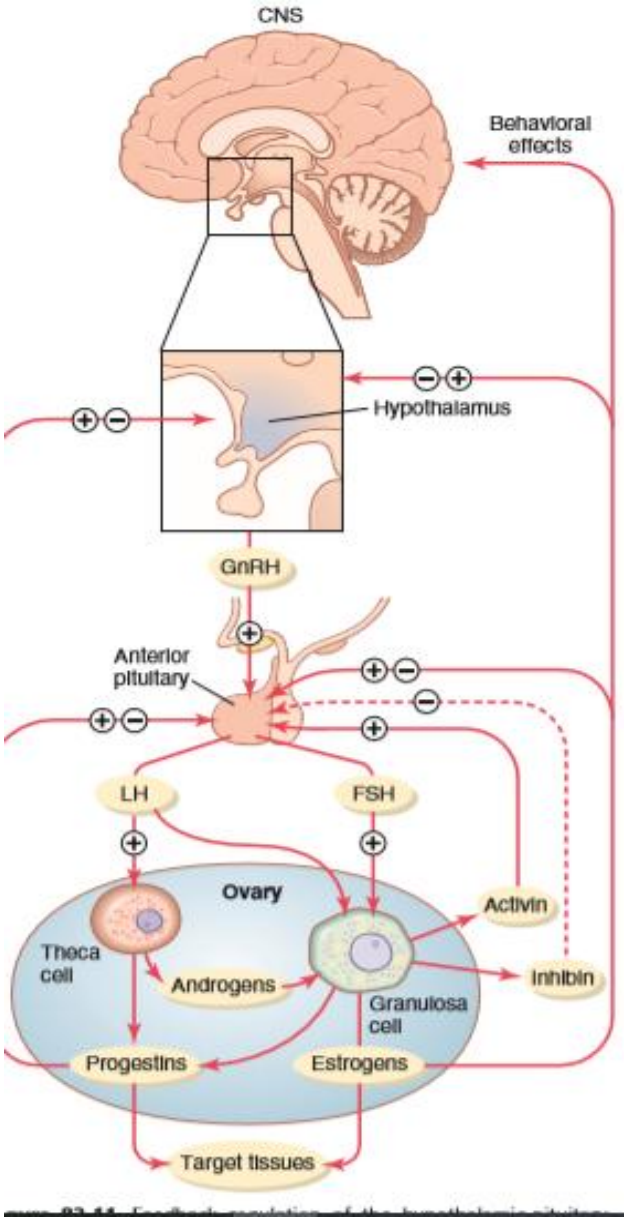
Duration of the cycle averages **28 days** (20-45 days).

There are 2 results of the female sexual cycle:

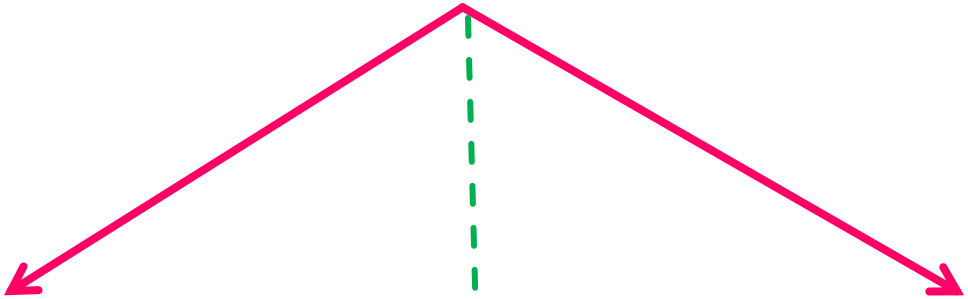
1. *Single* ovum is released from the ovaries each month
2. Uterine endometrium is prepared for implantation of the fertilized ovum.

GONADOTROPIC HORMONES AND THEIR EFFECTS ON THE OVARIES

- The **ovarian changes** during the sexual cycle depend completely on FSH & LH secreted by AP.
- **Both FSH and LH** stimulate their ovarian target cells by combining with highly specific receptors leading to an increase in the cells rates of secretion, growth & proliferation.



Ovarian Cycle



Follicular Phase (Preovulatory)

Ovulation

Luteal Phase (Postovulatory)

Ovarian follicle growth

"Follicular" phase of the ovarian cycle:

- In female child each ovum is surrounded by single granulosa cell sheath called *primordial follicle* which provides nourishment for the ovum & secrete oocyte *maturation-inhibiting factor* which keeps the ovum in its primordial state

- After puberty, AP secretes FSH and LH resulting in ovum to increase in size & growth of additional layers of granulosa cells of some follicles known as primary follicles

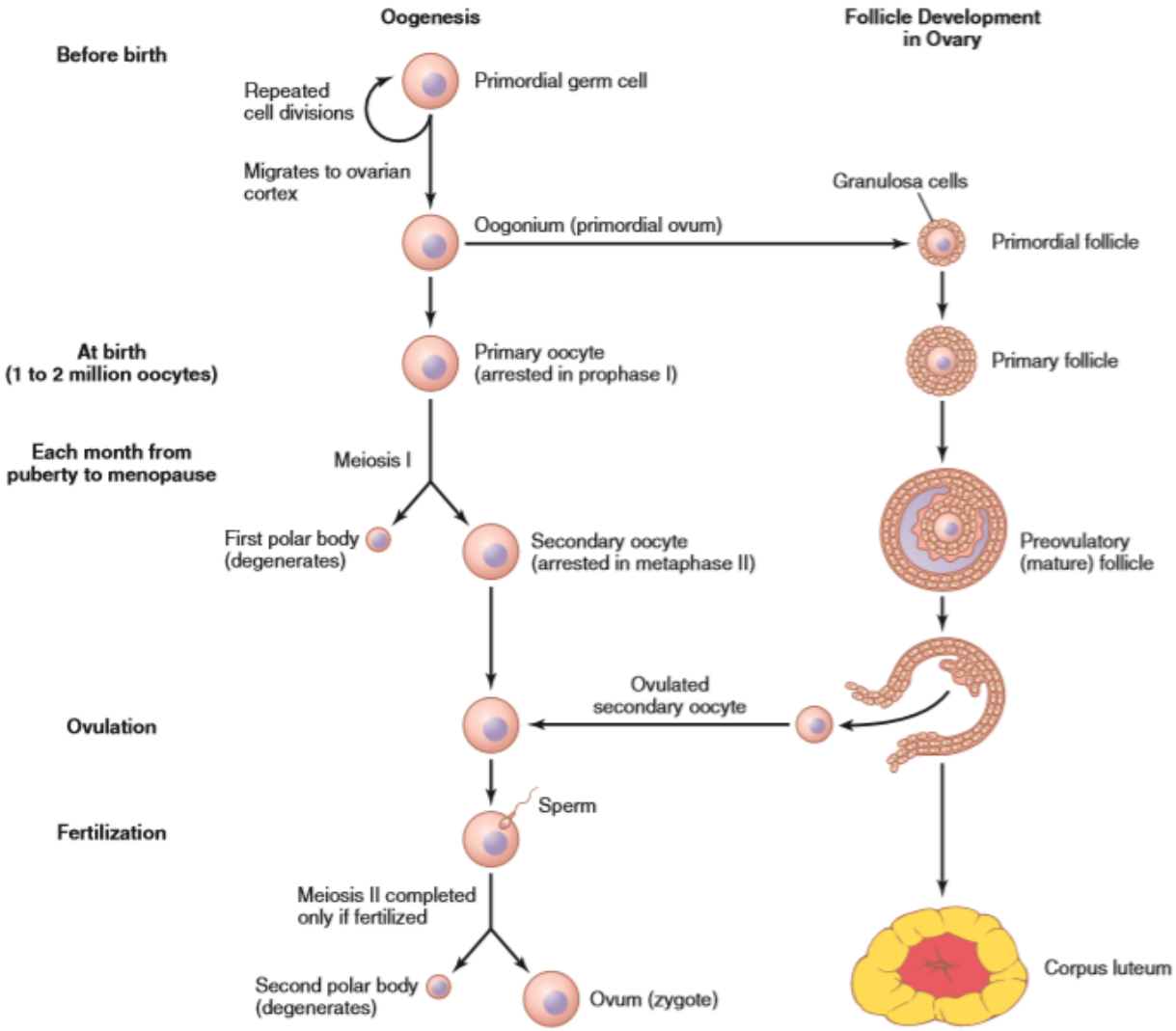


Figure 82-3. Oogenesis and follicle development.

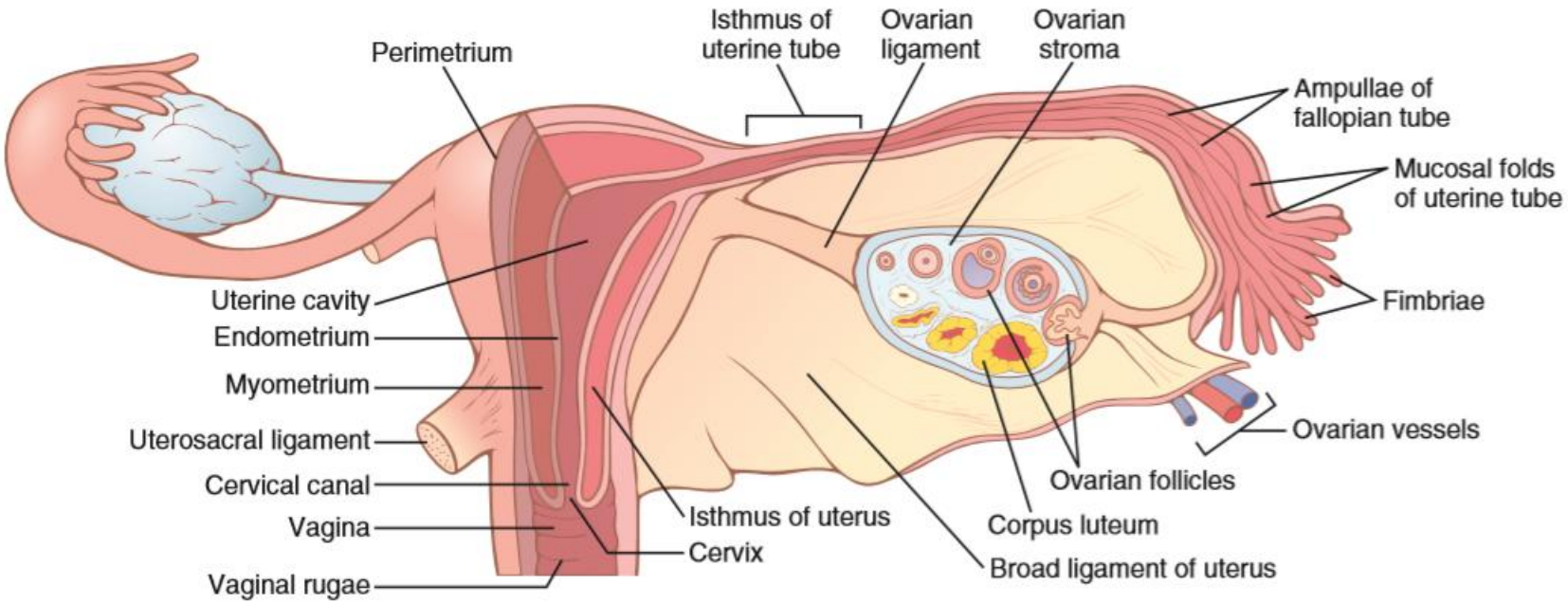


Figure 82-2. Internal structures of the uterus, ovary, and a uterine tube.

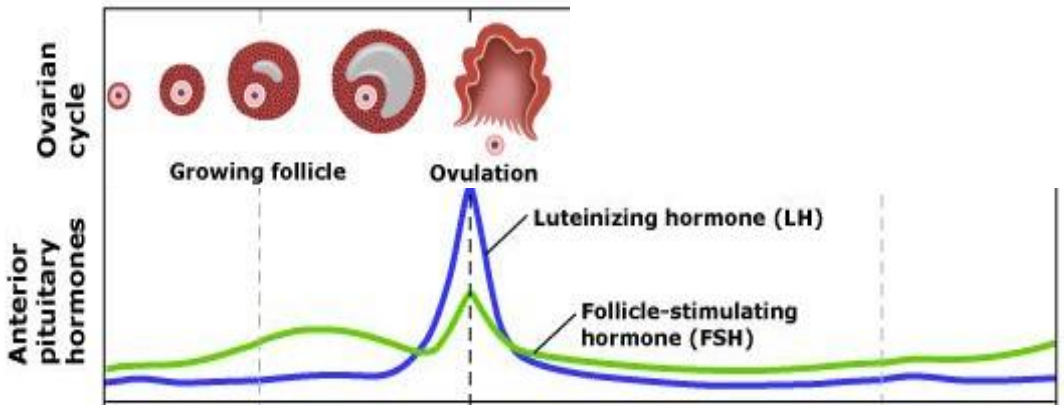
Ovarian follicle growth

During ***the first few days*** of the monthly female sexual cycle there is an increase secretion of **FSH and slightly LH**

- **FSH** increase is slightly more & earlier than LH which causes the acceleration of growth of many primary follicles each month.
- There is proliferation of the granulosa cells to many layers.
- The ovary interstitium collects in several layers outside the granulosa cells to form a second mass of cells called **theca**

Theca is divided into 2 layers:

1. ***theca interna***
2. ***theca externa***,



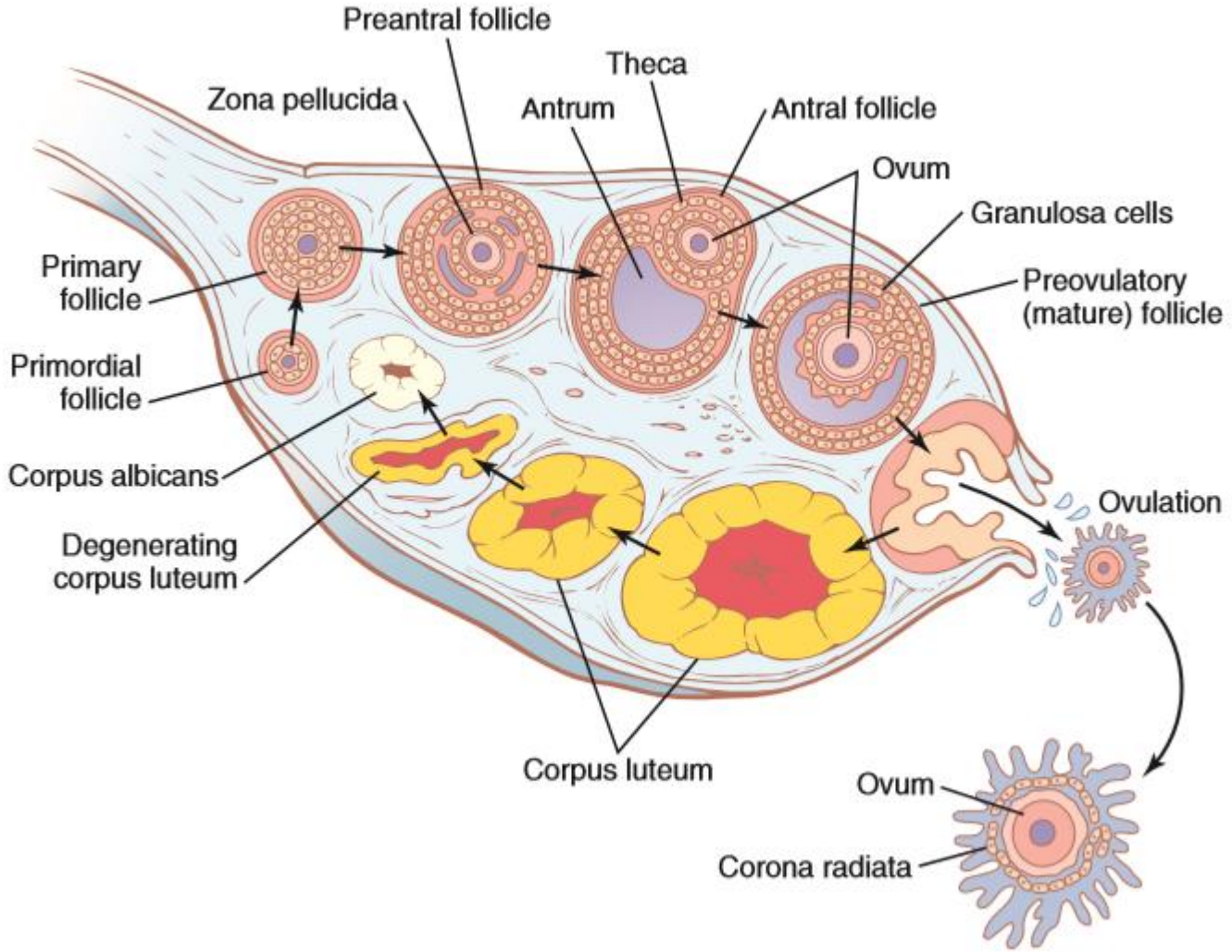
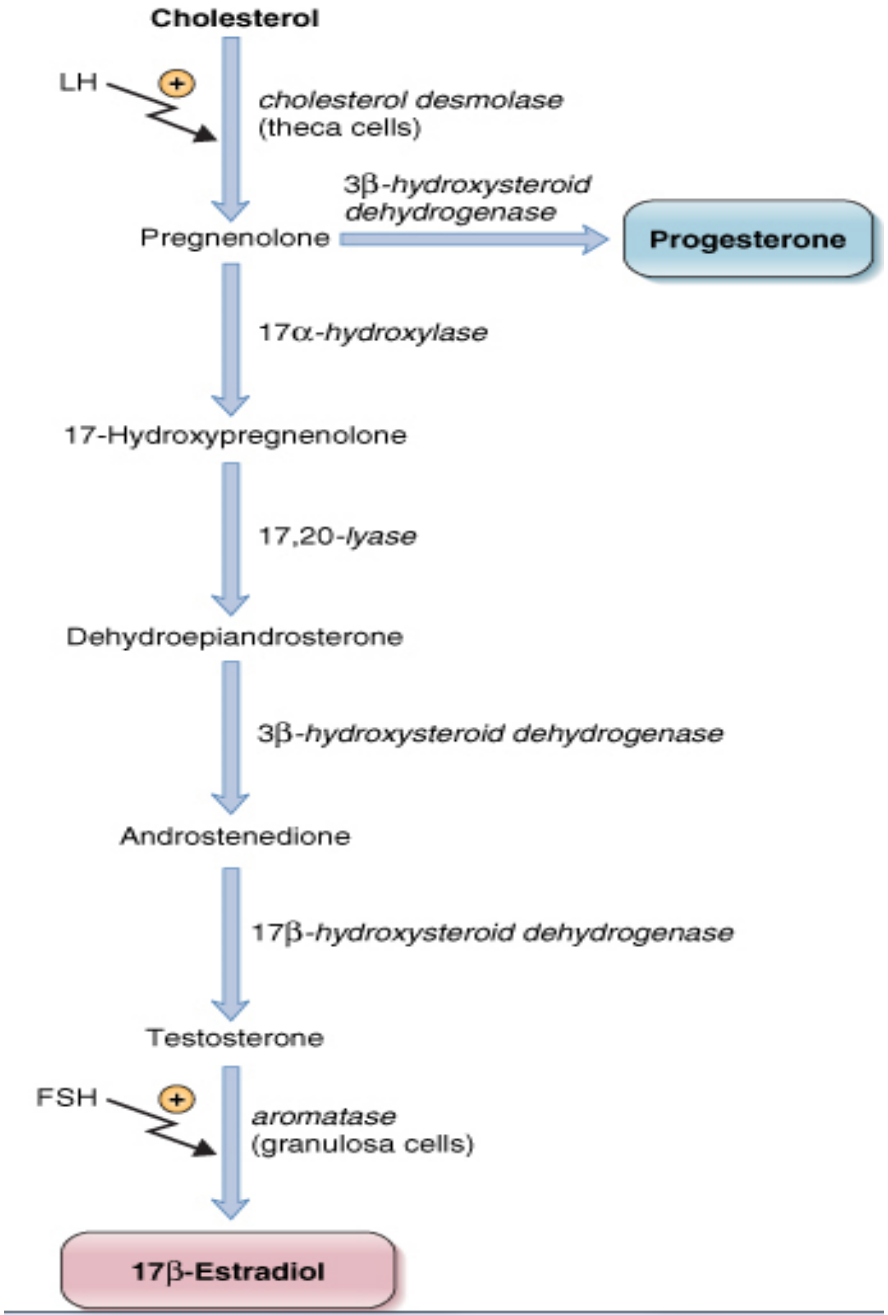
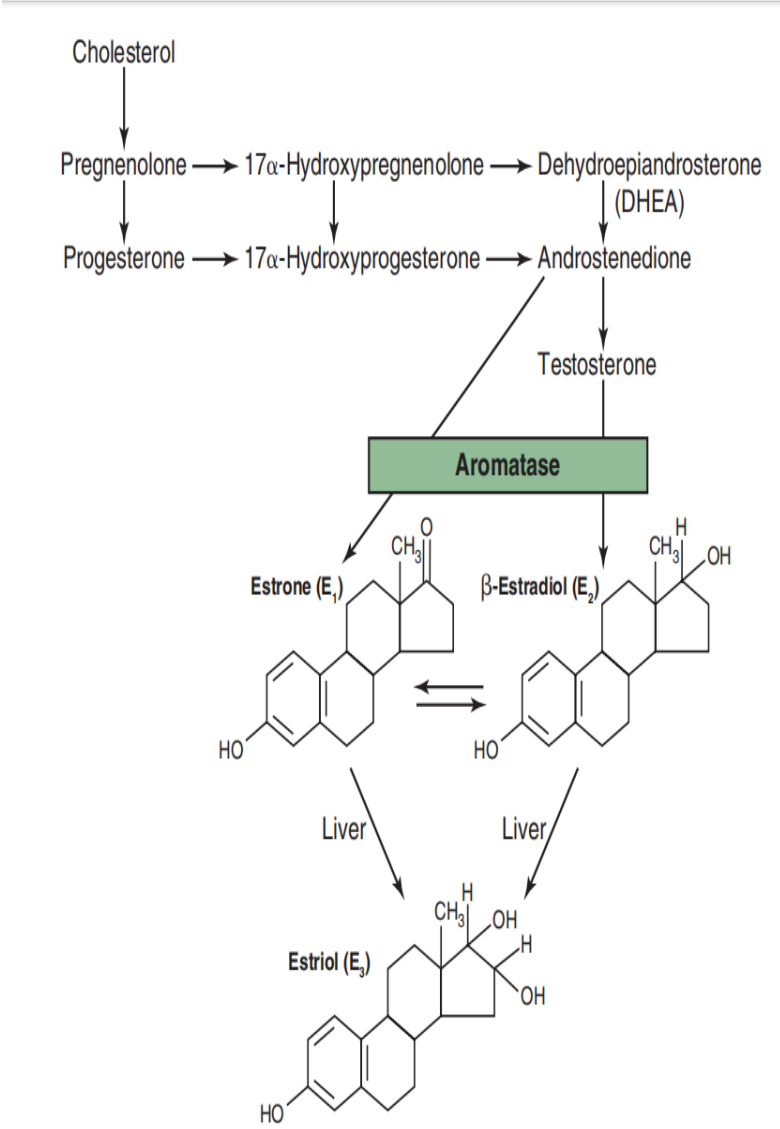


Figure 82-5. Stages of follicular growth in the ovary, also showing formation of the corpus luteum.

FEMALE SEX HORMONES

- The *granulosa cells* in the corpus luteum develop extensive intracellular smooth endoplasmic reticula that form large amounts of the female sex hormones *progesterone* and *estrogen* (with more progesterone than estrogen during the luteal phase).
- The *theca cells* form mainly the androgens *androstenedione* and *testosterone* rather than female sex hormones.
- However, most of theca hormones are also converted by the enzyme *aromatase* in the granulosa cells into estrogens, the female hormones.


Cholesterol
LH
+
cholesterol desmolase
(theca cells)
3β-hydroxysteroid
dehydrogenase
Pregnenolone
Progesterone
17α-hydroxylase
17-Hydroxypregnenolone
17,20-lyase
Dehydroepiandrosterone
3β-hydroxysteroid dehydrogenase
Androstenedione
17β-hydroxysteroid dehydrogenase
Testosterone
FSH
+
aromatase
(granulosa cells)
17β-Estradiol


Cholesterol
Pregnenolone
17α-Hydroxypregnenolone
Dehydroepiandrosterone
(DHEA)
Progesterone
17α-Hydroxyprogesterone
Androstenedione
Testosterone
Aromatase
Estrone (E1)
β-Estradiol (E2)
HO
Liver
Liver
Estriol (E3)
OH
H
CH3
O

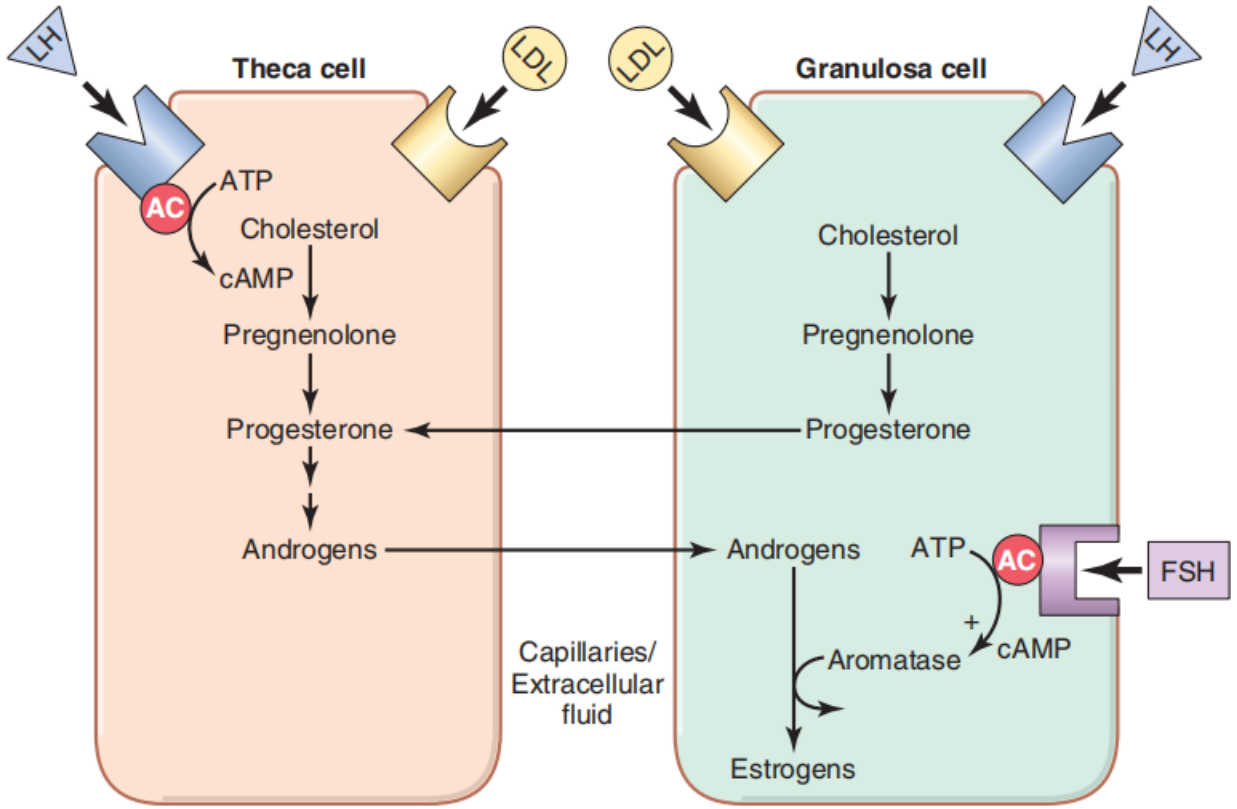
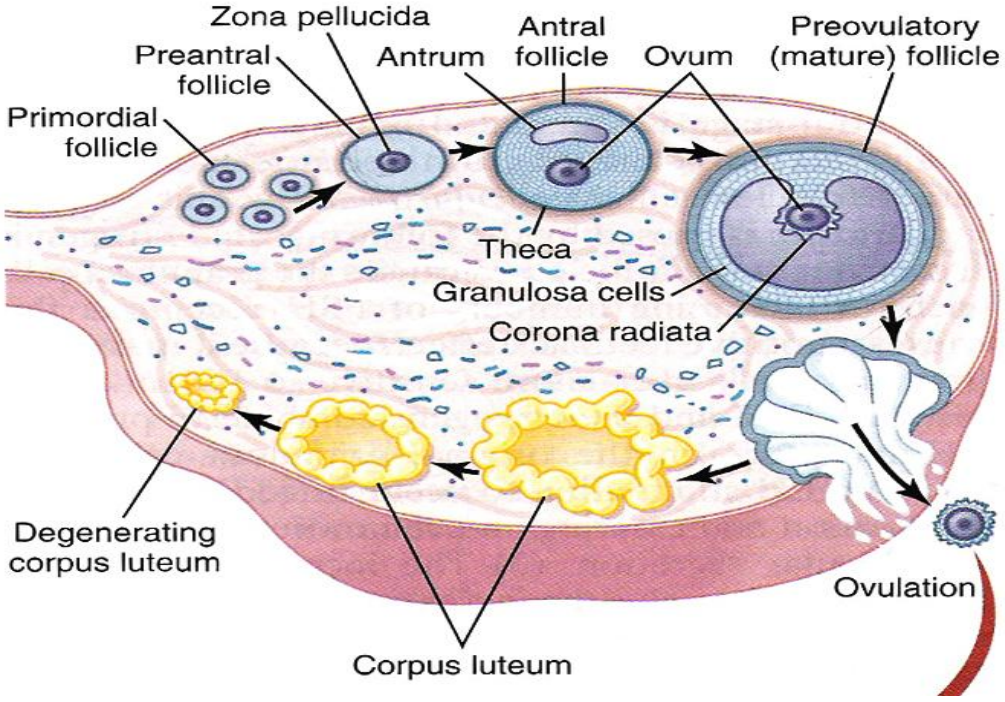


Figure 82-8. Interaction of follicular theca and granulosa cells for production of estrogens. The theca cells, under the control of luteinizing hormone *(LH)*, produce androgens that diffuse into the granulosa cells. In mature follicles, follicle-stimulating hormone *(FSH)* acts on granulosa cells to stimulate aromatase activity, which converts the androgens to estrogens. AC, adenylate cyclase; ATP, adenosine triphosphate; cAMP,

Ovarian follicle growth

Few days after proliferation & growth of the follicles, the granulosa cells secrete follicular fluids that contain high concentration of **estrogen**. This fluid accumulates to form **antrum** within the mass of the granulosa cells



Ovarian follicle growth

The early growth of the primary follicle up to the antral stage is under FSH stimulation only. Then there is **accelerated growth** of the follicle to larger follicle called vesicular follicle (Graffian) caused by:

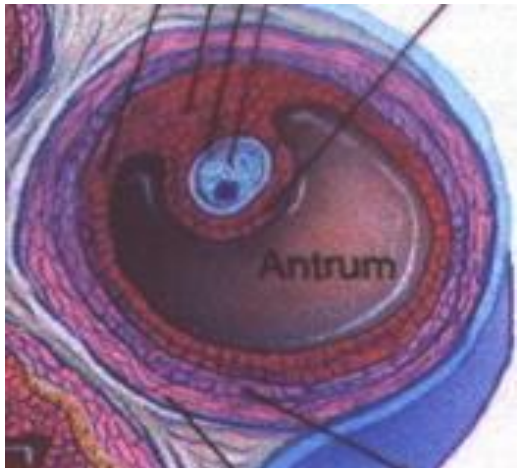
1. Estrogen secreted into the follicle caused the granulosa cells to increase FSH receptors (**positive feedback effect)**
2. Both estrogen & FSH promote LH receptors on granulosa cells in addition to FSH stimulation, allowing more rapid increase in follicular secretion
3. Increasing estrogen from the follicle and increasing LH from the AP causes proliferation of the follicular theca cells & increase their secretion

Ovarian follicle growth

- The **antral follicles** begin to grow. The ovum enlarges & remains embedded at one pole of the granulosa cells of the follicle

- During all the reproductive years of adult life, between about 13 and 46 years of age, **400 to 500** of the primordial follicles develop enough to expel their ova—**one** each month.

- The remaining follicles (5 to 11) undergo ***atresia*** or involute



OVULATION

- **LH is necessary for final follicular growth and ovulation:**

- 2 days before ovulation → rate of LH secretion ↑ to 6-16 fold & peaks about 16 hrs before ovulation.

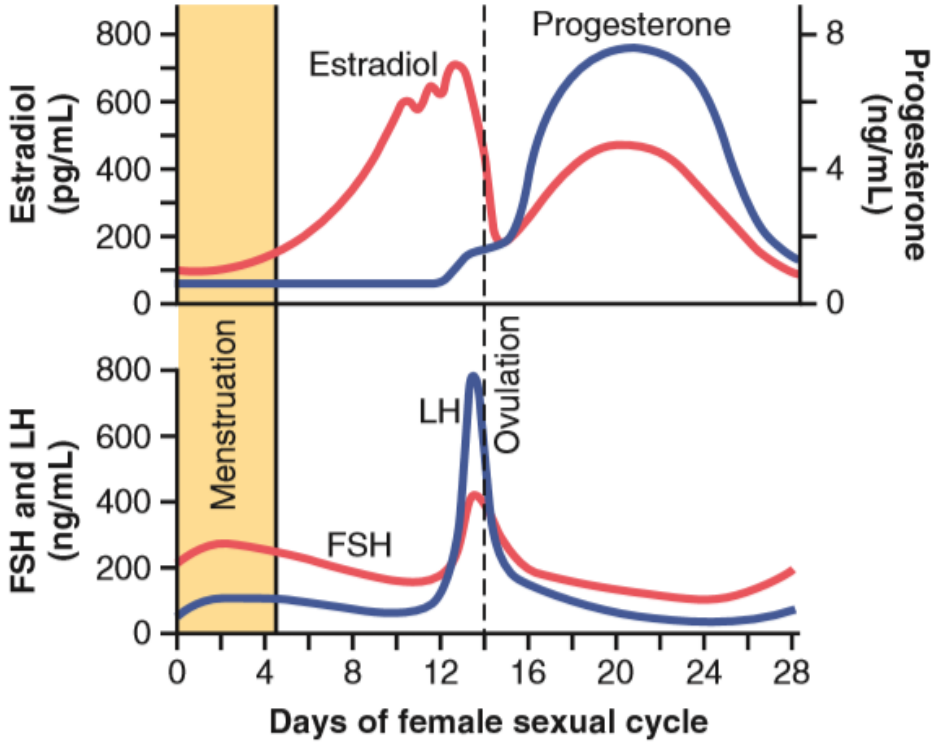


Figure 82-4. Approximate plasma concentrations of the gonadotropins and ovarian hormones during the normal female sexual cycle. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Ovulation

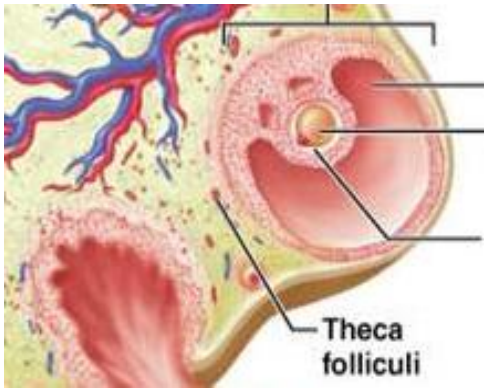
- LH Surge is necessary for final follicular growth and ovulation:

- FSH also ↑ 2 to 3 fold & acts synergistically with LH to cause swelling of the follicle before ovulation.

- LH has specific effect on the granulosa cells & theca cells converting them to *progesterone-secreting cells* ⟶ rate of estrogen secretion ↓ about 1 day **before ovulation** while progesterone secretion begin to ↑

Initiation of ovulation

Surge of LH causes rapid secretion of progesterone from the follicle. Within a few hours 2 events occur which are necessary for ovulation:

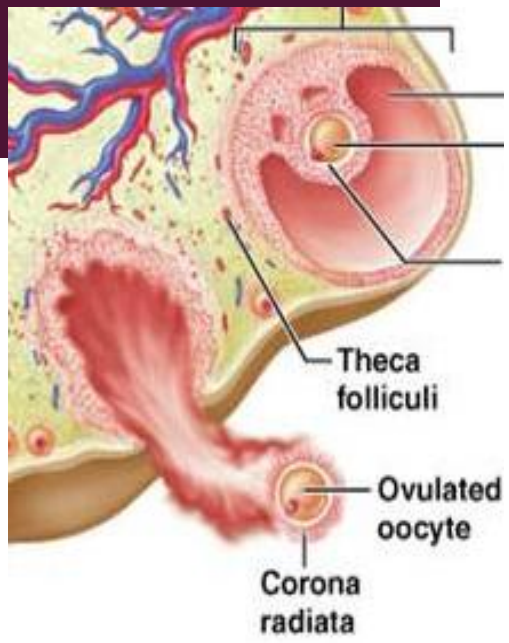


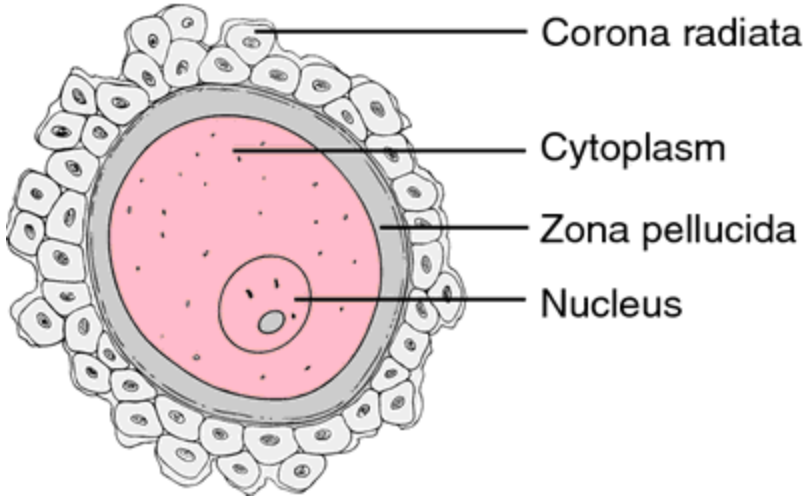
1. The **theca externa** begins to secrete proteolytic enzymes & causes weakening of the wall resulting in swelling of the follicle & degeneration of the stigma
2. Rapid growth of **new blood vessels** into the follicle wall & prostaglandins are secreted into the follicular tissue.

Ovulation

It occurs 14 days after the onset of menstruation in 28 days cycle.

During ovulation, stigma protrudes & fluids ooze from the follicle & the stigma ruptures allowing more viscous fluid outward carrying with it the ovum surrounded by mass of granulosa cells called corona radiata





OVULATION

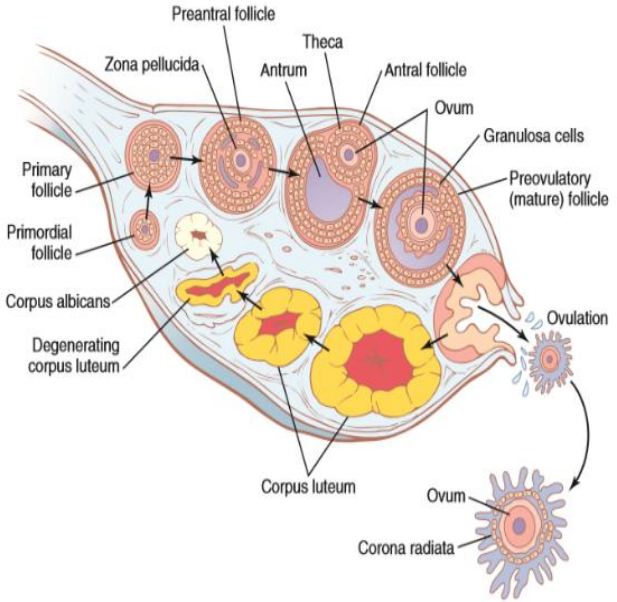


Figure 82-5. Stages of follicular growth in the ovary, also showing formation of the corpus luteum.

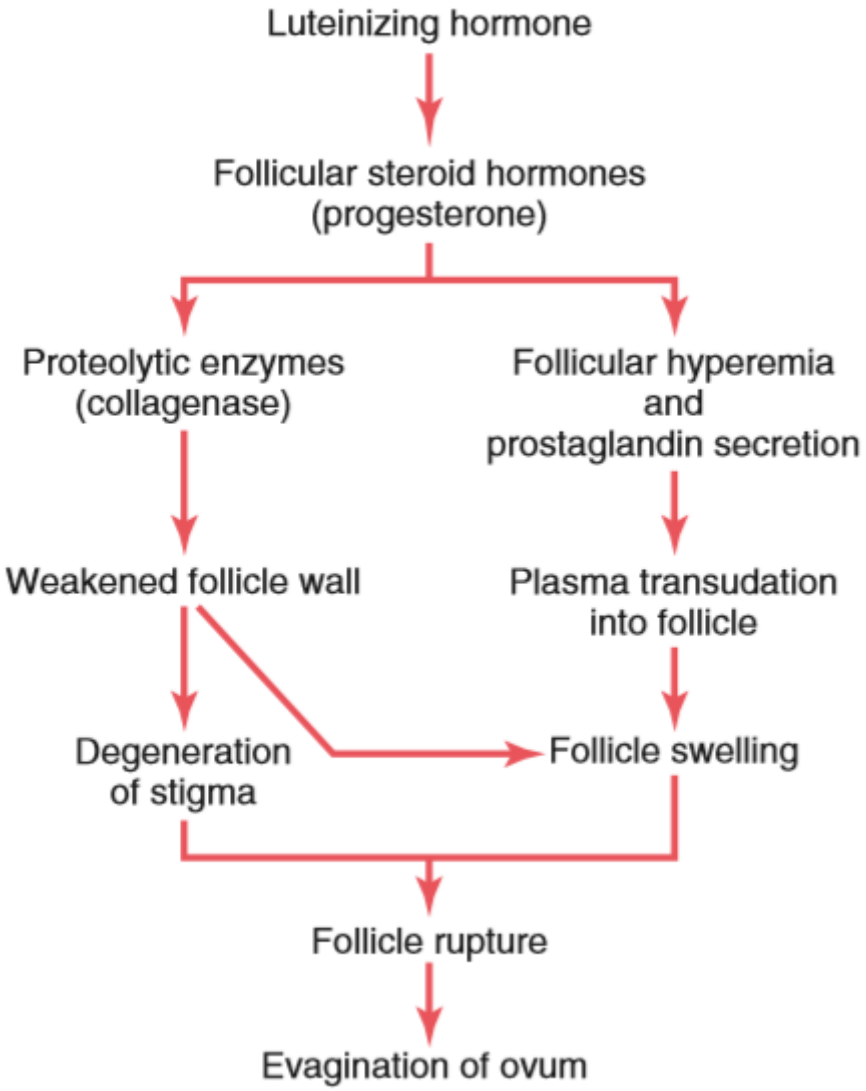
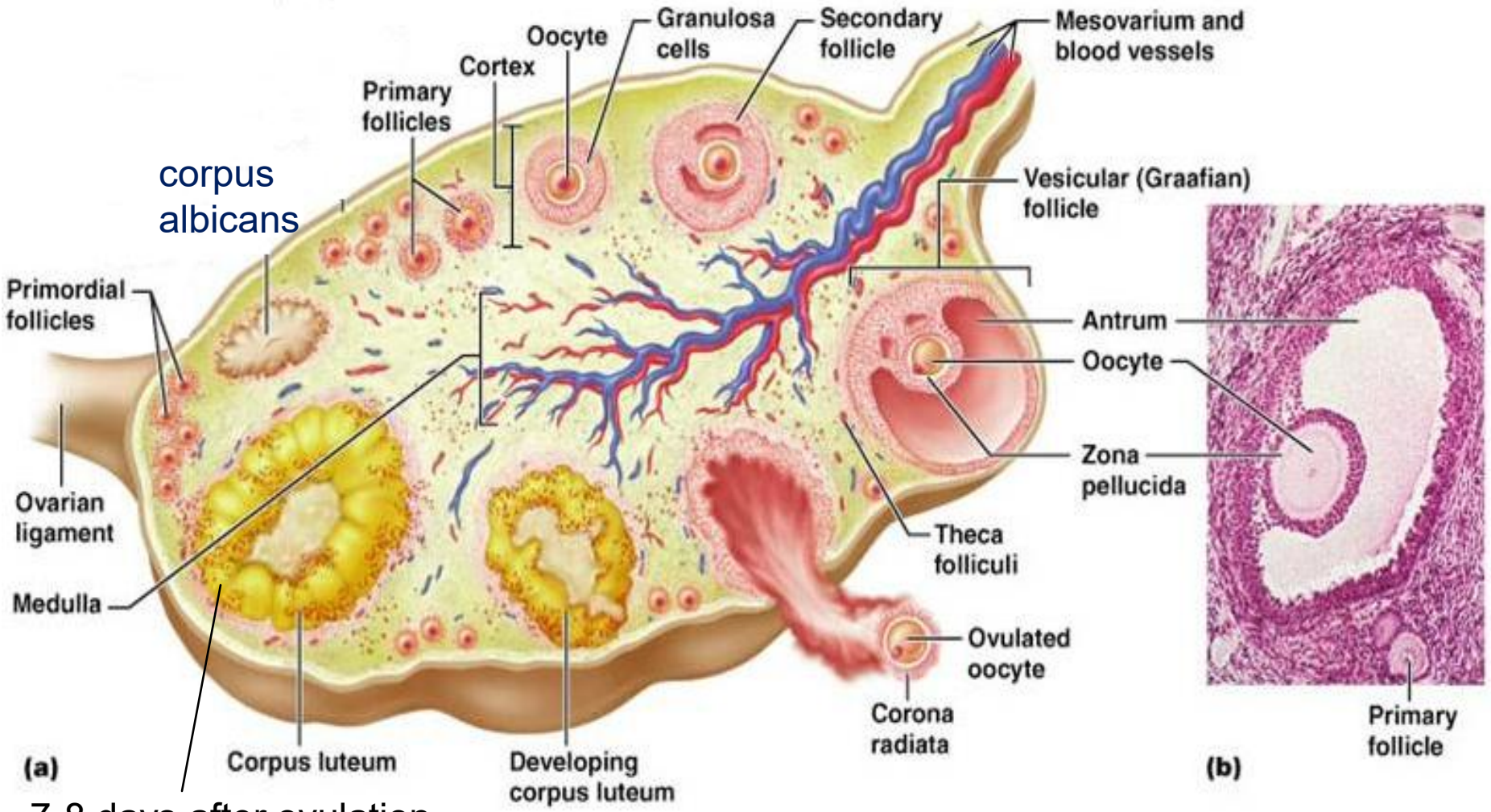


Figure 82-6. The postulated mechanism of ovulation.

Corpus Luteum



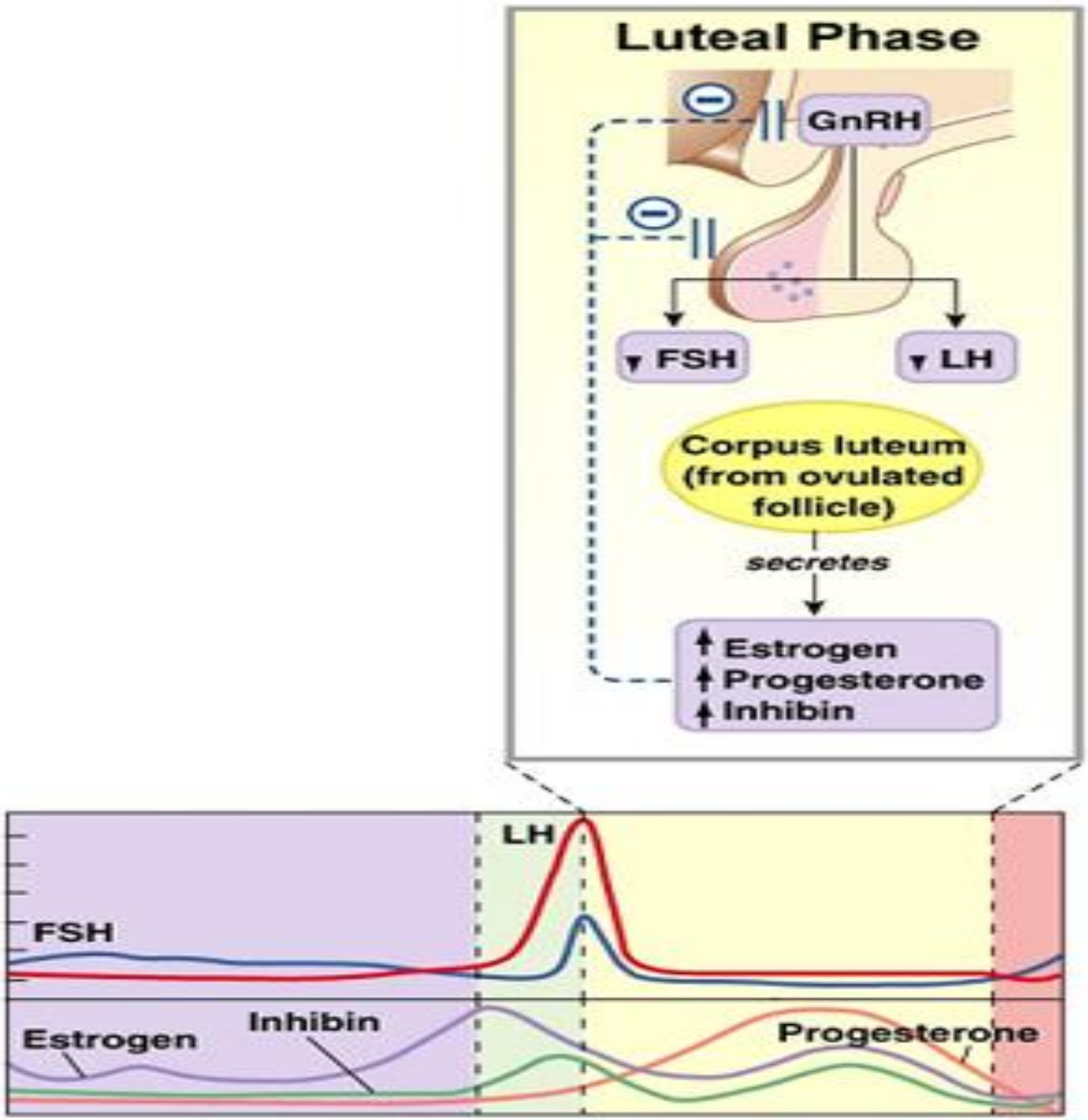
7-8 days after ovulation
~ 1.5 cm in diameter

The granulosa cells with the theca cells are called **corpus luteum.**

Corpus Luteum
"Luteal" phase of the ovarian cycle

- After expulsion of the ovum from the follicle, the remaining granulosa & theca interna cells change to **lutein cells** & become filled with lipid inclusions giving them yellowish appearance.

- The granulosa cells in corpus luteum form large amount of progesterone & estrogen. The theca cells form mainly androgens which are converted by granulosa cells into female hormones.


Luteal Phase
GnRH
FSH
LH
Corpus luteum (from ovulated follicle)
secretes
Estrogen
Progesterone
Inhibin
LH
FSH
Estrogen
Inhibin
Progesterone

Corpus Luteum

Luteinizing function of LH:

1- Extrusion of the ovum from the follicle.

2- Change of granulosa and theca interna cells into **lutein cells**.

3- Secretion of progesterone & estrogen from the corpus luteum.

- If pregnancy occurs, the hCG from the placenta acts on the corpus luteum to prolong its life for 2 to 4 months of pregnancy

Corpus Luteum

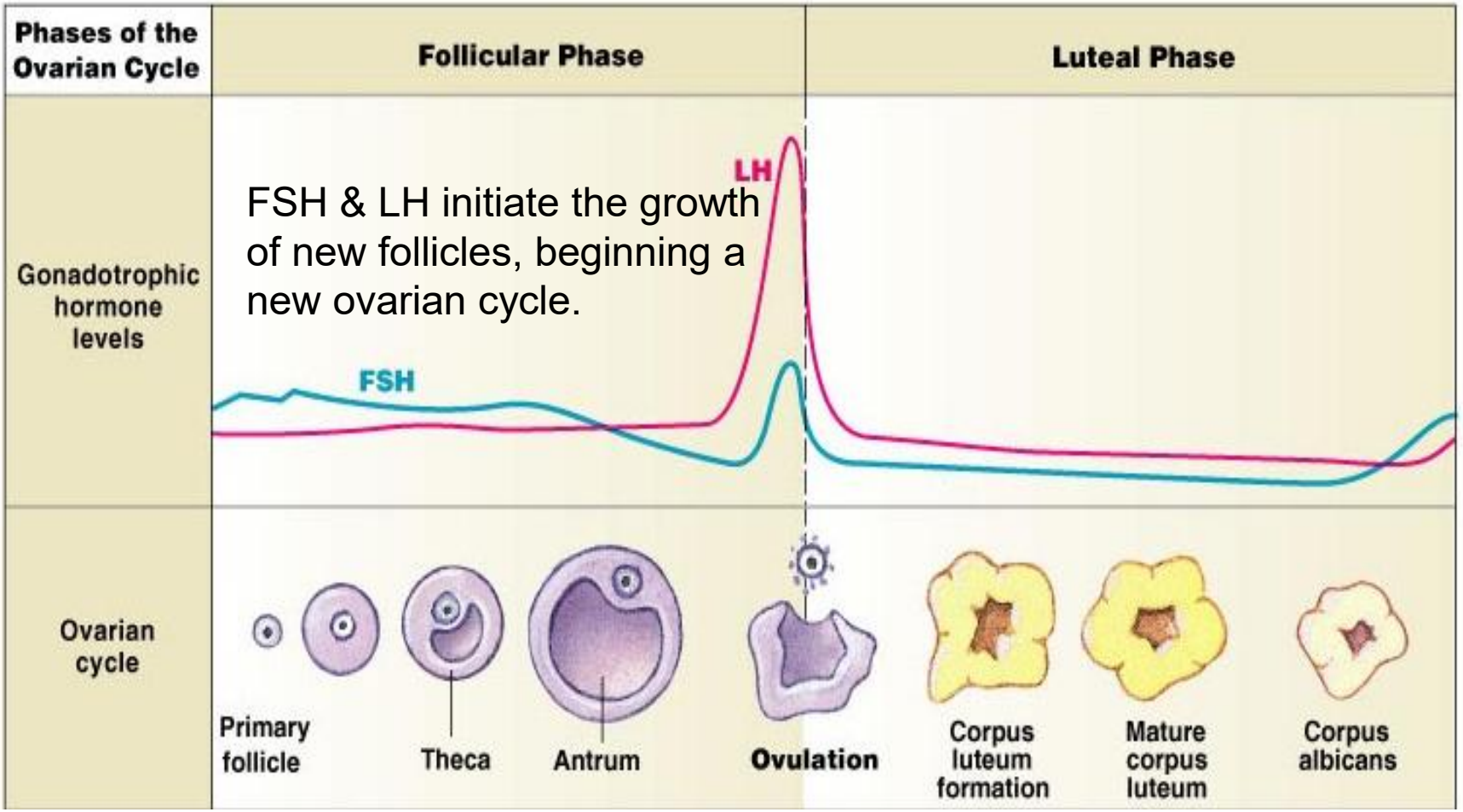
Involution of the corpus luteum and onset of the next ovarian cycle:

1- Estrogen & progesterone from corpus luteum (luteal phase) have strong negative feedback effect on AP to inhibit the secretion of FSH & LH.

2- The **lutein cells** secrete small amounts of inhibin which inhibit secretion of FSH by AP. ↓ FSH & LH & loss of these hormones >> complete degeneration of corpus luteum (involution)

3- Around **26th days** of normal sexual cycle & after involution of corpus luteum, sudden cessation of estrogen, progesterone & inhibin removes the negative feedback inhibition of the AP & allowing ↑ secretion of FSH & LH again.

Corpus Luteum



PHYSIOLOGY OF UTERINE (ENDOMETRIAL) CYCLE

GUYTON & HALL, CHAPTER 81

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OBJECTIVES

By the end of this lecture, you should be able to:

1. Descrive effects of estrogen and progestrone
2. Describe the normal menstrual cycle
3. Discuss the ***structural changes*** that occur in the endometrium during the menstrual cycle and explain how these changes are hormonally controlled
4. Recognize the phases of the menstrual cycle
5. Describe the physiology of menopause and the disorders of menstruation

EFFECTS OF ESTROGEN

A primary function of the estrogens is to cause cellular proliferation and growth of the tissues of the sex organs and other tissues related to reproduction.

- Growth of female sex The ovaries, fallopian tubes, uterus, and vagina all increase several times in size.
- Estrogens cause marked proliferation of the endometrial stroma and glands, (nutrition to ovum). Similarly in fallopian tubes and increase the number of ciliated epithelial cells.
- Effect of Estrogens on the Breasts. (1) development of the stromal (2) growth of ductile system, and (3) deposition of fat in the breasts. The lobules and alveoli of the breast develop slightly under estrogens alone, but progesterone and prolactin that cause the ultimate growth and function
- Effect of Estrogens on the Skeleton; inhibit osteoclastic activity in the bones and therefore stimulate bone growth. However, they cause uniting of the epiphyses with the shafts of the long bones. female usually ceases earlier than growth of the male.

(Osteoporosis of the Bones Caused by Estrogen Deficiency in Old Age)

ESTROGEN EFFECTS

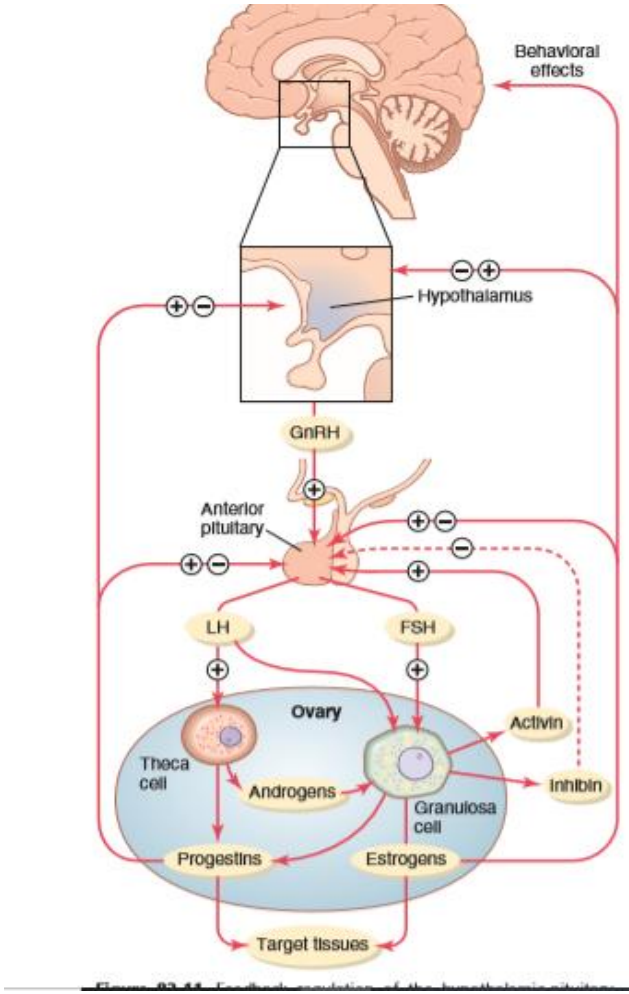
- Estrogens Slightly Increase Protein Deposition. Mainly due to growth of the sexual organs, the bones. Testosterone is much more general and much more powerful than estrogen.
- Estrogens Increase Body Metabolism (slightly) (only about 1/3 as much as by testosterone) and increase fat deposition .
- Estrogens Have Little Effect on Hair Distribution. Estrogens do not greatly affect hair distribution. adrenal androgens have greater effect on female hair
- Effect of Estrogens on the Skin. Development of a texture that is soft and usually smooth, but still thicker than in childhood
- Estrogens also cause the skin to become more vascular, which is often associated with increased warmth of the skin and also promotes greater bleeding of cut surfaces than is observed in men.
- Effect of Estrogens on Electrolyte Balance. Estrogens, like aldosterone and some other adrenocortical hormones, cause sodium and water retention by the kidney tubules. Significant during pregnancy due to estrogens by the placenta.

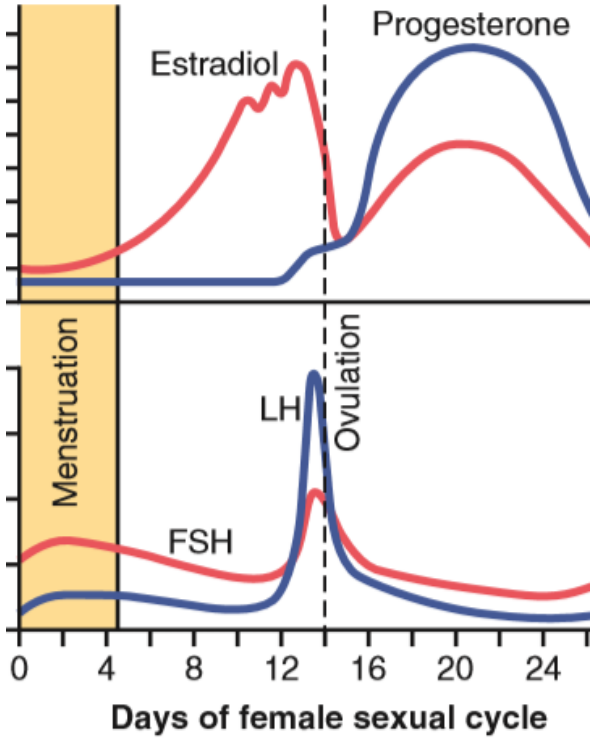
EFFECTS OF PROGESTERONE

- Progesterone Promotes Secretory Changes in the Uterus during the latter half of female cycle, thus preparing the uterus for implantation of the fertilized ovum, progesterone decreases the frequency and intensity of uterine contractions, thereby helping to prevent expulsion of the implanted ovum.
- Effect of Progesterone on the Fallopian Tubes. promotes increased secretion by the mucosal lining of the fallopian tubes. These secretions are necessary for nutrition of the fertilized, dividing ovum
- Progesterone Promotes Development of the Breasts. Progesterone promotes development and proliferation of the lobules and alveoli of the breasts, causing the alveolar cells to become secretory. Progesterone also causes the breasts to swell(secretory and fluids).

MONTHLY ENDOMETRIAL CYCLE AND MENSTRUATION

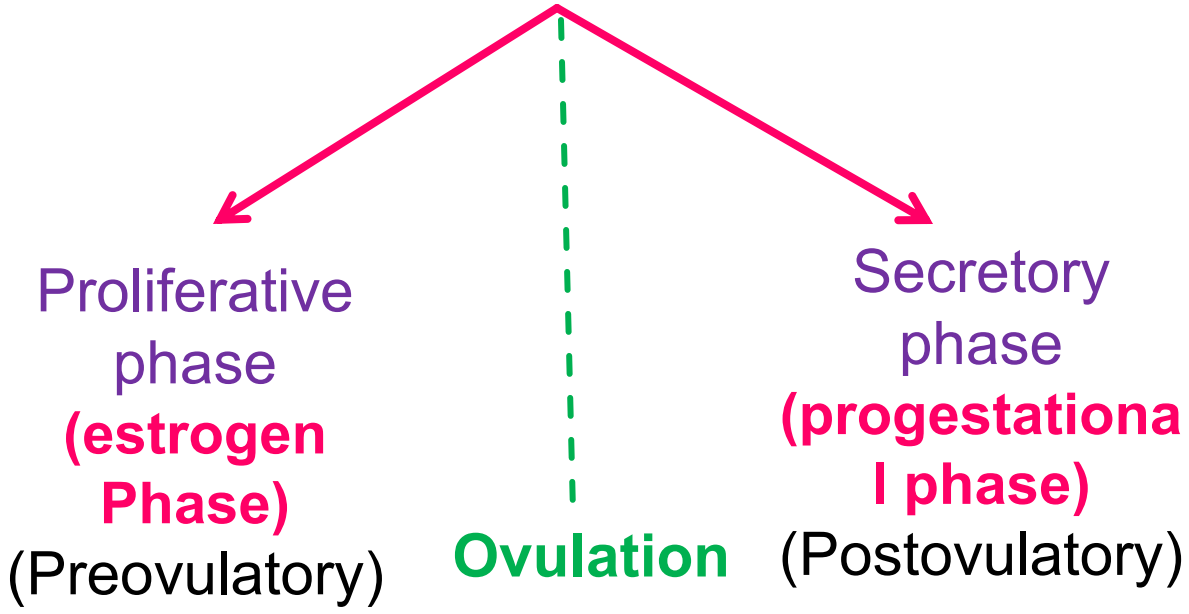
- It is associated with the monthly cyclical production of estrogens & progesterone by the ovaries in the lining of the uterus





Approximate plasma concentrations of t
arian hormones during the normal femal
stimulating hormone; LH, luteinizing horr

Uterine (endometrial) Cycle



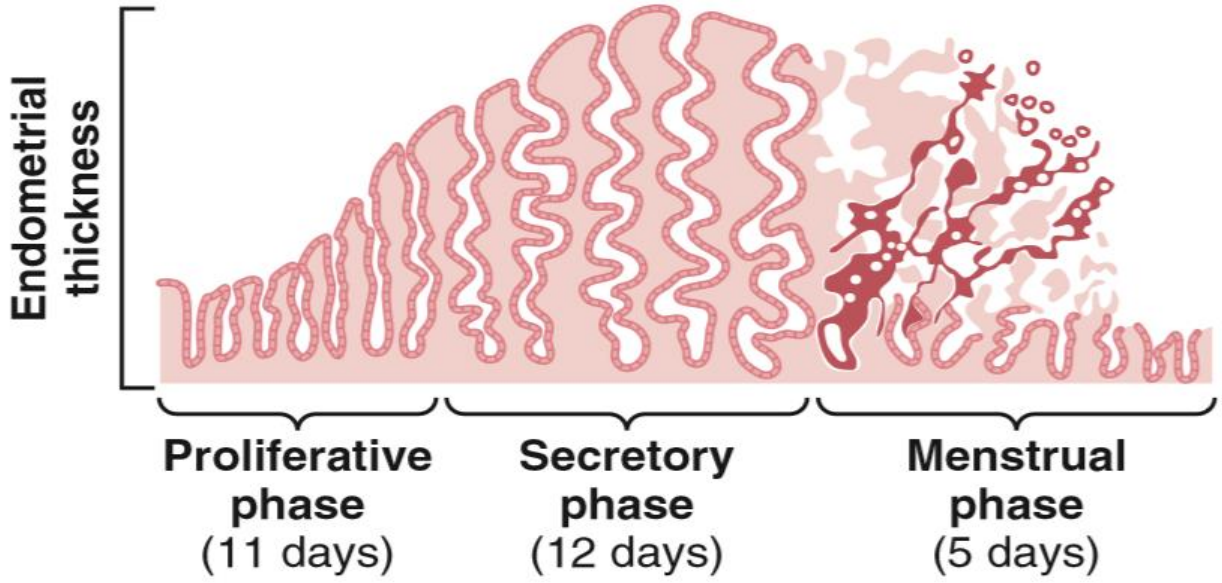
PROLIFERATIVE PHASE (ESTROGEN PHASE)

- At the beginning of each cycle, most of the endometrium has been desquamated by menstruation. After menstruation only thin layer of the endometrial stroma remains & the deeper portions of the glands &crypts of the endometrium.
- under the influence of **estrogens**, the stromal cells & epithelial cells proliferate rapidly.

- The endometrial surface re-epitheliaze within 4-7 days after the beginning of menstruation. Before ovulation the endometrium thickness increase, due to increase numbers of stromal cells &progressive growth of the glands & new blood vessels.

Uterine (endometrial) Cycle

At the time of ovulation, the endometrium is 3-5 mm thick. The endometrial glands, cervical region secrete a thin, stringy mucus which helps to guide sperm in the proper direction from the vagina into the uterus.

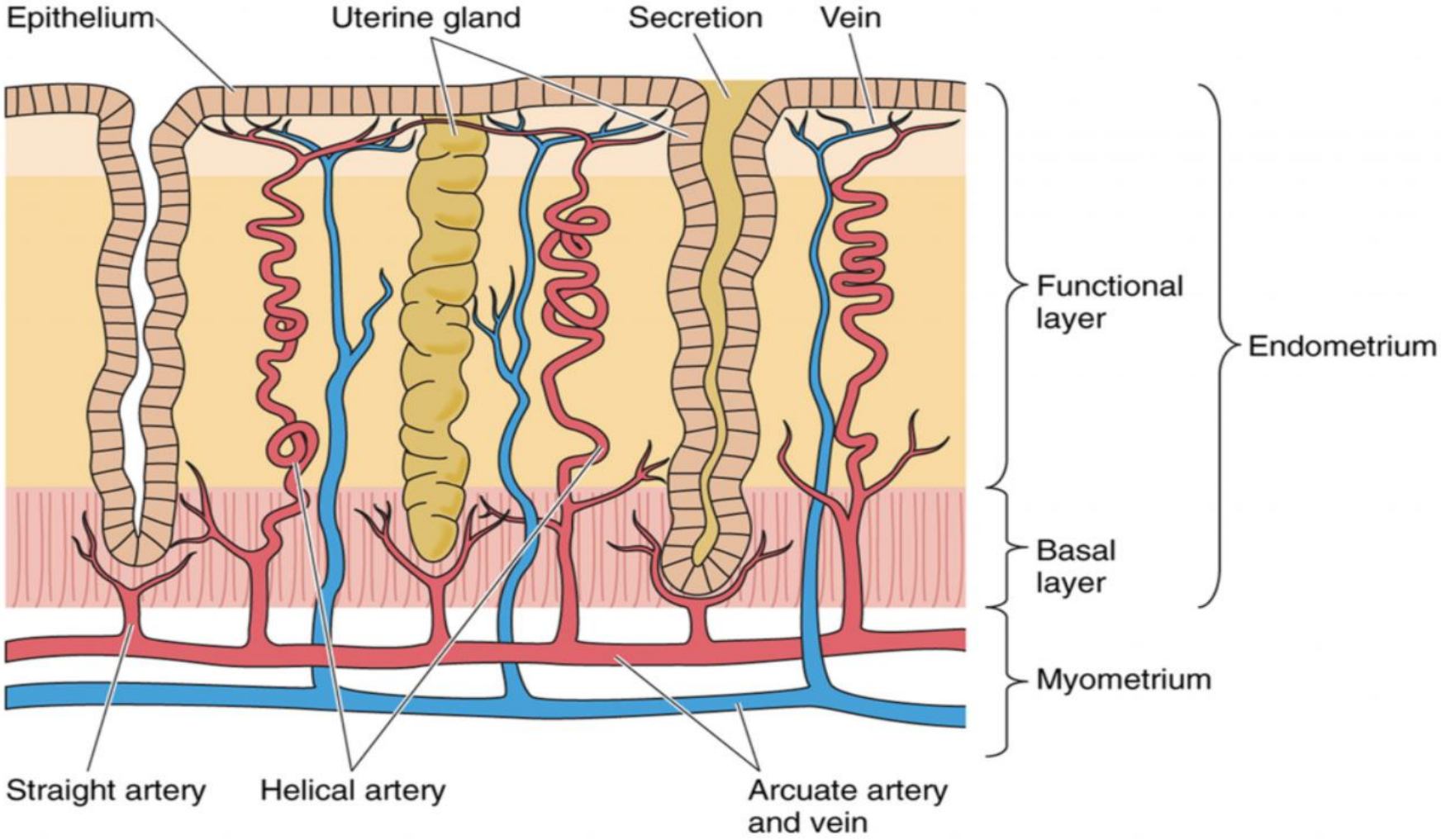


gure 82-9. Phases of endometrial growth and menstruation

Secretory phase (progestational phase)

- **After ovulation,** progesterone & estrogen are secreted in the later part of the monthly cycle by the corpus luteum. Estrogen causes slight proliferation in the endometrium& **progesterone** causes marked swelling & secretory development of the endometrium. The glands increase in tortuosity, excess secretory substances accumulate in the glands.
- Stromal cells cytoplasm increase lipid &glycogen deposits in the cells & blood supply to the endometrium increases and become more tortuous. 1 week after ovulation, endometrium thickness is 5-6 mm.

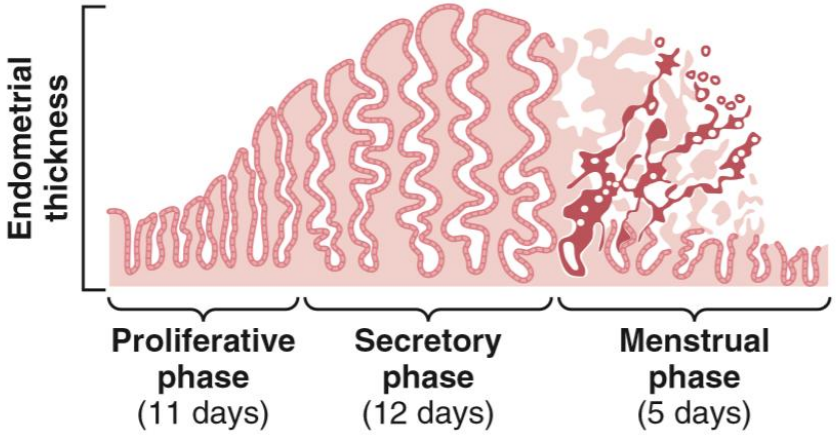
Uterine (endometrial) Cycle



Gartner & Hiatt (2007). Color Textbook of Histology: Saunders Elsevier, p. 477

Uterine (endometrial) Cycle

- The secretory changes prepare the endometrium (stored nutrients) for implantation of the fertilized ovum .
- Uterine secretions called “uterine milk” provide nutrition for the dividing ovum.
- The trophoblastic cells on the surface of the implanted ovum begin to digest the endometrium & absorb endometrial stored substances.



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 and the ovarian hormones (estrogens and progesterone) decrease to low levels of secretion,

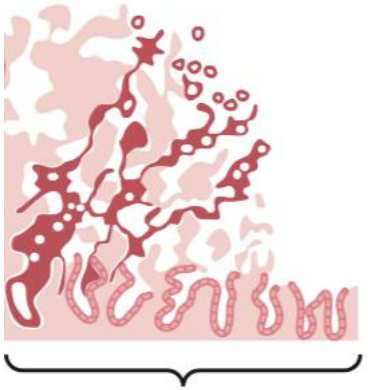
  - **Necrosis is initiated in the endometrial blood vessels, due to:**

  1) vasospasm

  2) decrease nutrients to the endometrium

  3) loss of the hormonal stimulation

- The mass of desquamated tissue & blood plus the contractile effects of prostaglandins all initiate contractions which expel the uterine contents.



Menstrual phase
(5 days)

Menstruation

- **In normal menstruation**, about 40 ml of blood + 35 ml of serous fluid are lost. The menstrual blood is normally non-clotting due to the presence of fibrinolysin.

-Within 4 to 7 days after menstruation, the loss of blood ceases & the endometrium become re-epithelialized.

Leukorrhea during menstruation:

During menstruation, leukocytes are released with the necrotic material & blood so the uterus is highly resistant to infection during menstruation as protective mechanism.

ANOVULATORY CYCLE

- When ovulation fails, mainly due to insufficient surge of LH, no ovum released, low progesterone in the second half.
- The phases of the sexual cycle continue, but they are altered in the following ways:

1- First, lack of ovulation causes failure of development of the corpus luteum so there is almost no secretion of progesterone during the latter portion of the cycle.

2- Second, the cycle is shortened by several days, but the rhythm continues. Therefore, it is likely that progesterone is not required for maintenance of the cycle itself, but it can alter the cycle's rhythm.

- The first few cycles after the onset of puberty and the cycles before menopause, presumably because \the LH surge is not potent enough at these times to cause ovulation.

Menopause

At the age of 40 to 50 years, the sexual cycle becomes irregular, ovulation fails to occur & the cycle ceases

The loss of estrogens causes marked physiological changes in the function of the body including:

1. “hot flushes” characterized by extreme flushing of the skin;
2. psychic sensations and dyspnea;
3. irritability;
4. fatigue;
5. anxiety;
6. occasionally various psychotic states
7. decreased strength and calcification of bones throughout the body.

MENOPAUSE

menopause in the female.

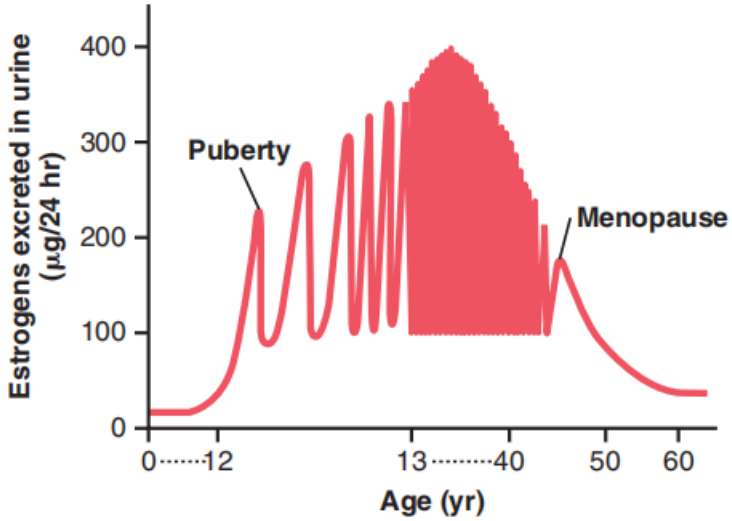


Figure 82-13. Estrogen secretion throughout the sexual life of the female human being.

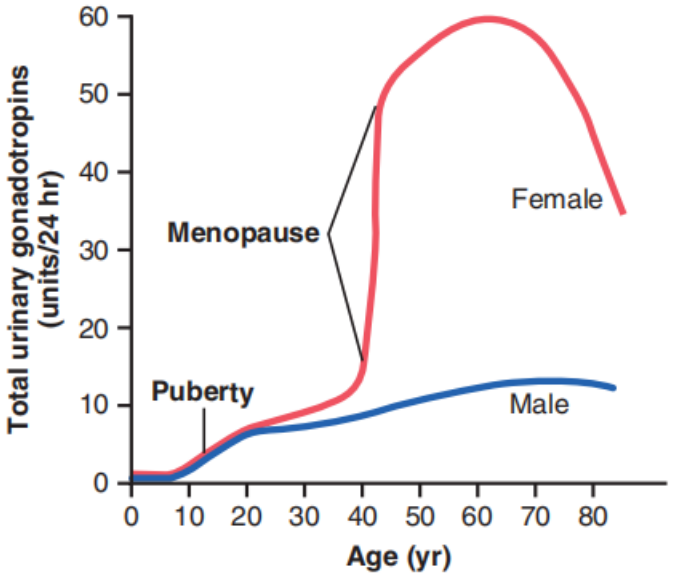
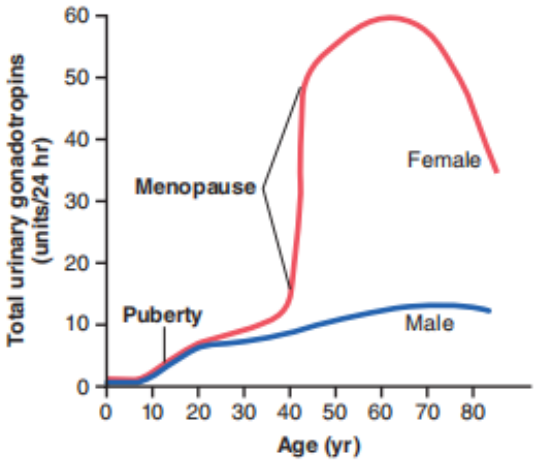


Figure 82-12. Total rates of secretion of gonadotropic hormones throughout the sexual lives of female and male human beings, showing an especially abrupt increase in gonadotropic hormones at menopause in the female.

PUBERTY AND MENARCHE

- Puburty: physical maturation and capability to reproduce
- Menarche: the beginning of the cycle of menstruation.
- the pituitary, beginning in about the eighth year of life, anc usually culminating in the onset of puberty and menstruati between ages 11 and 16 years in girls (average, 13 years).
- In the female, as in the male, the infantile pituitary gland an ovaries are capable of full function if they are appropriatel stimulated.
- However, as is also true in the male, and for reasons that are not understood, the hypothalamus does not secrete significant quantities of GnRH during childhood.
- Hypothalamus may be capable of secreting this hormone, but the appropriate signal is lacking.
- it is now believed that the onset of puberty is initiated by some maturation process that occurs elsewhere in the brain, perhaps in the limbic system

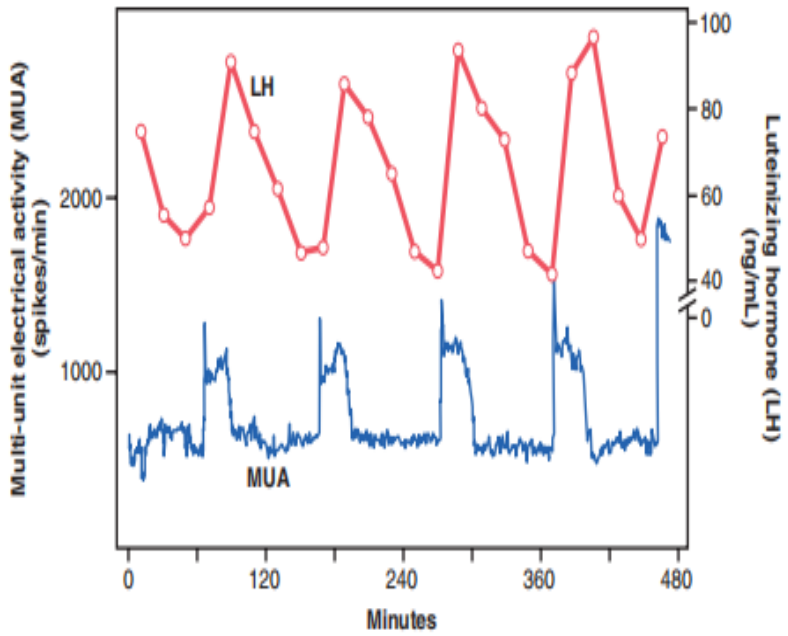


PUBERTY AND MENARCHE

- **Intermittent, Pulsatile Secretion of GnRH by the**

Hypothalamus Stimulates Pulsatile Release of LH from the Anterior Pituitary Gland.

- pulses lasting 5 to 25 minutes that occur every 1 to 2 hours.
- when GnRH is infused continuously its ability to cause the release of LH and FSH by the anterior pituitary gland is lost.



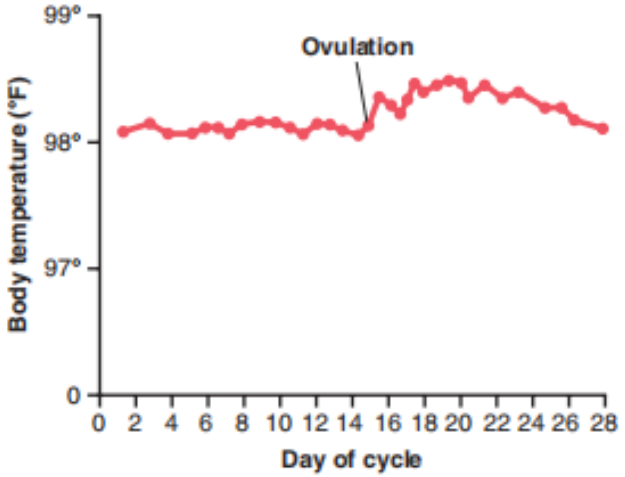
HYPOTHALAMIC CENTERS FOR RELEASE OF GONADOTROPIN RELEASING HORMONE.

- The neuronal activity that causes pulsatile release of GnRH occurs primarily in the mediobasal hypothalamus, especially in the arcuate nuclei of this area. Therefore, it is believed that these arcuate nuclei control most female sexual activity,
- The neurons located in the preoptic area of the anterior hypothalamus also secrete GnRH in moderate amounts.
- Multiple neuronal centers in the higher brain's "limbic" system (the system for psychic control) transmit signals into the arcuate nuclei to modify both the intensity of GnRH release and the frequency of the pulses, thus providing a partial explanation of why psychic factors often modify female sexual function.

FEMALE FERTILITY

- Fertile Period of Each Sexual Cycle.
- The ovum remains viable and capable of being fertilized probably no longer than 24 hours after it is expelled from the ovary. Therefore, sperm must be available soon after ovulation if fertilization is to take place.
- A few sperm can remain fertile in the female reproductive tract for up to 5 days.
- Therefore, for fertilization to take place, intercourse must occur sometime between 4 and 5 days before ovulation up to a few hours after ovulation.
- Thus, the period of female fertility during each month is short—about 4 to 5 days.

BODY TEPMERATURE

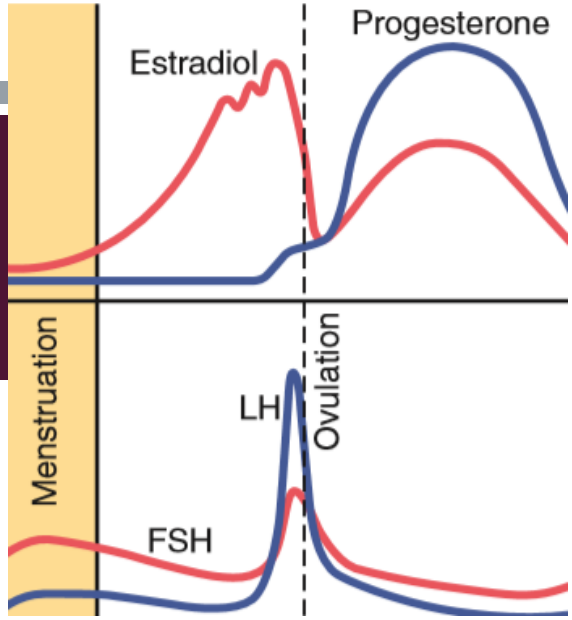


- Another common test is for the woman to chart her body temperature throughout the cycle. Secretion of progesterone during the latter half of the cycle raises the body temperature about 0.5°F, with the temperature rise coming abruptly at the time of ovulation. Such a temperature chart, showing the point of ovulation

CONTRACEPTION

- Rhythm Method of Contraception: To avoid intercourse near the time of ovulation.
- The difficulty with this method, is predicting the exact time of ovulation. Yet, the interval from ovulation until the next succeeding onset of menstruation is almost always between 13 and 15 days.
- If the menstrual cycle is regular, ovulation usually occurs within 1 day of the 14th day of the 28 cycle. (subtract 14 from the length of the cycle)
- ex, if the cycle is 40 days, ovulation usually occurs within 1 day of the 26th day of the cycle. if the periodicity of the cycle is 21 days, ovulation usually occurs within 1 day of the seventh day of the cycle.
- Therefore, avoidance of intercourse for 4 days before the calculated day of ovulation and 3 days afterward may prevent conception.
- The failure rate of this method of contraception, resulting in an unintentional pregnancy, may be as high as 20 to 25%/year.

HORMONAL SUPPRESSION OF FERTILITY—"THE PILL"



- It has long been known that administration of either

estrogen or progesterone, if given in appropriate quantities

during the first half of the monthly cycle, can inhibit ovulation.

The reason for this is that appropriate administration of either of these hormones can prevent the preovulatory surge of LH secretion by the pituitary gland, which is essential in causing ovulation.

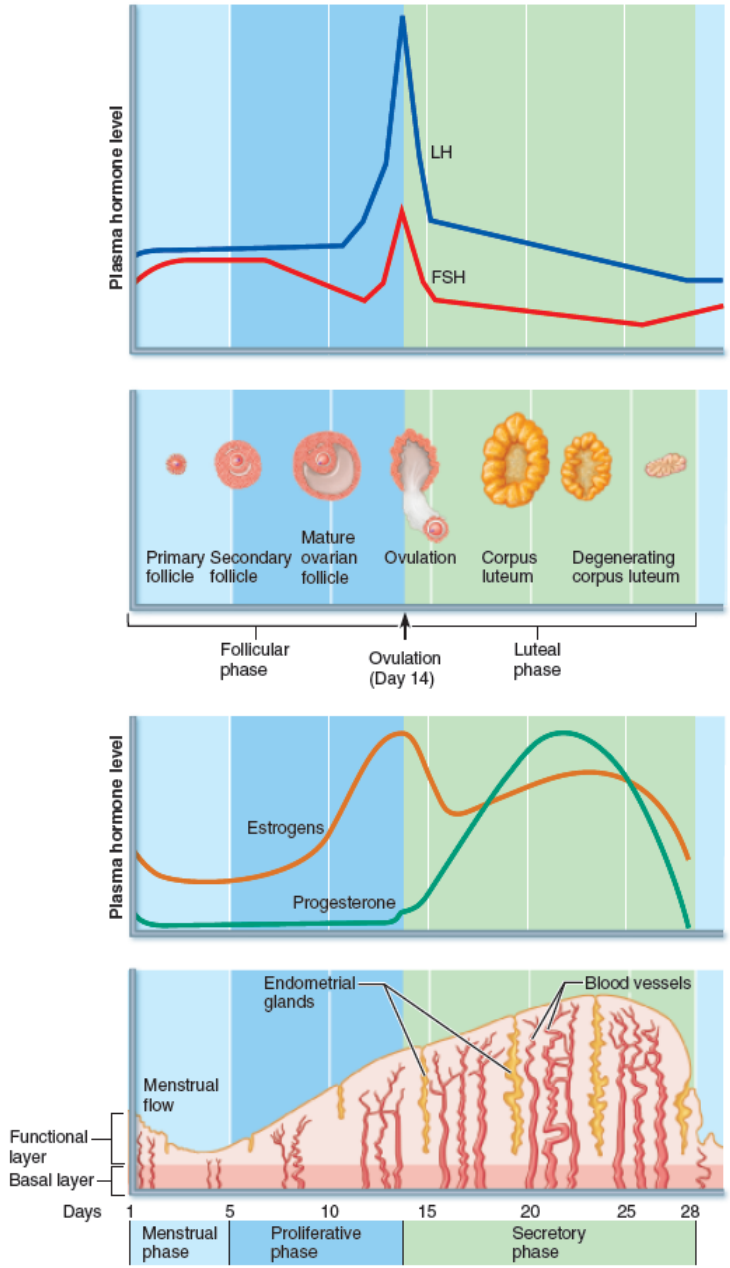
- Why administration of estrogen or progesterone prevents the preovulatory surge of LH secretion.

1-Immediately before the surge occurs, a sudden depression of estrogen secretion by the ovarian follicles probably occurs, which might be the necessary signal that leads to the LH surge. The administration of sex hormones (estrogens or progesterone) could prevent the initial ovarian hormonal depression that might be the initiating signal for ovulation. Progesterone has a negative feedback on GnRH and LH

2-Steady levels of OCP unlike normal cyclical female hormones

- Failure around 8-9 %year

Summary



(a) Fluctuation of gonadotropin levels: Fluctuating levels of pituitary gonadotropins (follicle-stimulating hormone and luteinizing hormone) in the blood regulate the events of the ovarian cycle.

(b) Ovarian cycle: Structural changes in the ovarian follicles during the ovarian cycle are correlated with (d) changes in the endometrium of the uterus during the uterine cycle.

(c) Fluctuation of ovarian hormone levels: Fluctuating levels of ovarian hormones (estrogens and progesterone) cause the endometrial changes of the uterine cycle. The high estrogen levels are also responsible for the LH/FSH surge in (a).

(d) The three phases of the uterine cycle
Menstrual: Shedding of the functional layer of the endometrium.
Proliferative: Rebuilding of the functional layer of the endometrium.
Secretory: Begins immediately after ovulation. Enrichment of the blood supply and glandular secretion of nutrients prepare the endometrium to receive an embryo.

Both the menstrual and proliferative phases occur before ovulation, and together they correspond to the follicular phase of the ovarian cycle. The secretory phase corresponds in time to the luteal phase of the ovarian cycle.

Human Anatomy / 8th edition / chapter 25