

Ovarian and Uterine Cycles

Objectives:

- ❖ Recognize the hypothalamic-pituitary-ovarian (HPO) axis.
 - ❖ Describe the physiological phases of ovarian and endometrial cycles.
 - ❖ Describe the structural changes that occur in the ovaries and endometrium during menstrual cycle and explain how these changes are hormonally regulated.
 - ❖ Describe the development and the fate of corpus luteum.
 - ❖ List the female hormones and describe their physiological functions
 - ❖ Describe the physiology of menopause and the disorders of menstruation.
-

Color index:

- ❖ **Important.**
- ❖ **Girls slide only.**
- ❖ **Boys slide only.**
- ❖ **Dr's note.**
- ❖ **Extra information.**



Editing File

Ovarian Cycle

Introduction:

01

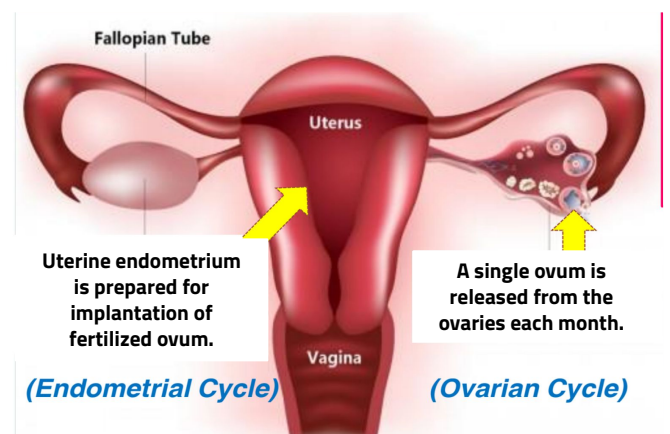
Monthly Ovarian Cycle: Monthly rhythmical changes in the rates of secretion of female hormones & corresponding physical changes in the ovaries & other sexual organs like the endometrial lining of the uterus.

02

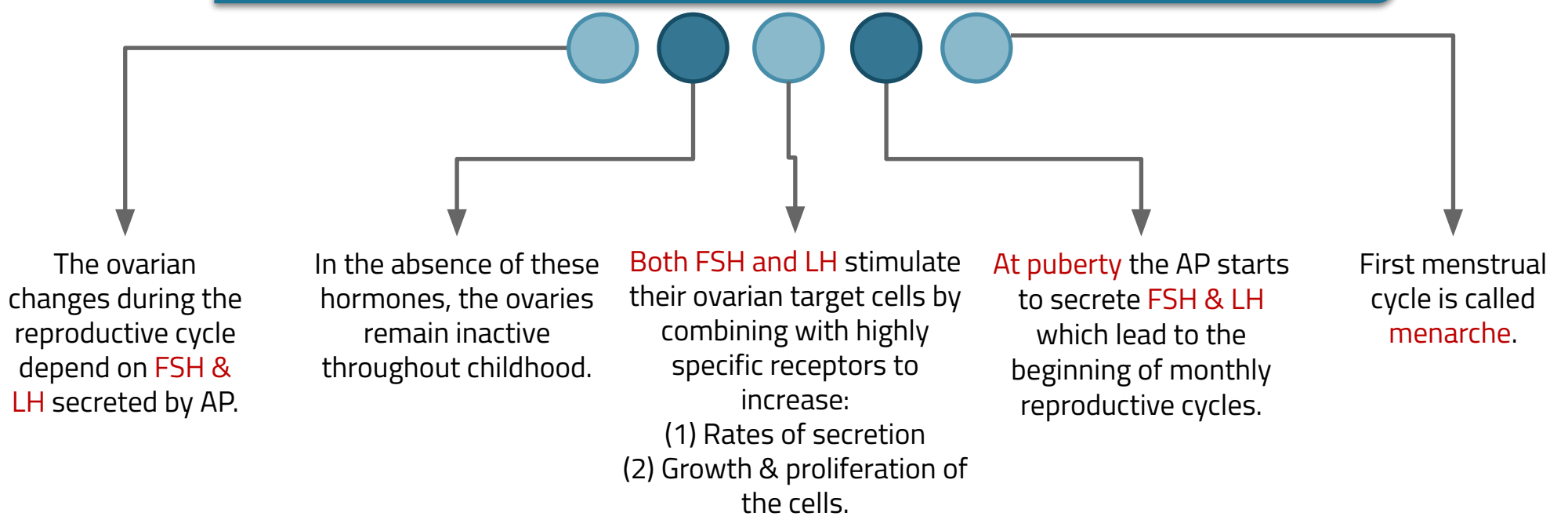
Duration of the cycle: average 28 days (but can range from 20-45 days). There are two results of the female sexual cycle:

03

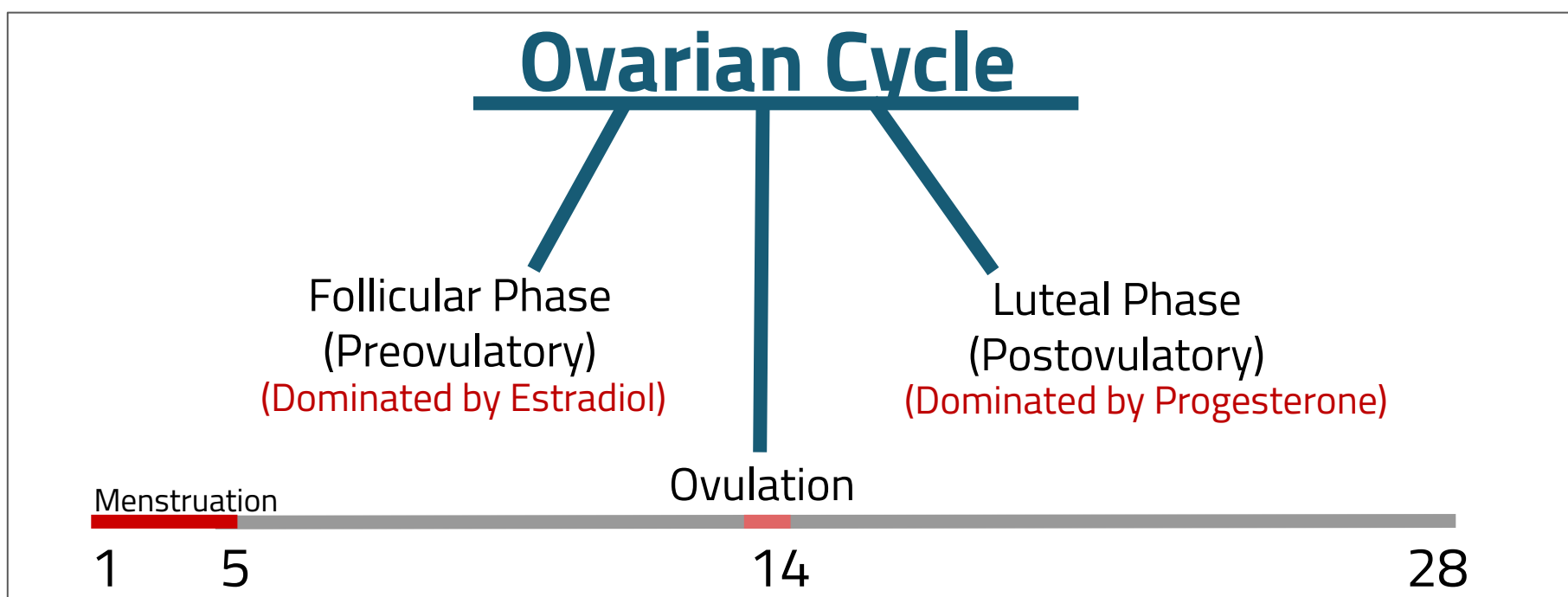
Ovary Functions:
1-Oogenesis.
2-Secretion of estrogens and progesterone.



Gonadotropic hormones and their effects on the ovaries:*



Between the age of 13 and 46, around 400-500 primordial follicles will be formed. Each month 5-11 cells will be released from the ovum each month. Once all primordial follicles are released, menopause is reached.



Ovarian Cycle: Follicular Phase

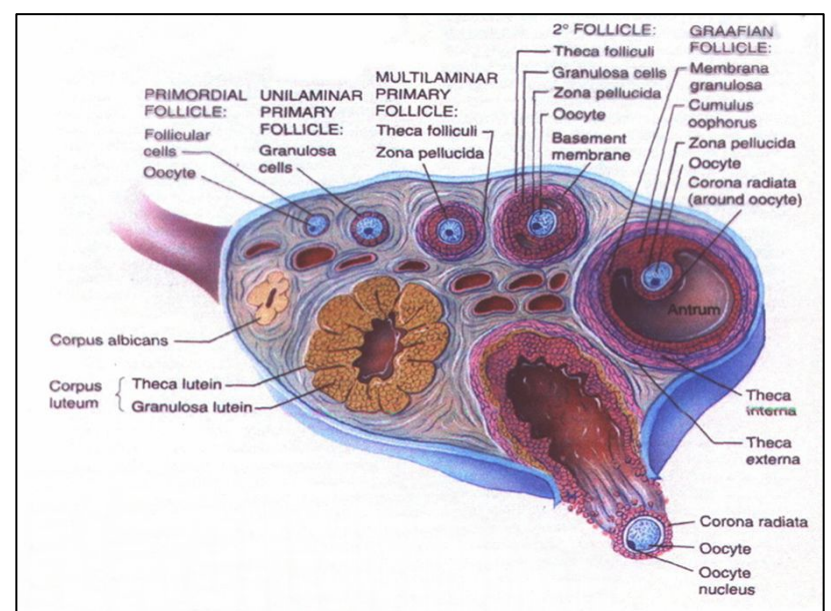
Follicular Development*

- ❖ At birth: 1-2 million oocytes.
- ❖ At puberty: 300,000 to 500,000 oocytes.
- ❖ 400-500 oocytes will normally ovulate during women's entire reproductive life.

What Happens From Childhood Until Puberty?

- ❖ In female child each ovum is surrounded by single granulosa cell sheath called primordial follicle.
- ❖ **During childhood**, the granulosa cells:
 - Provide nourishment for the ovum.
 - Secrete oocyte maturation inhibiting factor which keeps the ovum in its primordial state.
- ❖ **After puberty**, AP secrete **FSH and LH** which:
 - Stimulate the ovaries and result in growth of some follicles.
 - Growth of the follicle begins with increase in size of the ovum & growth of additional layers of granulosa cells of some follicles.
 - At this stage it is known as **primary follicles**.

In childhood single layer || in puberty multiple layers of granulosa



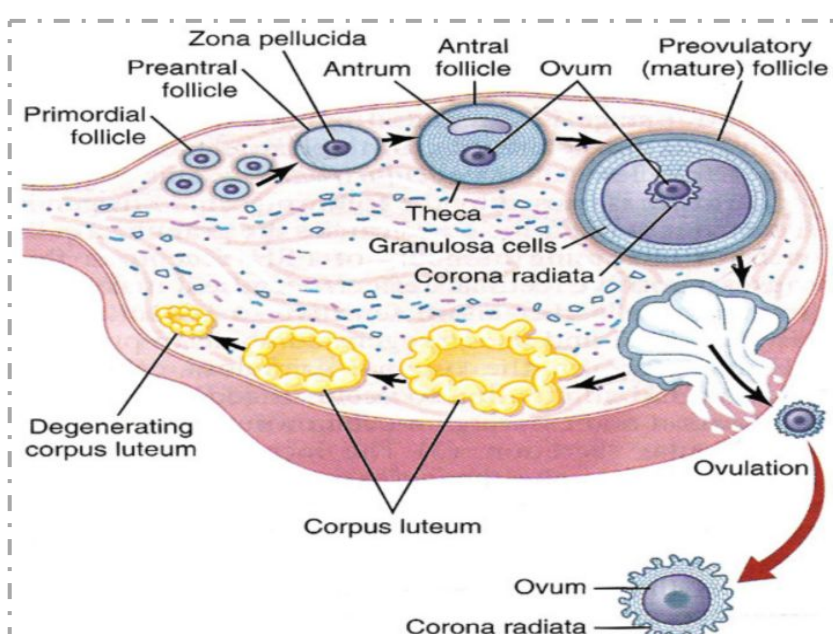
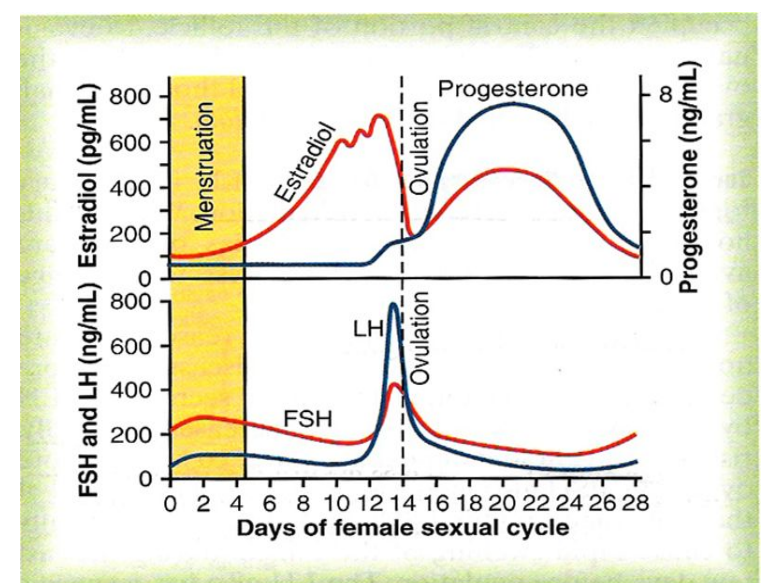
During the first few days of the monthly female reproductive cycle:

During the first few days of the monthly female reproductive cycle there is increase in secretion of **FSH and LH**:

- ❖ Increase in FSH 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 collect in several layers outside the granulosa cells to form a second mass of cells called **theca**.

This theca is divided into 2 layers:

1. Theca interna, the cells have epitheloid characteristics and similar to the granulosa cells and secrete sex hormones (estrogen and progesterone).
2. Theca externa, the outer layer, develops into a highly vascular connective tissue capsule of the developing follicle.



Explanation:

Before puberty: In the ovaries, we have the oocyte surrounded by a single layer of **granulosa/follicular cells** called the **primordial follicle**. This is only present during childhood. The main function of the single layer of follicular cells in childhood is protection, nourishment and secretion of maturation inhibiting factors.

At puberty: FSH will be secreted. This FSH will be increased gradually stimulating the receptors present on the follicular cells. When the cells are stimulated, the following processes occur:

- 1- Stimulation
- 2- Proliferation
- 3- Enlargement

The follicular cells over the ovum increase in size becoming a double layered cell.

As long as FSH is secreted, the follicles increase in size until they reach the pre-antrum. As the follicles increase in size, spindle shaped cells develop in the stroma of the ovaries. They are called **theca cells**. The greater the size of the ovaries, the more theca cells develop. Theca cells have 2 types: interna and externa.

Theca interna cells develop in the exterior portion, after that theca externa develops. LH will be secreted and attached only to theca interna cells. Once the LH stimulates the theca interna cells, it will secrete the male androgens which are the weak androgens. The androgens will diffuse to the adjacent granulosa cells. Then by the action of aromatase enzyme present in the granulosa cells, it will convert the weak androgens into estrogen. This estrogen is dependent on the estrogen precursor which is the male androgens and it will be stored in the antrum (fluid filled space filled with estrogen). As long as the follicles increase in size, the antrum will also increase in size causing the ovum to get embedded at one side. By about the 12th day, the follicle will be ready to rupture. The follicle will send great amounts of estrogen to the anterior pituitary causing it to secrete high amounts of LH. This is known as the LH surge. LH will now attach to the theca externa/capsule of follicles leading to proliferation followed by increase in size then weakening of the wall. The wall will protrude forming a nipple like structure called stigma of the follicle. (weakest point in follicle). As long as LH increases, the weaker the follicular wall gets leading to degeneration of the stigma and then rupture.

Follicular Phase Cont...

Multilaminar Primary Follicles and Secondary Follicles:

- ❖ Few days after proliferation & growth of the follicles, the granulosa cells secrete follicular fluids contain high concentration of **estrogen**.
- ❖ This fluid accumulate to form **antrum** within the mass of the granulosa cells. (single fluid filled state)
- ❖ The early growth of the follicle up to the antral is under **FSH** stimulation.

Tertiary Vesicular Follicles (Known As Graafian Follicles):

Then there is accelerated growth of the follicle to larger follicle called vesicular follicle (Graafian) caused by:

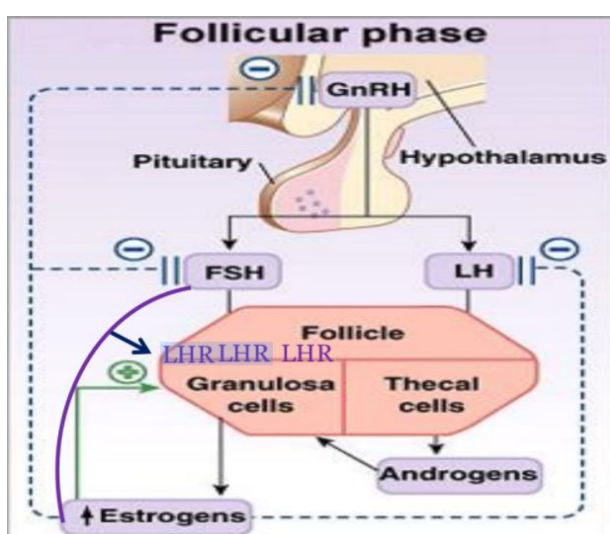
- 1- Estrogen secreted into the follicle causes the granulosa cells to form increasing number of FSH receptors which causes **positive feedback effect**.
2. Both estrogen & FSH combine to promote LH receptors on the granulosa cells **In addition to FSH stimulation**, allowing more increase follicular secretion.
3. The increasing estrogen from the follicle plus increasing LH from the AP causes proliferation of the follicular theca cells & increase their secretion.

This results in Proliferation of the follicular cells & increase their secretion.

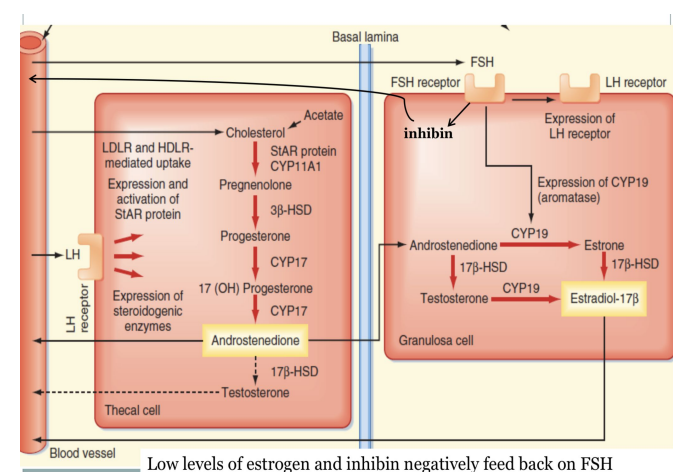
- ❖ The **antral follicles** begin to grow. The ovum enlarges & remains embedded at one pole of the granulosa cells of the follicle.
- ❖ After a week or more of growth—but before ovulation occurs—one of the follicles begins to outgrow all the others, and the remaining 5 to 11 developing follicles involute (a process called **atresia**) caused by:

- 1- Rising **estrogen** levels (positive feedback locally and negative feedback centrally),
- 2- Rising **inhibin** levels (further negative feedback).
- 3- Declining **FSH** levels (Withdraw growth support, causing atresia in lesser follicles).

This process of atresia is important because it normally allows only one of the follicles to grow large enough each month to ovulate, which usually prevents more than one child from developing with each pregnancy.



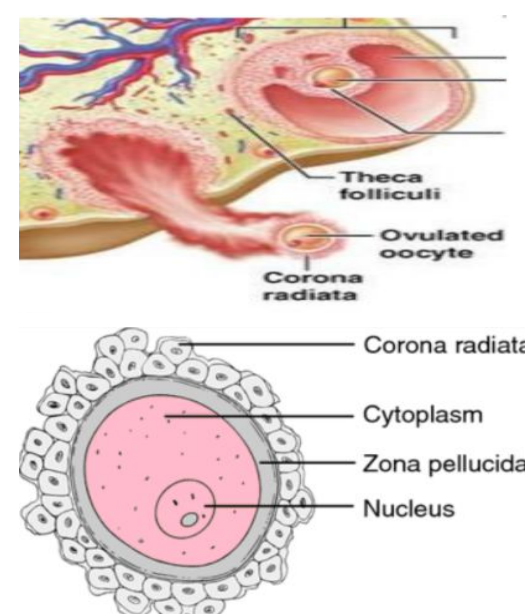
Before the antrum is formed, LH is released and it will bind to theca cells. When LH binds to theca cells it will secrete male weak androgens, which will diffuse to the adjacent granulosa cells. By the action of aromatase enzyme that is present in granulosa cell, it will convert weak androgen into estrogen, and then estrogen will be stored in the antrum.



Initiation of Ovulation: Rupture of Tertiary Follicles and Formation of Corpus Luteum:

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

- ❖ Before ovulation, a small area in the center of the follicle called **stigma** protrude & 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**.



LH surge is necessary for ovulation:

Females slides, but explained by males doctor

- 2 Days before ovulation, the rate of LH secretion from the AP increase markedly to 6-16 fold & peak about 16 hrs before ovulation.
- FSH also increases to 2 to 3 fold & acts synergistically with LH what's the point behind that?? to **cause rapid swelling of the follicle before ovulation.**
- LH has specific effect on the **granulosa cells & theca cells** converting them to **progesterone secreting cells** so the rate of **estrogen secretion begins to fall about 1 day before ovulation while progesterone secretion begin to increase.** Why progesterone increases before ovulation? We will see

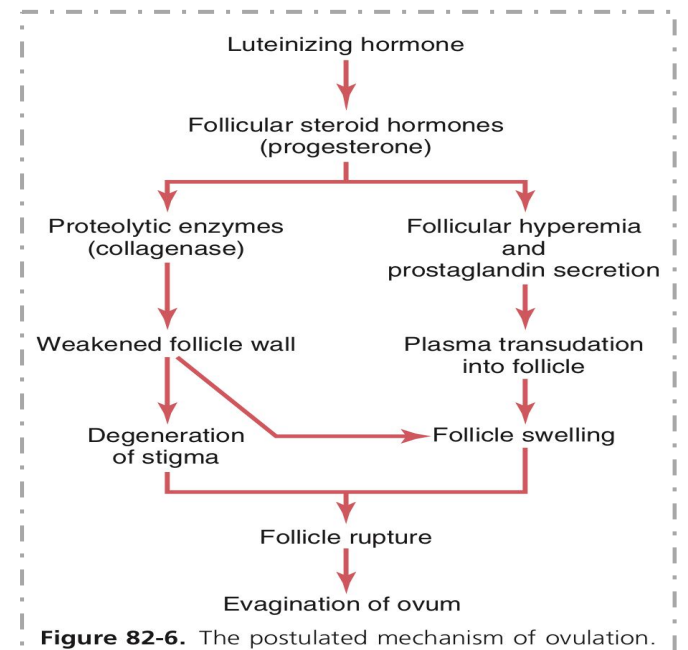
Initiation of ovulation:

Large quantity of LH secreted by the AP causes rapid secretion of **progesterone** from the follicle few hours.

2 events occur which are necessary for ovulation:

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

Those two changes causes **swelling** of the follicle & plasma transudation into the follicle & **degeneration of the stigma with discharge of the ovum.**



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 with the theca cells called corpus luteum.
- The granulosa cells in corpus luteum develop extensive intracellular endoplasmic reticula & form large amount of progesterone & estrogen.
- The theca cells form mainly androgens which are converted by granulosa cells into female hormones.
- The corpus luteum grow to about 1.5 cm in diameter, at about 7 to 8 days after ovulation .
- Then begins to involute & losses its secretory function & its yellowish characteristic about 12 days after ovulation becomes corpus albicans & replaced by connective tissue & absorbed. **It is removed by macrophages.**
- **The corpus luteum has no need for FSH, and it is dependent mainly on LH for its growth. LH maintains the life of corpus luteum, the excess estrogen and progesterone and small amount of inhibin from corpus luteum will decrease LH production from AP by negative feedback. Therefore corpus luteum kills itself by this mechanism.**
- **At the end of the cycle when corpus luteum degenerates, there is no negative feedback on the anterior pituitary anymore, FSH & LH are released again to initiate the beginning of a new cycle.**

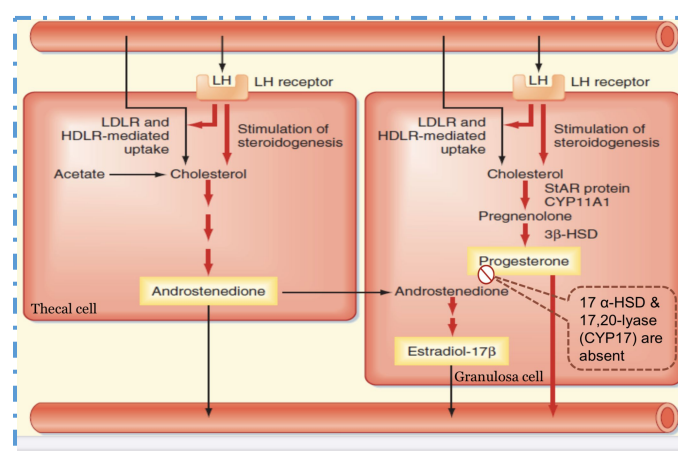
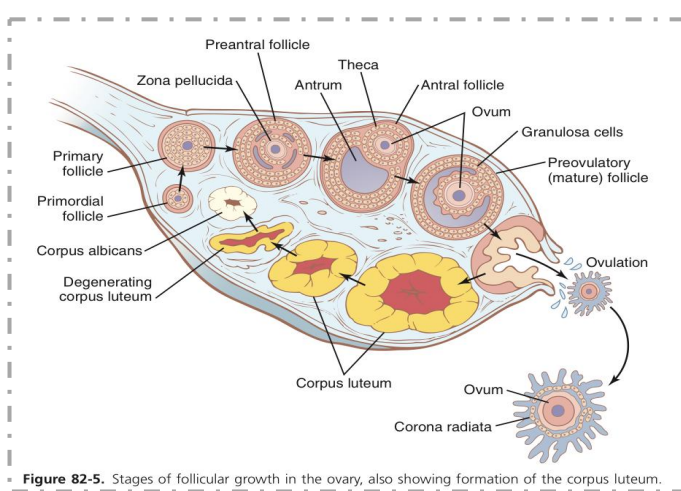


Figure 2-10 Vascularization of the corpus luteum makes low LDL available to the granulosa-lutein cells. LH causes upregulation of 3β -HSD, CYP17 and cholesterol uptake.

- Consequently large amounts of progesterone are formed, and not all of it can be converted to androgens and then to estrogens.
- Consequently, both estrogen and progesterone secretion is increased in this stage.
- Degeneration of the basal lamina between the two cells that was present in the previous stage creating a *Lutein cell*.
- The absence of the hormones in the figure will prevent conversion of progesterone into androgens, therefore more progesterone will be released.

Luteinizing function of LH

A local hormone in the follicular fluid called luteinization – inhibiting factor hold the luteinization process until after ovulation.

After extrusion of the ovum from the follicle the following changes occur:

- Ovulation
- Conversion of granulosa and theca interna cells into lutein cells.
- Secretion of progesterone & estrogen from the corpus luteum.

If pregnancy occur, the chorionic gonadotropin from the placenta act on the corpus luteum to prolong its life for 2 to 4 months of pregnancy.

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

❖ Lutein cells of the corpus luteum secrete:

- Progesterone & Estrogen which inhibit the secretion of FSH & LH.
- Inhibin which inhibit secretion of FSH by AP.

❖ Low levels of both FSH & LH & causes the corpus luteum to degenerate completely, called involution of the corpus luteum.

❖ Around 26th days of normal reproductive cycle & after involution of corpus luteum, sudden cessation of secretion of estrogen, progesterone & inhibin removes the feedback inhibition of the AP & allowing increase secretion of FSH & LH again.

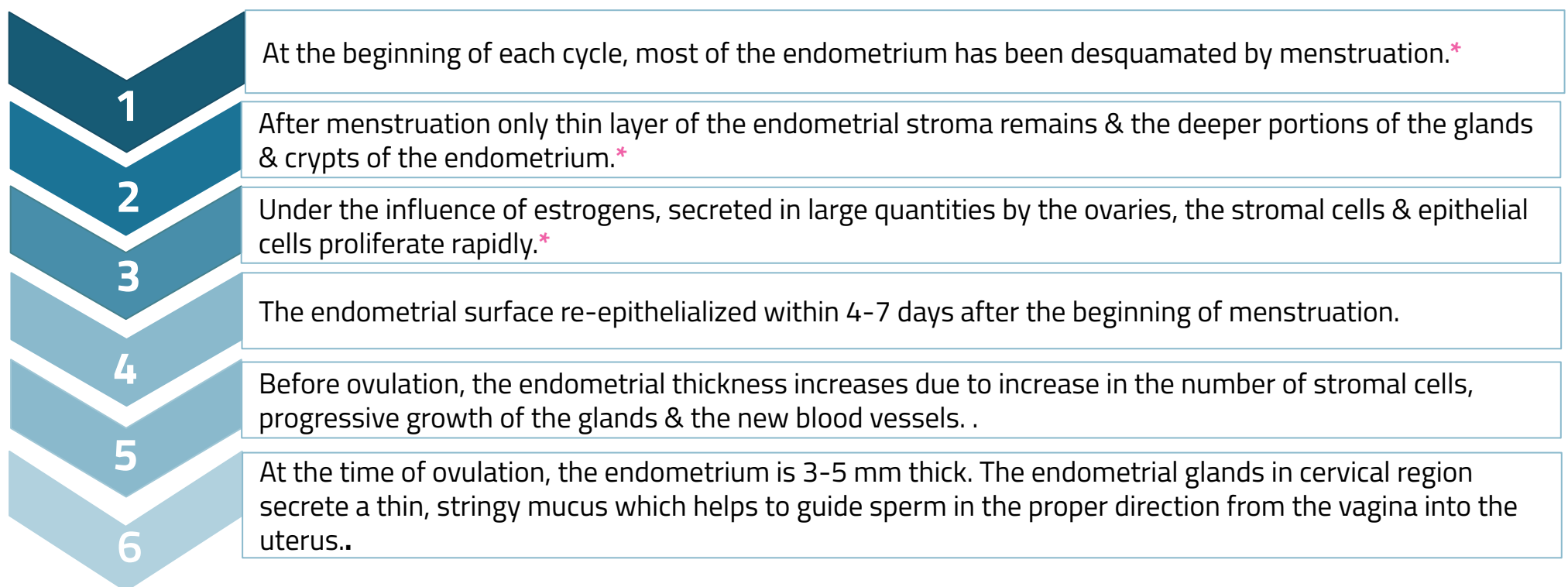
❖ FSH & LH initiate the growth of new follicles, beginning a new ovarian cycle.

End of lecture 2

Uterine Cycle

Monthly endometrial cycle and menstruation: Associated with monthly cyclical production of estrogen & Progesterone by the ovaries. The endometrial lining of the uterus passes through the following stages*

Proliferative Phase (estrogen Phase) Occurring before Ovulation



Secretory Phase (Progestational Phase) Occurring After Ovulation

After ovulation, during most of the latter half of the monthly cycle, **estrogen** and **progesterone** are secreted in large quantities by the corpus luteum.

Estrogen causes slight cellular proliferation in the endometrium, whereas **progesterone** causes marked swelling and secretory development of the endometrium.

❖ The glands increase in tortuosity, and an excess of secretory substances accumulates in the glandular epithelial cells.

Stromal cells cytoplasm increases due to the increase in lipid and glycogen deposits.

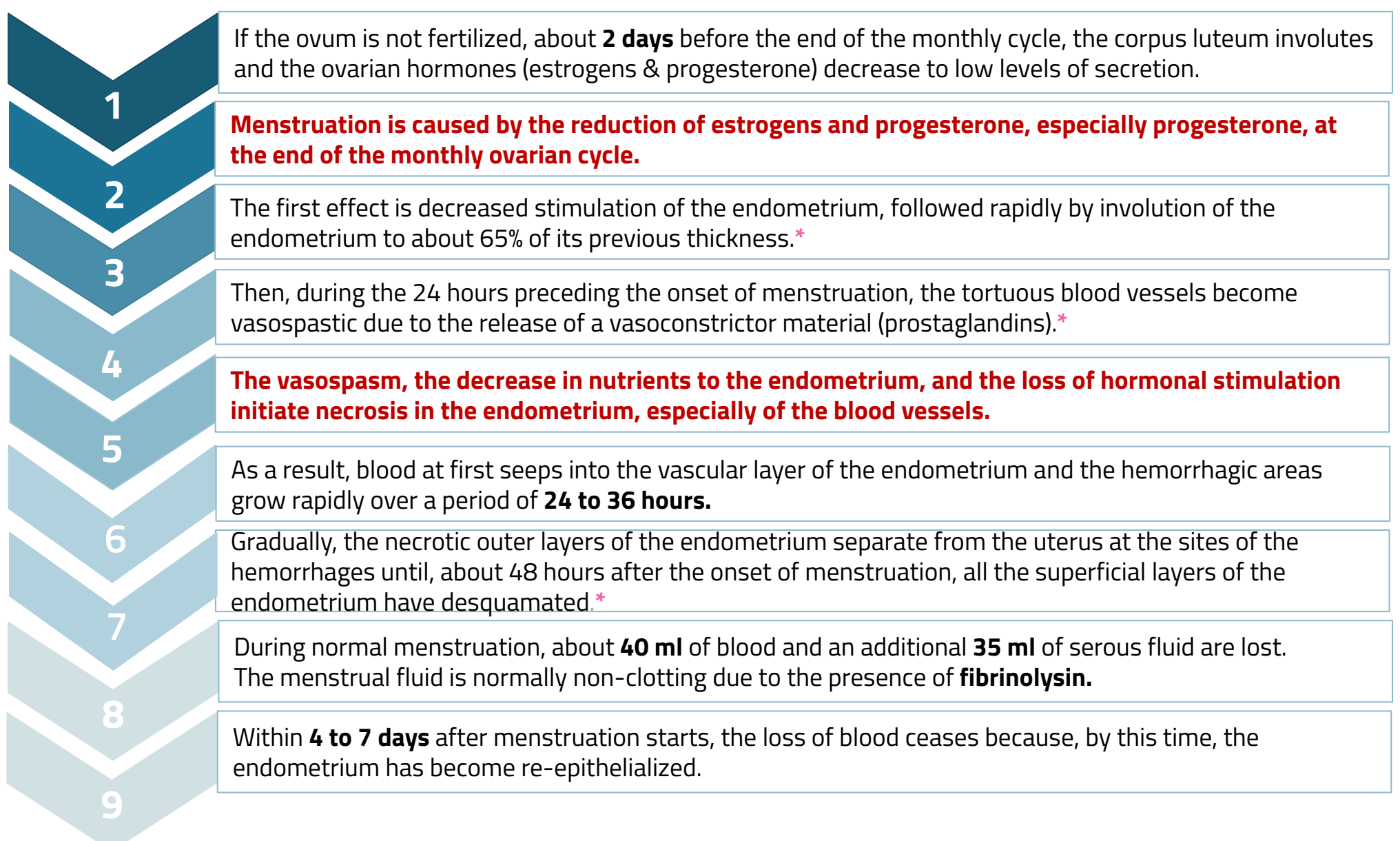
❖ The blood supply to the endometrium increases with the blood vessels becoming more tortuous.

About **1 week** after ovulation (**day 21**), the endometrium has a thickness of **5-6 mm**.

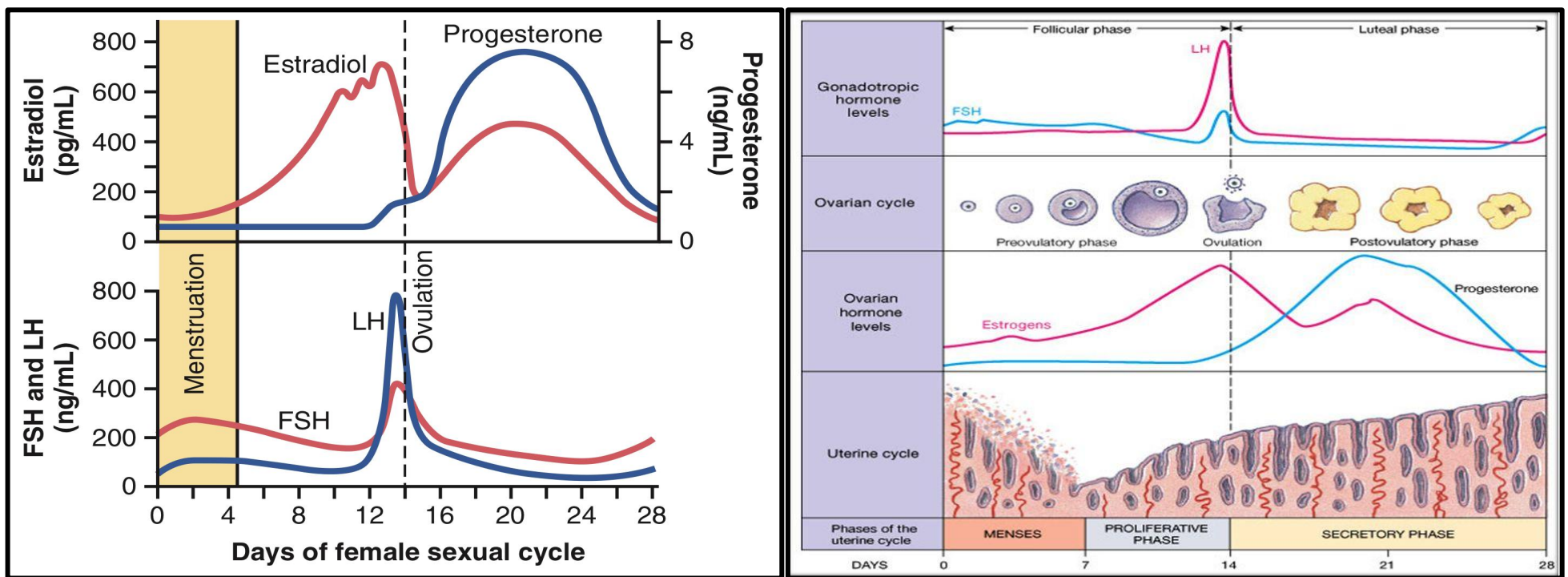
The whole purpose of all these changes is to produce a highly secretory endometrium that contains large amounts of stored nutrients to provide appropriate conditions for implantation of a fertilized ovum.

- The uterine secretions, called "uterine milk", provide nutrition for the diving ovum.
- The trophoblastic cells on the surface of the implanting ovum begin to digest the endometrium and absorb the endometrial stored substances.

Uterine Cycle: Menstruation



Continued...



Approximate plasma concentrations of the gonadotropins and ovarian hormones during the normal female sexual cycle.

Leukorrhea During Menstruation

During menstruation, large numbers of **leukocytes** are released along with the necrotic material and blood. As a result of these leukocytes and possibly other factors, the uterus is highly resistant to infection during menstruation (**protective mechanism**).

Feedback Oscillation of the Hypothalamic-Pituitary-Ovarian System*

- 1 Postovulatory secretion of the ovarian hormones and depression of the pituitary gonadotropins: Between ovulation and the beginning of menstruation, the corpus luteum secretes large quantities of **progesterone** and **estrogen**, as well as the hormone **inhibin**.
- 2 All these hormones together have a combined negative feedback effect on the anterior pituitary gland and hypothalamus, causing the suppression of both **FSH** and **LH** secretion and decreasing them to their lowest levels about **3 to 4 days** before the onset of menstruation.

Functions of Estrogen and Progesterone*

Estrogen	Progesterone
<ul style="list-style-type: none"> ❖ Estrogens increase the size of ovaries, fallopian tubes, uterus, and external genitalia. ❖ Estrogens cause marked proliferation of the endometrial stroma and greatly increased development of the endometrial glands. ❖ Estrogens cause: <ul style="list-style-type: none"> ◇ Development of the stromal tissues of the breasts ◇ Growth of an extensive ductal system ◇ Deposition of fat in the breasts. ❖ Estrogens stimulate bone growth and slightly increase protein deposition. ❖ Estrogens increase body metabolism and fat deposition. ❖ Estrogens cause sodium and water retention by the kidney tubules. 	<ul style="list-style-type: none"> ❖ Progesterone promotes the secretory changes in the uterine endometrium. ❖ Progesterone promotes increased secretion by the mucosal lining of the fallopian tubes. ❖ Progesterone promotes development of the lobules and alveoli of the breasts, causing the alveolar cells to proliferate, enlarge, and become secretory in nature. ❖ Progesterone decreases the frequency and intensity of uterine contractions.

Menopause

The period during which the cycle ceases and the female sex hormones diminish to almost none is called menopause.

At age 40 to 50 years, the sexual cycle usually becomes irregular and ovulation often fails to occur. After a few months to a few years, the cycle ceases altogether.

When **estrogens** production falls below the critical value, the **estrogens** can no longer inhibit the production of the gonadotropins **FSH & LH** (Due to removal of the negative feedback effect there is increased secretion of FSH and LH).*

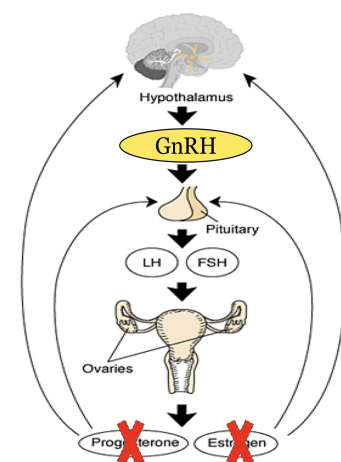
With advanced age the ovaries become unresponsive to gonadotropins (decline in the number of Primordial follicles), and their function declines so that reproductive cycles disappear (menopause). The ovaries no longer secrete estrogen and progesterone.*

Uterine and vaginal atrophy.*

Physiological changes due to loss of estrogens

The loss of estrogens often 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 (increase risk of fractures and osteoporosis).



Menstrual Disorders

Amenorrhea (absence of menstruation)	Primary amenorrhea: in which menstrual bleeding has never occurred.
	Secondary amenorrhea: the abnormal cessation of cycles in a woman with previously normal periods. Causes: <ul style="list-style-type: none"> ● Pregnancy (the most common cause). ● Emotional stimuli and changes in the environment. ● Hypothalamic diseases (decreased GnRH pulses). ● Pituitary disorders (decreased FSH & LH) e.g. Sheehan syndrome (postpartum hypopituitarism) ● Hypothyroidism (TRH stimulates prolactin which decreases GnRH) ● Primary ovarian disorders and various systemic disease.
Menorrhagia	Refers to abnormally heavy or prolonged bleeding or profuse flow during regular periods.
Hypomenorrhea	Refers to scanty flow.
Dysmenorrhea	Painful menstruation (cramps due to accumulation of prostaglandins in the uterus) <ul style="list-style-type: none"> - Treated with inhibitors of prostaglandin synthesis.
Oligomenorrhea*	Refers to infrequent (irregular) menstrual periods.

MCQ & SAQ:

Q1: Which of the following is true regarding the accelerated growth of follicle into graffian follicle:

- A. Positive feedback of estrogen
- B. Combining of progesterone with LH
- C. Promotion of LH receptors on theca cells
- D. Positive feedback of progesterone

Q3: What is the effect of LH on granulosa cells & theca cells?

- A. converting them to estrogen secreting cells
- B. converting them to progesterone secreting cell
- C. converting them to testosterone secreting cell
- D. converting them to androgen secreting cell

Q5: Dysmenorrhea refers to?

- A. Failure to have menstrual periods
- B. heavy or prolonged bleeding
- C. Painful menstruation
- D. infrequent menstrual periods

Q2: The anterior pituitary secretes which 2 hormones after puberty?

- A. LH & GH
- B. FSH & LH
- C. FSH & ACTH
- D. GH & Prolactin

Q4: Menstruation is caused by the reduction of which hormones?

- A. estrogens
- B. progesterone
- C. Inhibin
- D. A&B

Q6: in menopause the rate of secretion of FSH and LH are?

- A. Normal
- B. Pulsatile
- C. Decrease
- D. Increase

6: D
5: C
4: D
3: B
2: B
1: A
key:
answer

1- Explain why ovulation occurs to one follicle while the other follicles involute?

2- What happens during menstruation?

3- What is the purpose of Leukorrhea?

4- What are the causes of Secondary amenorrhea?

A1: 1-Rising **estrogen** levels (positive feedback locally and negative feedback centrally),
2-Rising **inhibin** levels (further negative feedback). 3-Declining **FSH** levels (Withdraw growth support, causing atresia in lesser follicles).

A2: slide 7

A3: To keep the uterus highly resistant to infection during menstruation (protective mechanism).

A4: 1. Pregnancy 2. Emotional stimuli 3. Hypothalamic diseases
4. Pituitary disorders 5. Hypothyroidism 6. Primary ovarian disorders

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