

PHYSIOLOGY OF MENSTRUAL CYCLE

- Specialist in infertility & IVF

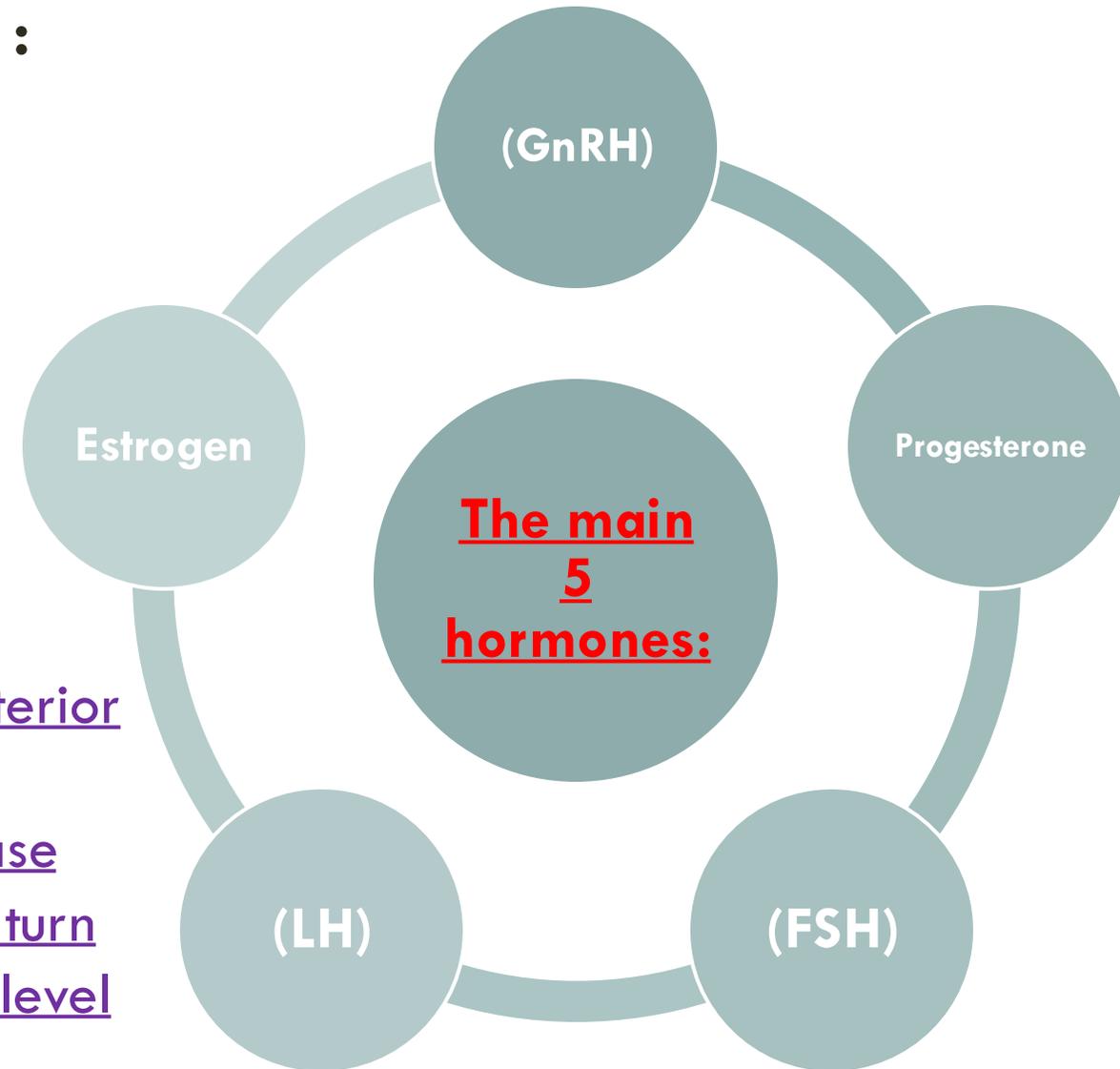
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THE DEFINITION OF MENSTRUATION:

Menstruation (Greek word, men-month) is defined as visible manifestation of cyclic uterine bleeding due to shedding of the endometrium as a result of hormonal changes operated through hypothalamopituitary ovarian axis.

GnRH is secreted by the hypothalamus, the gonadotropins FSH and LH are secreted by the anterior pituitary gland, and estrogen and progesterin are secreted from the ovary. GnRH stimulates the release of LH and FSH from the anterior pituitary, which in turn stimulate release of estrogen and progesterin at the level of the ovary.

There are five main hormones that are involved in the regulation of menstrual cycle :



HORMONES OF MENSTRUAL CYCLE

There are five main hormones that are involved in the regulation of menstrual cycle :

- ❖ 1. Gonadotropin releasing hormone (GnRH)
- ❖ 2. Follicle stimulating hormone (FSH)
- ❖ 3. Luteinizing hormone (LH)
- ❖ 4. Estrogen
- ❖ 5. Progesterone.

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1. GONADOTROPIN RELEASING HORMONE (GNRH)

- ❑ Is a decapeptide, secreted from the hypothalamus in a pulsatile manner throughout the menstrual cycle. To maintain the menstrual cycle normal, *GnRH must be released in pulses.*
- ❑ The pulsatile release of GnRH varies in both frequency and amplitude throughout the menstrual cycle and tightly regulated.
- ❑ On average, the frequency of GnRH secretion is once per 90 minutes during the early follicular phase, increases to once per 60–70 minutes, and decreases with increased amplitude during the luteal phase.
- ❑ GnRH induces the release of both FSH and LH; however, LH is much more sensitive to changes in GnRH levels.

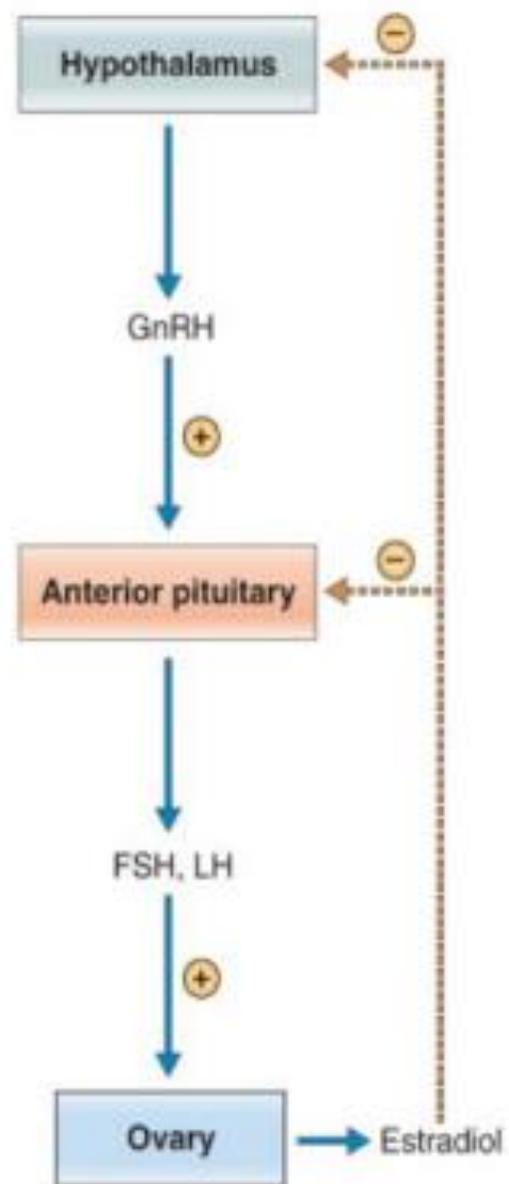
2. FOLLICLE STIMULATING HORMONE (FSH)

- Follicle stimulating hormone (FSH) is secreted by the anterior pituitary gland and is essential for follicular growth **until** the antrum develops.
- FSH secretion is highest and most critical during the first week of the follicular stage of the menstrual cycle.
- FSH **stimulates** granulosa cells in newly recruited follicles and produce increasing quantities of estrogen and inhibin blood serum levels of two hormones rise progressively and produces **a negative feedback effect** on pituitary FSH secretion and serum FSH levels progressively declines.
- FSH further induces the expression of LH receptors **on granulosa cells**.

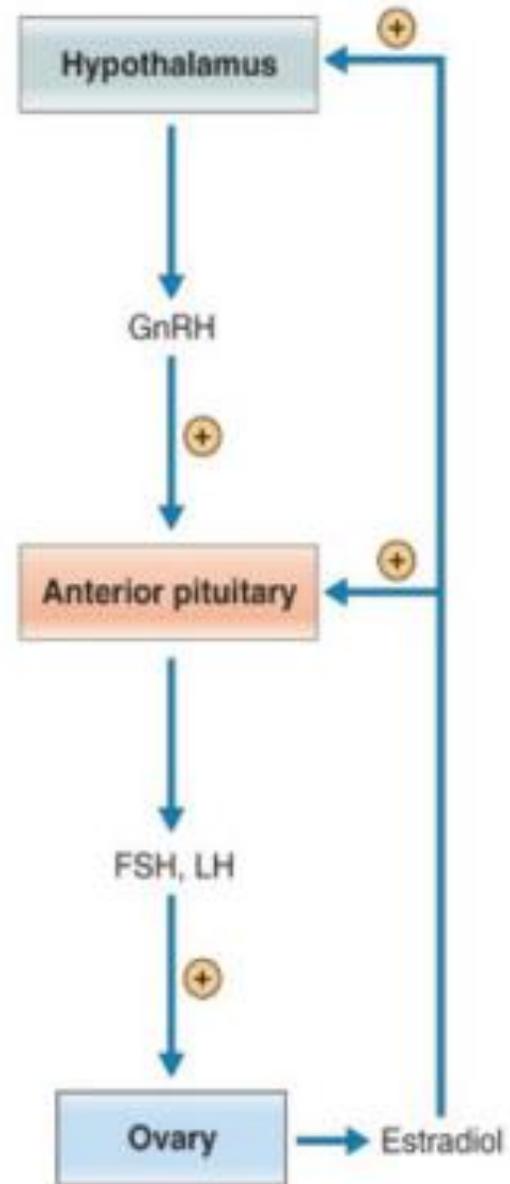
3. LUTEINIZING HORMONE (LH):

- ❖ Luteinizing hormone (LH) is secreted by the anterior pituitary gland and is required for both growth of pre-ovulatory follicles and luteinization and ovulation of the dominant follicle.
- ❖ During the follicular phase of the menstrual cycle, LH stimulates (proliferation and differentiation) theca cells for androgen synthesis and androgen is then transported to the granulosa cells for conversion into estrogens.
- ❖ The pre-ovulatory LH surge drives the oocyte into the first meiotic division and initiates luteinization of thecal and granulosa cells.
- ❖ The resulting corpus luteum produces high levels of progesterone and some estrogen.

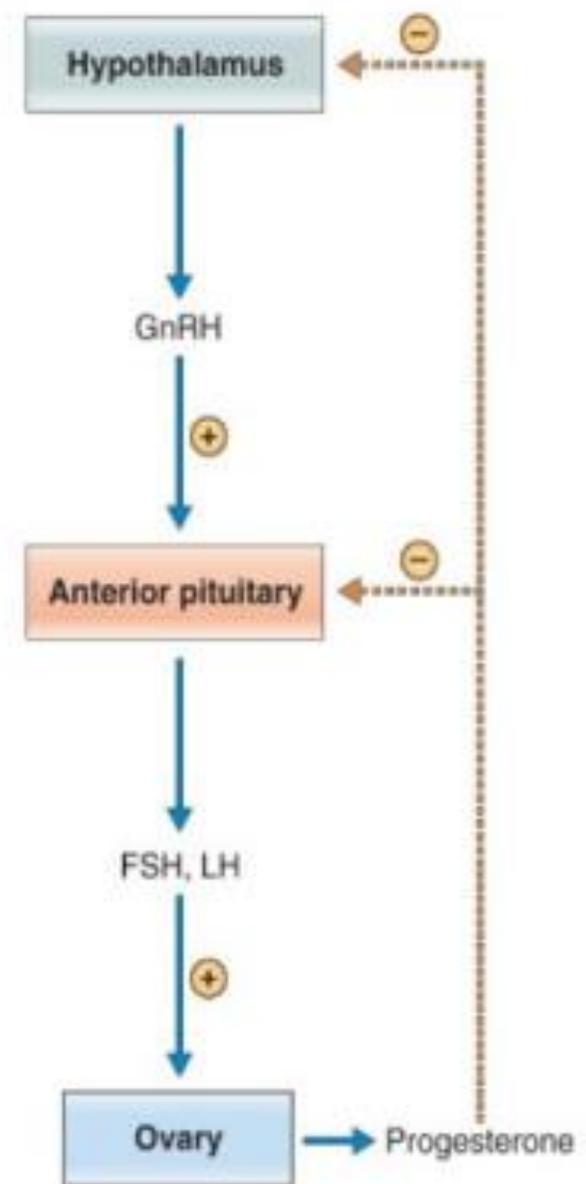
FOLLICULAR PHASE



MIDCYCLE



LUTEAL PHASE



4. Estrogen pt.1 :

- ❖ Estradiol is the most potent and abundant estrogen produced from ovary.
- ❖ Other types are **Estrone and Estriol.**
- ❖ Estradiol is primarily derived from androgens **produced by theca cells.**
- ❖ The androgens migrate from the theca cells to the granulosa cells, where they are converted into estradiol **by aromatase enzyme.**
- ❖ Some estradiol can also be produced via de novo synthesis by **thecal cells.**

To be continued....



Estrogen pt.2 :

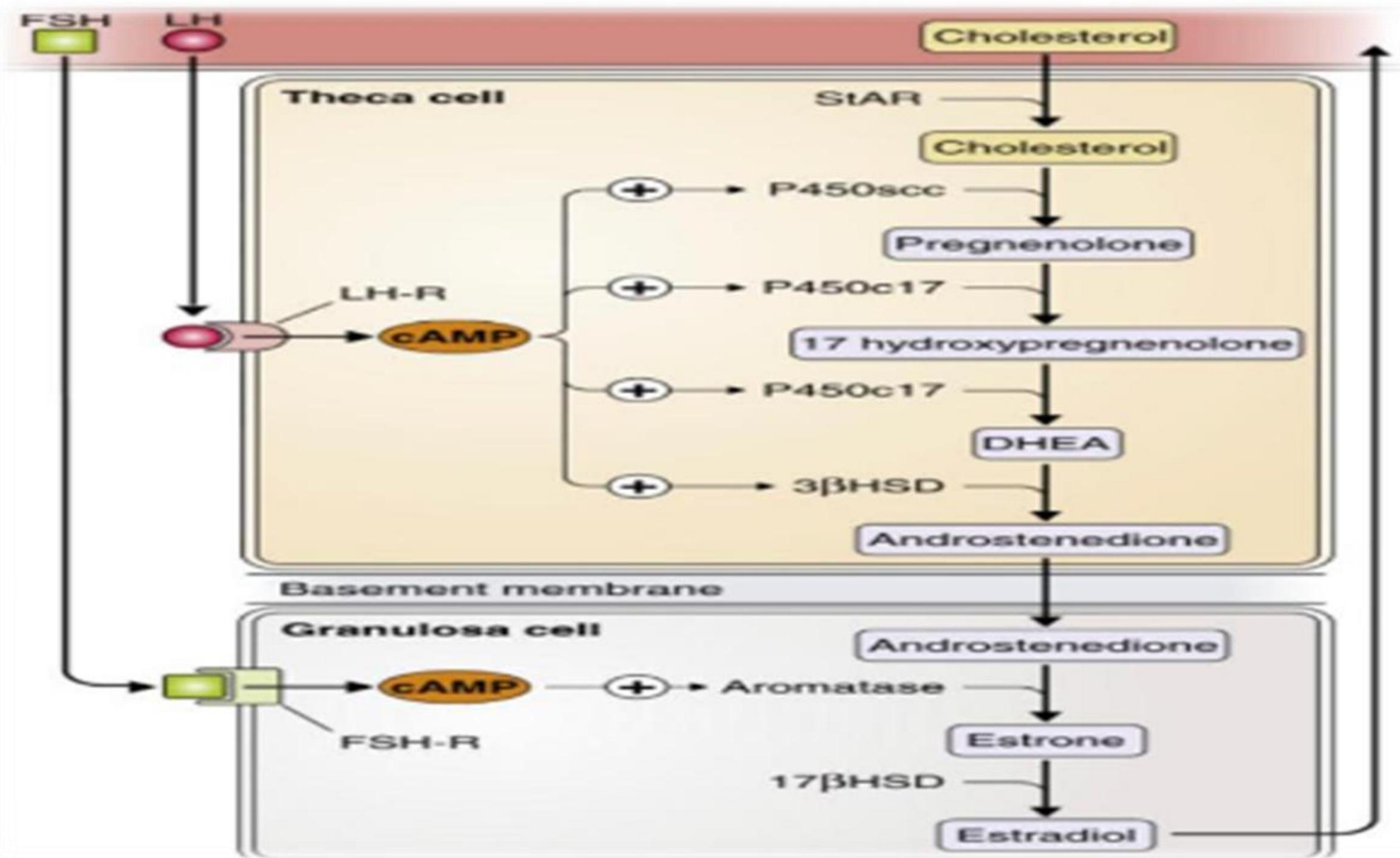
- ❖ The actions of estradiol include **induction of FSH receptors** on granulosa cells, proliferation and secretion of follicular theca cells, induction of LH receptors on granulosa cells, and proliferation of endometrial stromal and epithelial cells.
- ❖ At low circulating levels (**at early follicular phase**), estrogens exert **negative feedback** on LH and FSH secretion; however, at very high levels (prior ovulation) estrogens exert positive feedback on LH and FSH secretion.
- ❖ In the uterine endometrial cycle, estrogen induces proliferation of the endometrial glands, **increases motility of fallopian tubes** and have other effects on breast, behavior.

5. PROGESTERONE PROGESTIN PT.1:

- Progesterone progestin is secreted at the level of the ovary, **primarily by corpus luteum**.
- Progestin levels **increase** just prior to ovulation and peak five *to seven days post-ovulation*.
- The first step in progestin synthesis requires P450 enzyme and the two circulating forms of progestin are progesterone and 17-hydroxyprogesterone.
- Progestins stimulate the release of **proteolytic enzymes** from thecal cells that ultimately prepare for ovulation.
- Progestin further **induce** migration of blood vessels into the follicle wall and stimulate prostaglandin secretion in follicular tissues.

5. PROGESTERONE PROGESTIN PT.2:

- During the luteal phase, progestins induce swelling and increased secretion of the endometrium.
- According to the two-cell-two-gonadotrophin theory, the ovary has two cellular compartments that are driven independently by LH and FSH to produce ovarian steroids.
- LH stimulates the theca cell segment of the follicle and induces production of androgens from cholesterol, while FSH is responsible for promoting conversion of androgen precursors to estrogens in the granulosa cell compartment.



Mineralocorticoids

Glucocorticoids

Sex hormones

Cholesterol

Mitochondria ← StA

Pregnenolone

17 α -OH

3- β HSD

Progesterone

17 α -OH

21-OH

11-Deoxycorticosterone

11- β OH

Corticosterone

18-OH

18-OH Corticosterone

18-Oxidase

Aldosterone

17-OH Pregnenolone

3- β HSD

17-OH Progesterone

21-OH

11-Deoxy Cortisol

11- β OH

Cortisol

Dehydroepiandrosterone (DHEA)

3- β HSD

Δ^4 -Androstenedione

17- β HSD

Testosterone

5 α -reductase

Dihydrotestosterone

Aromatase

Estradiol

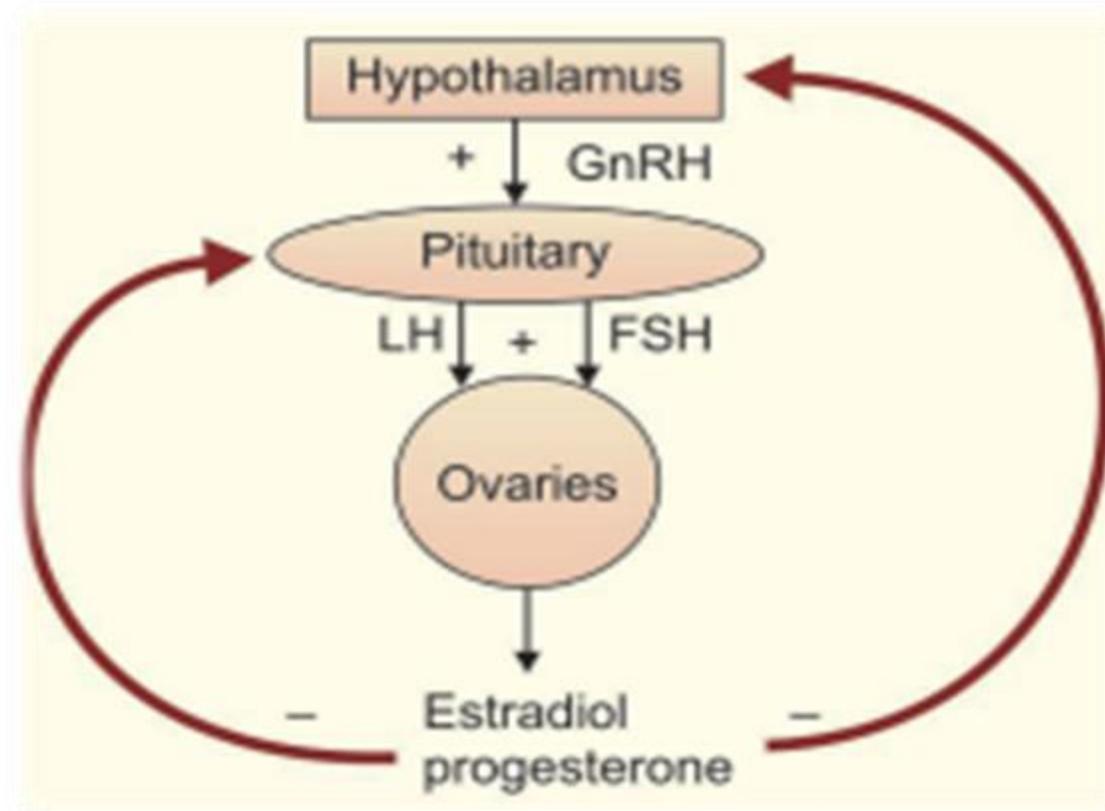
17,20 Lyase

17,20 Lyase



HYPOTHALAMOPITUITARY OVARIAN AXIS:

- In the presence of a GnRH pulse, the pituitary and ovarian hormones exert mutual control over the circulating levels of one another.
- The complex interactions between pituitary and ovarian hormones involve forward control, positive feedback and negative feedback.
- mechanisms, and serve to sustain **a self perpetuating** monthly endocrine cycle.



HORMONAL CHANGES IN MENSTRUAL CYCLE:

The interplay between pituitary and ovarian hormones gives rise to a stereotyped pattern of hormone levels during the menstrual cycle. The picture in the next slide shows relative hormone levels in an average 28-day cycle. The sequence of events in the menstrual cycle is determined by the relative hormone levels at each stage.

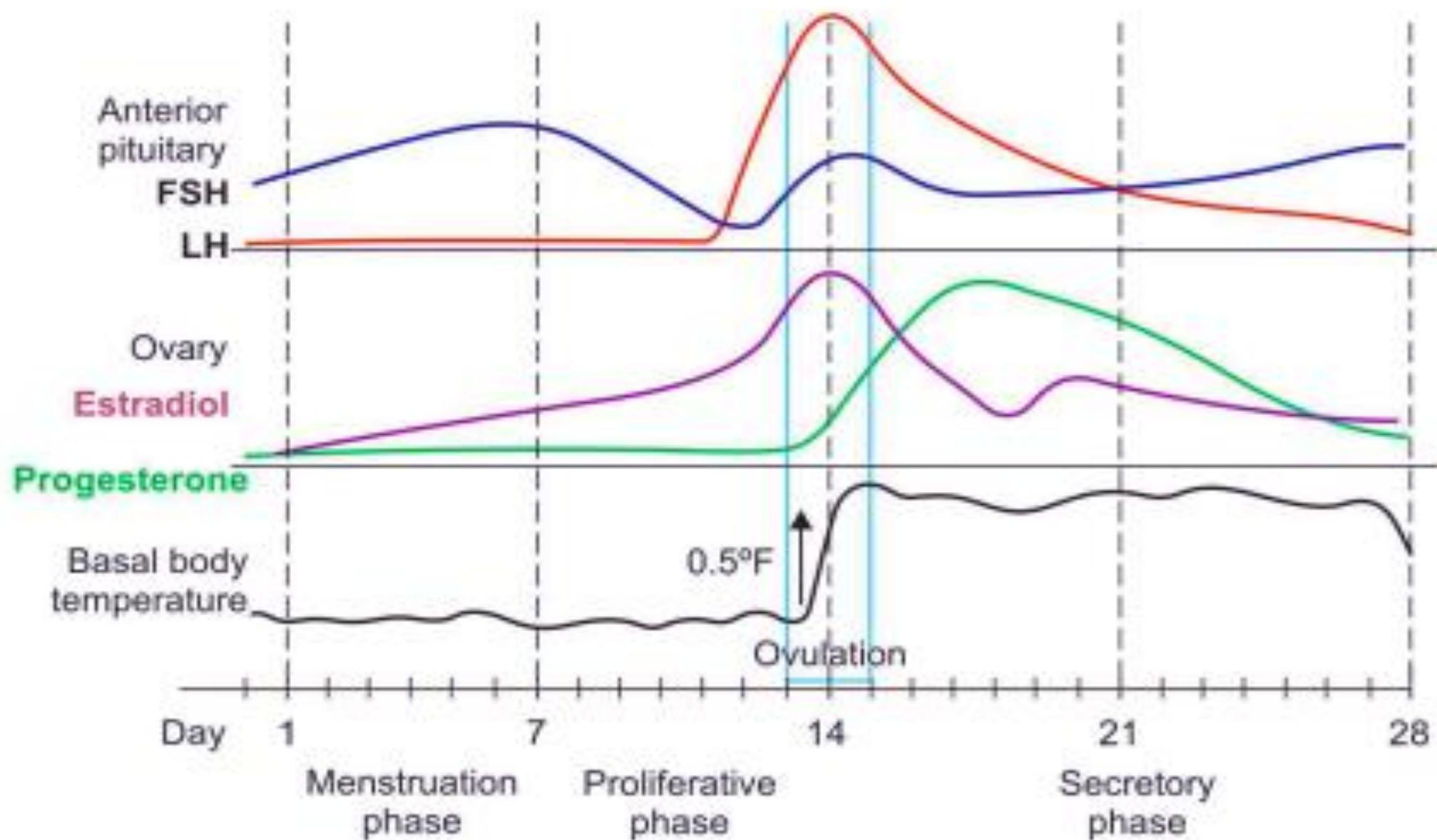
❖ **For better understanding, menstrual cycle can be classified in different ways.**

1. On the basis of changes that occur in the ovaries (ovarian cycle)

- a. Follicular phase
- b. Ovulatory phase
- c. Luteal phase

2. On the basis of changes that take place in the linings of the uterus (uterine cycle/ endometrial cycle)

- a. Proliferative phase
- b. Secretory phase
- c. Menstrual phase



A) THE FOLLICULAR PHASE PT.1:

- ❖ The follicular phase of the menstrual cycle starts from the first day of menstruation until ovulation.
- ❖ The primary goal during the follicular phase is to develop a follicle which will undergo ovulation.
- ❖ The early events of the follicular phase are initiated by a rise in FSH levels at the first day of the cycle.
- ❖ The rise in FSH levels can be attributed to a decrease in progesterone and estrogen levels at the end of the previous cycle.
- ❖ FSH stimulates the **development of 15–20 follicles each month** and stimulates follicular secretion of estradiol by inducing the aromatase enzyme receptor on granulosa cells.
- ❖ As estradiol levels increase under the influence of FSH, estradiol inhibits the secretion of FSH and FSH levels decrease.
- ❖ Under normal circumstances, one follicle evolves into the dominant follicle, destined for ovulation, while the remaining follicles undergo atresia.

A) THE FOLLICULAR PHASE PT.2:

- The fully mature graffian follicle just prior to ovulation measures about 20 mm. It is currently **not known** how the dominant follicle is selected; yet it has been observed that the dominant follicle always expresses an abundance of FSH receptors. The dominant follicle, with *its high concentration of FSH receptors*, continues to acquire more FSH even as **FSH levels decrease**.
- The dominant follicle can continue to synthesize estradiol, which is essential for its complete maturation. The remaining, poorly FSH receptor-endowed follicles **can not** produce the requisite amount of estradiol.
- These follicles cease to develop and ultimately **undergo atresia**.
- The dominant follicle matures and secretes increasing amounts of estrogen. Estrogen levels peak towards **the end of the follicular phase of the menstrual cycle**.
- At this critical moment (serum estradiol level 200 pg/ml persisting approximately 50 hrs), estrogen **exerts positive feedback on LH**, generating a dramatic preovulatory LH surge.
- Estrogen can only **exert positive feedback on LH** at this precise stage in the menstrual cycle; if estrogen is artificially provided earlier in the cycle, ovulation will not be induced.

B. OVULATION:

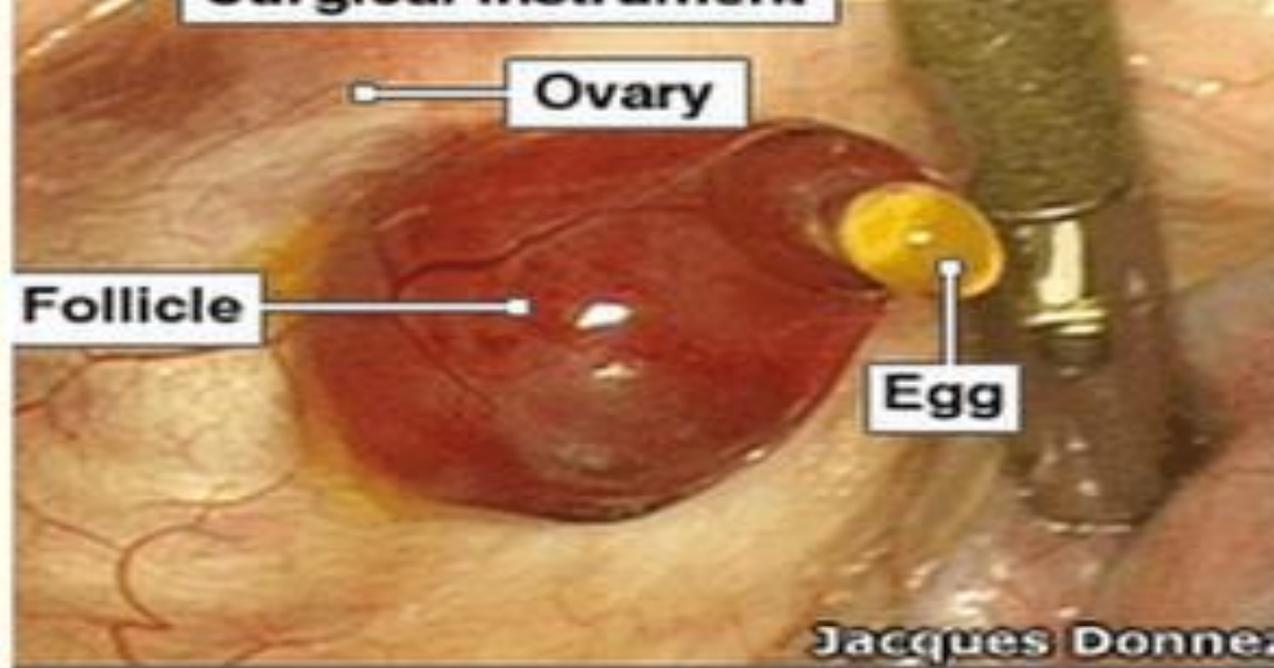
The LH surge is the key event for ovulation. Under the influence of LH, the primary oocyte enters the final stage of the first meiotic division and divides into a secondary oocyte and the first polar body.

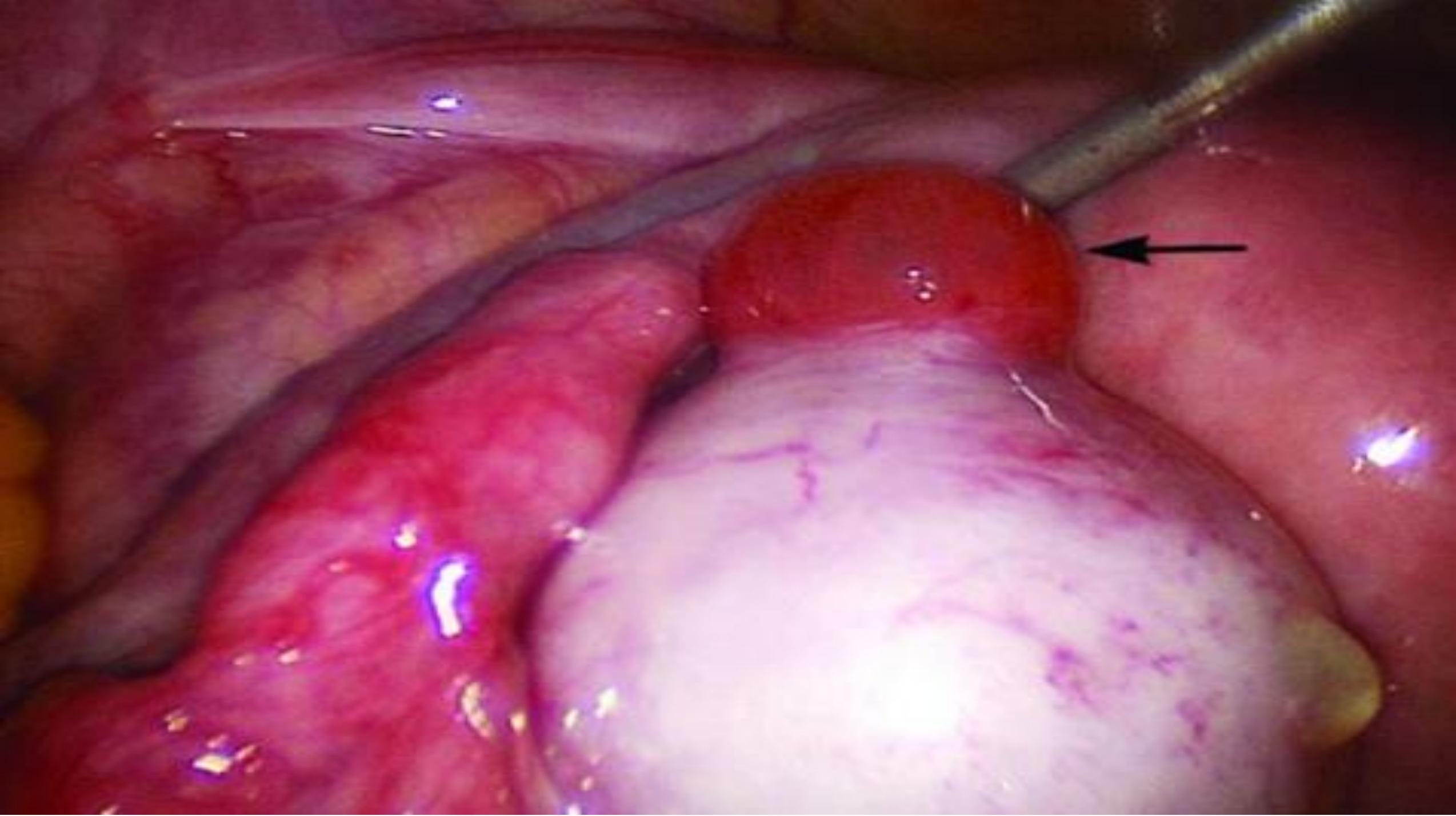
The LH surge induces release of proteolytic enzymes, which degrade the cells at the surface of the follicle, and stimulates angiogenesis in the follicular wall and prostaglandin secretion.

These effects of LH cause **the follicle to swell and rupture**. At ovulation, the oocyte and corona radiata are expelled into the peritoneal cavity.

The oocyte adheres to the ovary and muscular contractions of the fallopian tube bring the oocyte into contact with the tubal epithelium to initiate migration through the oviduct.

Ovulation occurs approximately 10–16 hours of LH peak and 32–36 hours after the onset of LH surge.





C. THE LUTEAL PHASE PT.1:

- The luteal phase is defined by the luteinization of the components of the follicle which were not ovulated and is initiated by the LH surge.
- The granulosa cells, theca cells, and some surrounding connective tissue are all converted into the corpus luteum, which eventually undergoes atresia.
- The major effects of the LH surge are the conversion of granulosa cells from predominantly androgen-converting cells to predominantly progesterone-synthesizing cells.
- This results in increased progesterone secretion with some estrogen secretion.
- Progesterone secretion by the corpus luteum peaks between five and seven days post-ovulation and can be used as presumptive sign that ovulation has occurred.
- High progesterone levels exert negative feedback on GnRH and subsequently GnRH pulse frequency decreases.

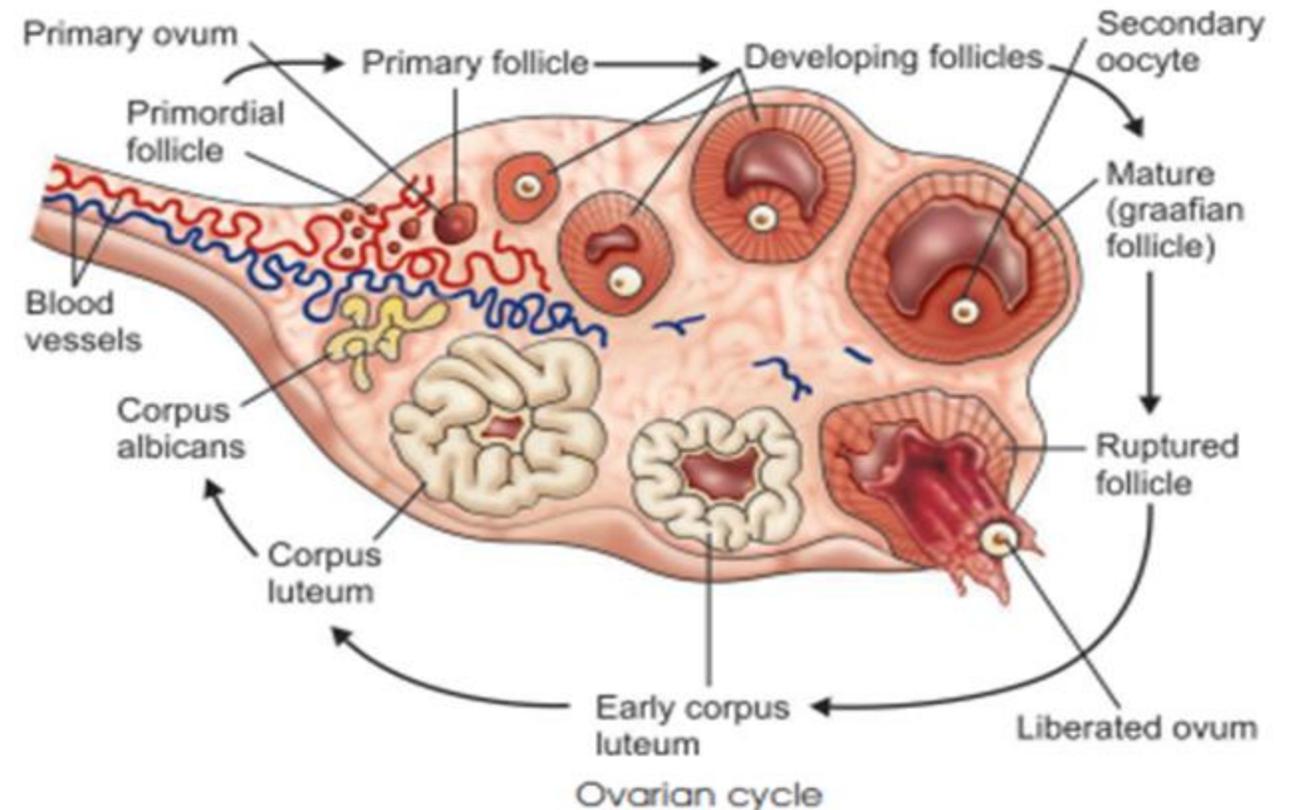
C. THE LUTEAL PHASE PT.2:

- ❖ As GnRH pulse frequency decreases, FSH and LH secretion also decreases.
- ❖ Lacking stimulation by FSH and LH, *after 14 days corpus luteum* undergoes atresia and begins evolving into the corpus albicans.
- ❖ With the decline of both estrogen and progesterone levels, an ***important negative feedback control*** on FSH is removed and FSH levels rise once again to initiate ***the next menstrual Cycle***.

FOLLICULAR DEVELOPMENT:

During embryogenesis, primordial germ cells develop from mesoderm in the allantois, migrate to the ovary, and then proliferate and differentiate into primordial follicles. Primordial follicles are **arrested in growth until menarche**, and some remain so until menopause. At the beginning of each menstrual cycle, **between 15 and 20 primordial follicles develop into primary follicles**. Under the influence of gonadotropins and ovarian hormones, primary follicles grow; ultimately, however, **only one primary follicle develops into a graafian follicle** and the remaining follicles undergo atresia.

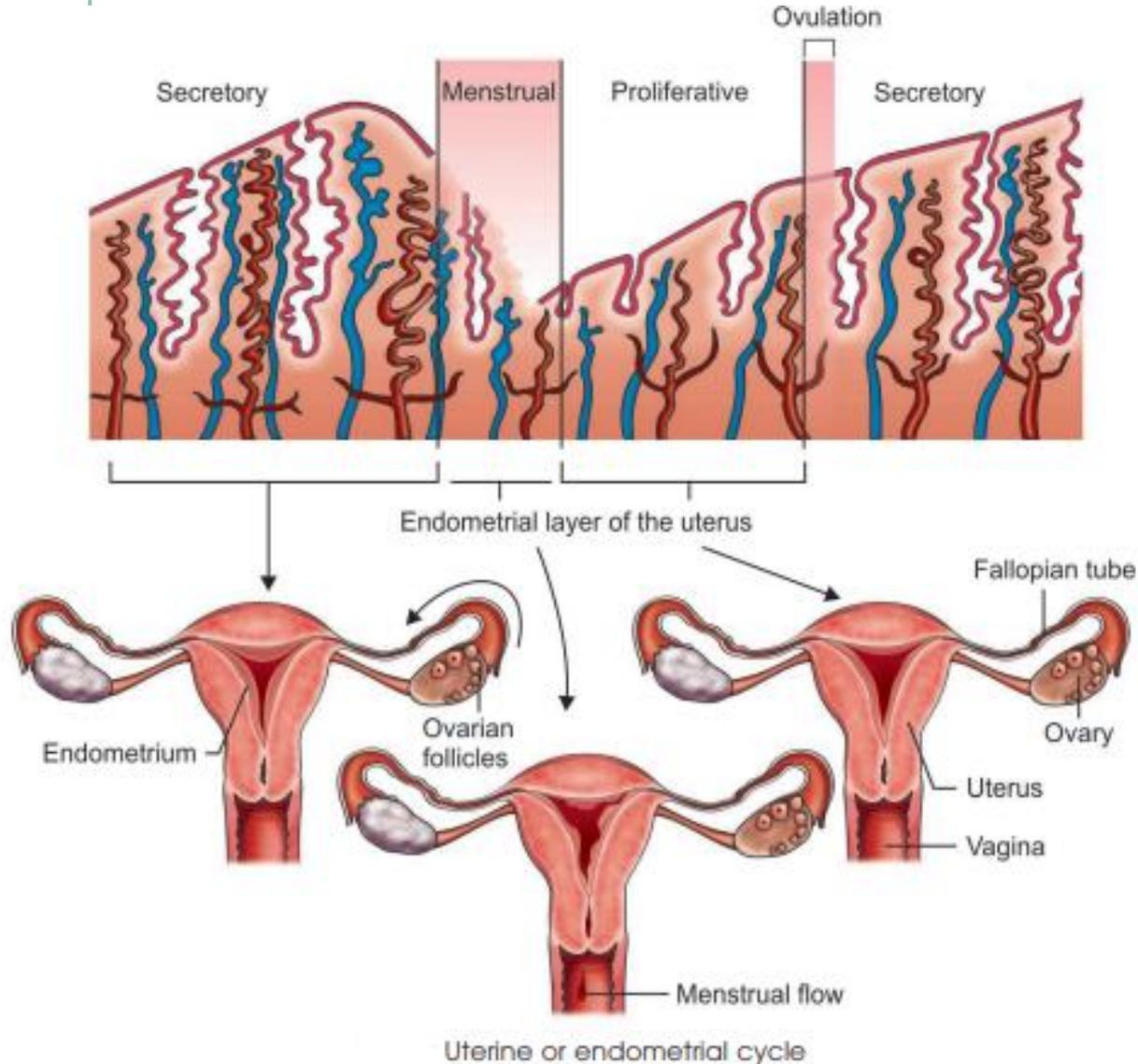
The graafian follicle **is ovulated**, expelling the oocyte and corona radiata into the peritoneum while the zona granulosa cells remain in the ovary. The zona granulosa and surrounding theca cells develop into the corpus luteum, **which in turn becomes atretic after 14 days**. After several months, the corpus luteum has fully devolved **into the corpus albicans**.



2) UTERINE OR ENDOMETRIAL CYCLE:

- ❑ Cyclical changes in the endometrium prepare for implantation in the event of fertilization and necessitate menstruation in the absence of fertilization.
- ❑ The endometrium is divided into two portions which are stratum functionalis and stratum basalis.
- ❑ The functionalis undergoes changes throughout the menstrual cycle and is shed during menstruation while the basalis remains constant during the menstrual cycle and regenerates the functionalis each month.

A. PROLIFERATIVE PHASE:



The proliferative phase, spans from the end of the menstruation until ovulation.

Increasing levels of estrogen induce proliferation of the functionalis from stem cells of the basalis, proliferation of endometrial glands, and proliferation of stromal connective tissue.

Endometrial glands are elongated with narrow lumens and their epithelial cells contain some glycogen.

Glycogen, however, *is not secreted* during the follicular phase.

Spiral arteries elongate and span the length of the endometrium

Uterus
Har-mid
Pwr 100 %
Gn -6
C7 / M5
E3
1 / CRI 3



1 D 1.18cm

B. SECRETORY PHASE:

- ❖ The luteal, or secretory phase, begins at ovulation and lasts until the menstrual phase of the next cycle.
- ❖ At the beginning of the secretory phase, **progesterone induces the endometrial glands to secrete glycogen, mucus, and other substances.** These glands become tortuous and have large lumens due to increased secretory activity.
- ❖ The spiral arteries extend into the superficial layer of the endometrium. ***In the absence of fertilization by day 23 of the menstrual cycle,*** the corpus luteum begins to degenerate and consequently ovarian hormone levels decrease.
- ❖ As estrogen and progesterone levels decrease, the endometrium undergoes involution. Days 25–26 of the menstrual cycle, **endothelin and thromboxin begin to mediate vasoconstriction of the spiral arteries.** The resulting ischemia ***may cause some early menstrual cramps.***
- ❖ By day 28 of the menstrual cycle, intense vasoconstriction and subsequent ischemia cause mass apoptosis of the functionalis.

CLINICAL ASPECTS AND MANAGEMENT OF MENSTRUATION

❖ Clinical Features: Menstruation is physiological function of body. Most women will have menstrual **bleeding for 3–5 days with no discomfort**. However around one-fourth women get menstrual discomforts, known as menstrual molimina. These discomforts do not interfere with usual day's activity and require no treatment. Only 5–10 percent develops during some part in their about 30 years menstrual life, painful mens interfering day's activities (dysmenorrhoea). The menstrual molimina are as follows:

1) SYMPTOMS

4) BLOOD LOSS

2) SIGNS

5) MANAGEMENT

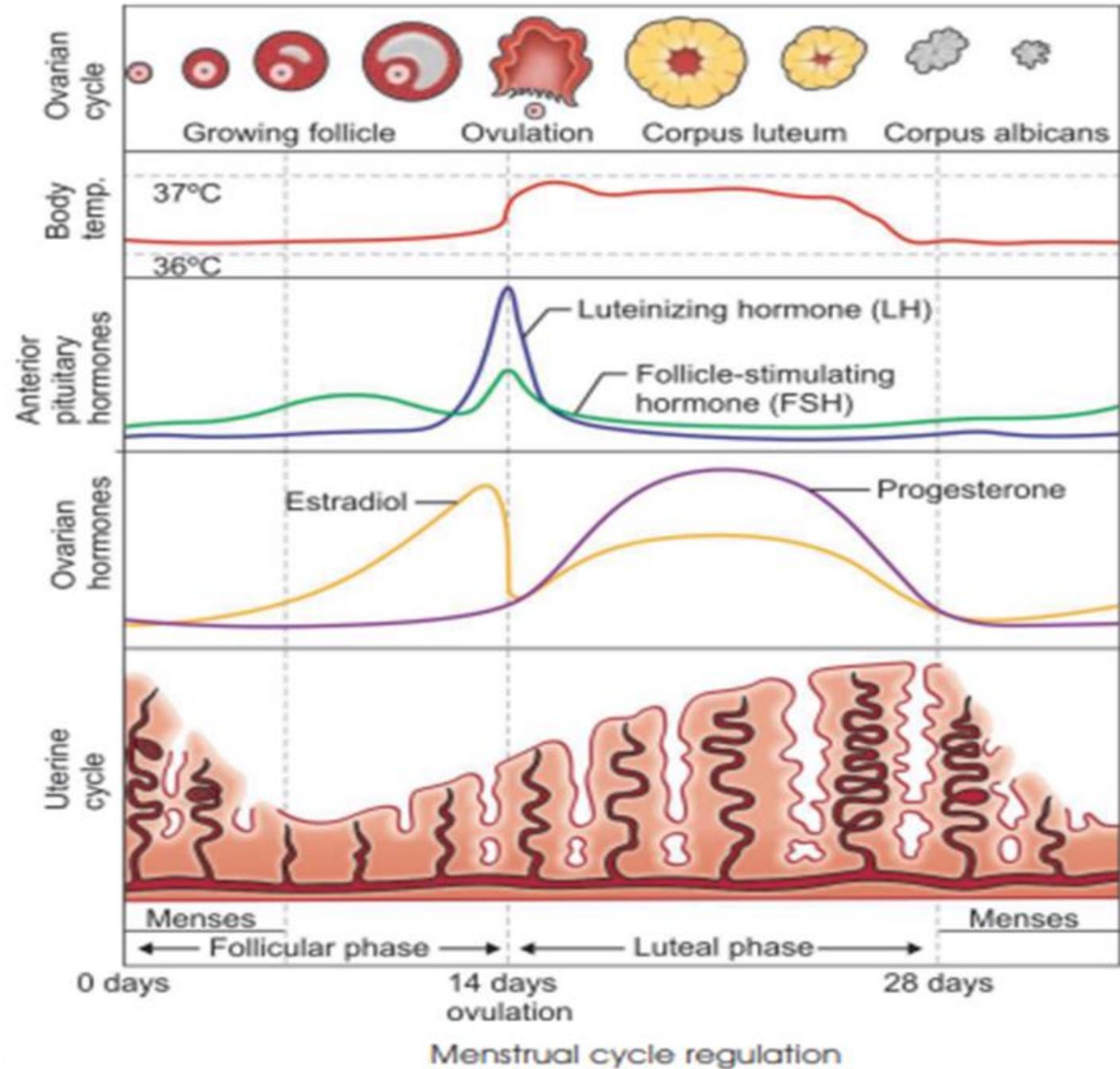
3) INTERVAL AND DURATION

6) POSTPONEMENT OR ADVANCEMENT OF MENSTRUATION

C. MENSTRUAL PHASE:

- The menstrual phase begins as the spiral arteries rupture secondary to ischemia, releasing blood into the uterus, and the apoptosed endometrium is sloughed off and usually lasts four days.
- During this period, the functionalis **is completely shed**.
- Arterial and venous blood, remnants of endometrial stroma and glands, leukocytes, and red blood cells are all present in the menstrual flow.

SUMMARY OF MENSTRUAL CYCLE REGULATION:



NEXT SLIDE

1. GnRH is secreted from the hypothalamus in pulsatile fashion and reaches to anterior pituitary through portal circulation.
2. Ovarian follicular development moves from a period of gonadotrophin independent to a phase of FSH dependence.
3. As the corpus luteum of previous cycle degenerates, luteal production of progesterone and inhibin decreases, allowing FSH level to rise.
4. In response to FSH stimulus, follicles grow and differentiate and secrete increasing amount of estrogen.
5. Estrogen stimulates growth and differentiation of functional layer of the endometrium, which prepares for implantation.
6. Two cell two Gonadotrophin theory dictates that with LH stimulation of the ovarian theca cells will produce androgens that are converted by the granulosa cells into estrogen under the stimulus of FSH.

7. Rising estrogen level negatively feedback on the pituitary gland and the hypothalamus and decrease the secretion of FSH.
8. The one follicle destined to ovulate each cycle is called the dominant follicle. It has relatively more FSH receptors and produce a large concentration of estrogens than the follicles that will undergo atresia. It is able to continue to grow despite falling FSH levels.
9. Sustained high estrogen level will cause a surge in pituitary LH secretion that triggers ovulation, progesterone production and the shift to the secretory or luteal phase.
10. Luteal function is dependent on the presence of LH. Without continued LH secretion, the corpus luteum will regress after 14 days.
11. If pregnancy occurs, trophoblast secretes hCG, which mimic the action of LH by sustaining the corpus luteum. The corpus luteum continue to secrete progesterone and the supports the secretory endometrium, allowing the pregnancy to continue to develop.

NORMAL LIMITS OF MENSTRUATION :

- The first menstruation (menarche) occurs between 10 and 16 years with a mean of 13 years.

Once menstruation starts, it continues

- Cyclically at intervals of 21–35 days with a mean of 28 days.
- Normal menstrual cycle is considered to be between 21 and 35 days long with any irregularity being *less than 7 days.*
- Duration of menstrual flow is normal between 2 and 7 days.
- Only 15% of women have a 28 day cycle.
- Length of the menstrual cycle is determined by the follicular phase.
- Luteal phase is fairly fixed at **14 days.**
- Normal menstrual loss is around 35 ml (20– 60 ml).
- Above 80 ml is considered *excessive.*

1) SYMPTOMS

1. Feeling of heaviness and discomfort in the pelvis, lower abdomen and in the back.
2. Feeling of pricking and fullness in the breasts.
3. Frequency of urination and constipation.
4. The Feeling of exhaustion, irritability, and headache. Above symptoms vary in severity from individual to individual. Rarely, bleeding from nose may occur as vicarious menstruation.

2) SIGNS

1. Sudden drop in temperature of about 1° but with individual variations.
2. Pulse rate and blood pressure tend to drop.
3. Gain in weight occurs during premenstrual fortnight up to about 1 kg due to retention of water and salt; it occurs in about half of women. There is loss of weight with the onset of flow.
4. Menstrual loss (mens). The vaginal menstrual bleeding mainly arterial, partly venous is a dark reddish liquid (not clotted) blood with shed endometrial tissue bits.

NOTE:

The discharge has disagreeable smell due to the secretion of vulvar sebaceous glands and decomposition of blood elements.

Menstrual blood is deficient in prothrombin, and fibrinogen but rich in calcium.

Microscopically, it contains red cells, large number of leucocytes, vaginal epithelium, cervical mucus, fragments of endometrium with macrophages, histiocytes, mast cells and bacteria, menstrual discharge also contains cholesterol, oestrogen, lipids and prostaglandins.

Menstrual blood from the endometrium clots in the uterine cavity by its thromboplastic property.

The clots are dissolved by the fibrinolysins released from the endometrium.

Fibrin degradation products therefore circulate in increased amount during menstruation.

In general menstrual blood does not clot.

Clots are passed when menstrual bleeding becomes excessive.

3) INTERVAL & DURATION

The menstrual cycle lasts on an average 28 days.

A deviation of 2 to 3 days can be frequently encountered. The extremes of 21 and 35 days interval may also be found. In any woman's menstrual life, the interval can vary. The usual duration is 3 to 5 days with essentially normal extremes of 2 and 7 days.

4) BLOOD LOSS

The average total blood loss during menstruation has been estimated as 35 ml (range 5–60 ml); average loss of iron was found as 12 mg.

A rough clinical estimate is that normally not more *than three fresh pads are necessary in the 24 hours*, two during the day and one at night, thus requiring total 12–15 pads during a mens. This loss widely varies and becomes *greater in women living in warm climate than those living in cold climate*.

5) MANAGEMENT :

- Proper education on menstruation is important.
- Women should be educated that menstruation is not the drainage of toxic blood from the body but a normal manifestation of womanhood.
- During menses, **she should carry on her usual activities** including daily bathing, playing games. Personal hygiene is maintained by changing regularly sanitary pads.
- Intravaginal tampons can be used by the married provided she does not forget to leave it behind.
- Healthy couple **can have** sexual intercourse during menses.

6) POSTPONEMENT OR ADVANCEMENT OF MENSTRUATION :

This becomes at times necessary for important social reason like marriage.

○ This is not to be advocated on fragile ground. The hormone therapy employed is the following:

1. Progesterone—Norethisterone one tab **thrice daily** starting from 20th day of menstrual cycle till beyond the date of postponement.

2. Oestrogen progestogen contraceptive pills, two a day is started from the 20th day.

Menstrual flow is expected 2 to 3 days after the treatment is suspended. Menstruation can be prematurely brought by starting hormone therapy from 5th day of mens for 14 days, The therapy is:

(a) oestrogen ethinyl oestradiol 0.05 mg tds

(b) oestrogen progestogen oral pill once daily. Anovular menstrual flow is likely to begin within 2–3 days of the cessation of therapy.

THANK YOU FOR YOUR ATTENTION
GOOD LUCK