

# The Menstrual Cycle

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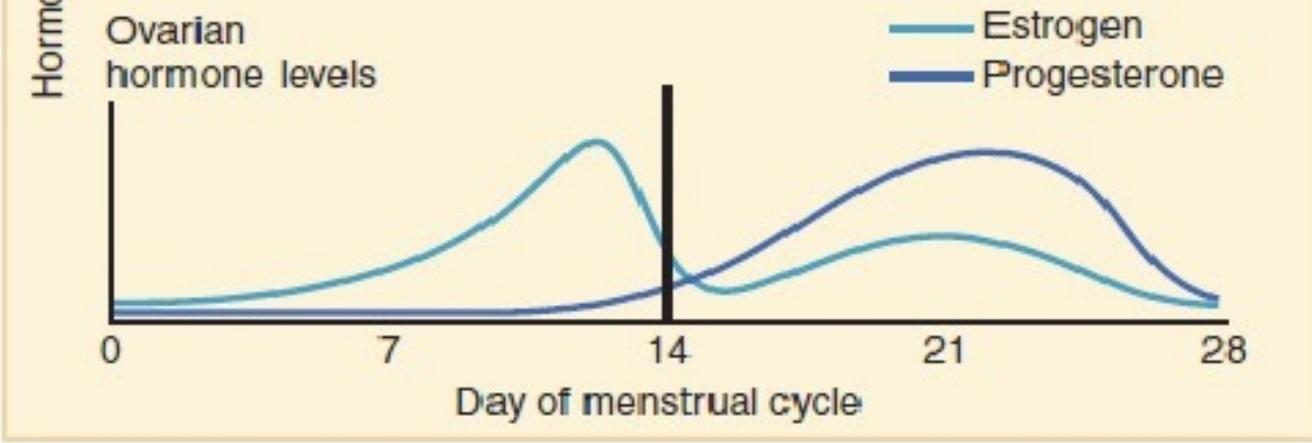
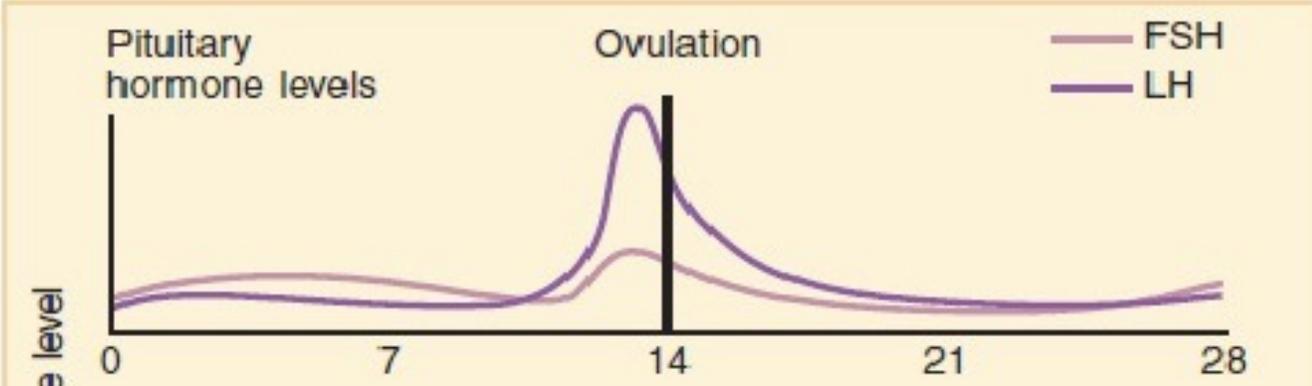
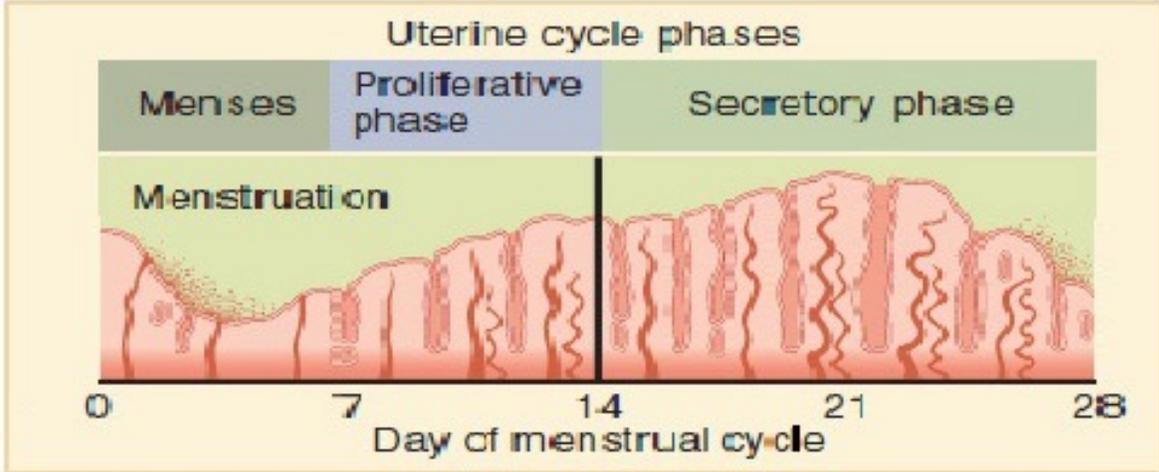
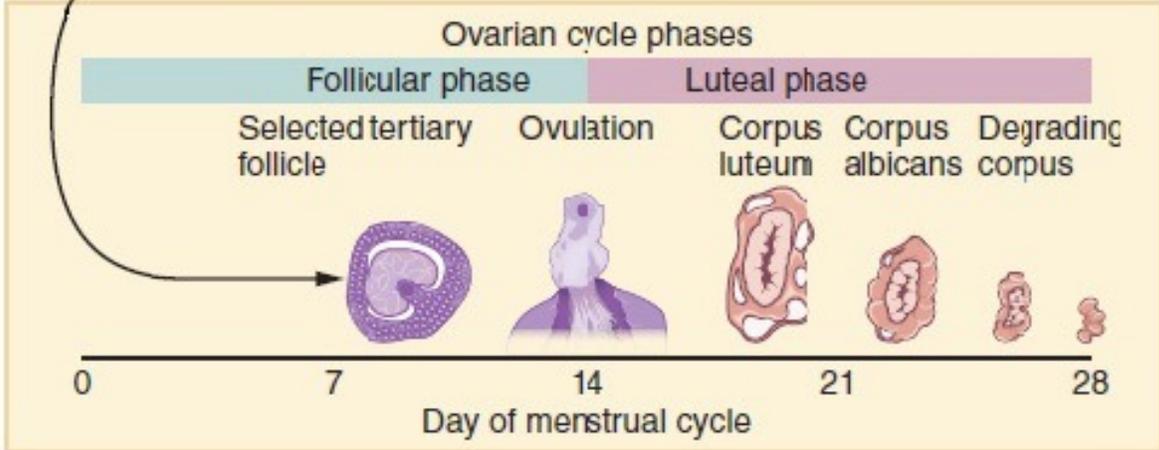
## Female Reproductive Physiology

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# Seven stages of a woman's life

1. Fetal period
2. Neonatal period
3. Childhood
- 4. Puberty or adolescence**
- 5. Sexual maturity**
- 6. Menopausal transition period**
7. Postmenopausal period



# Normal Menstrual Cycle

The normal human menstrual cycle can be divided  
(based on the organ ):

**The ovarian cycle** may be further divided into :

The follicular phase, ovulation, and the luteal phase

**The uterine cycle** is divided into :

Menstruation, proliferative and secretory phase

# OUTLINE

**I. Ovarian Cycle**

**II. Ovarian Steroidogenesis**

**III. Uterine Cycle**

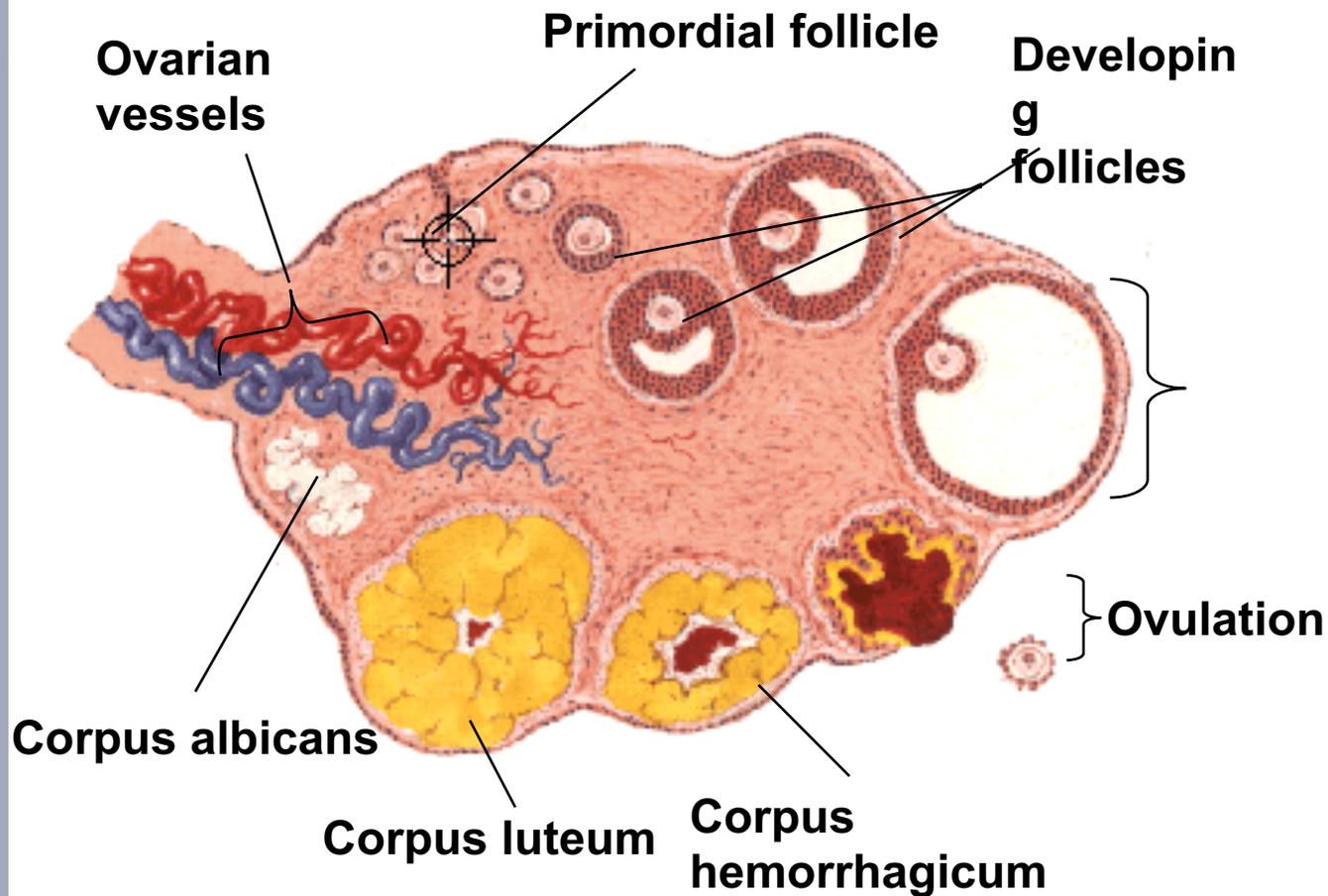
**IV. The Hormones Change During Menstrual Cycle**

# Ovarian Cycle

## Key points

- Follicular Phase:  
the Development Of Oocyte And Follicle
- Ovulation
- Luteal Phase

# Oocyte and Follicle Development



- From the time of birth, there are many primordial follicles under ovarian capsule.
- Each follicle contains an immature oocyte.

# The Development of Oocyte the Meiosis

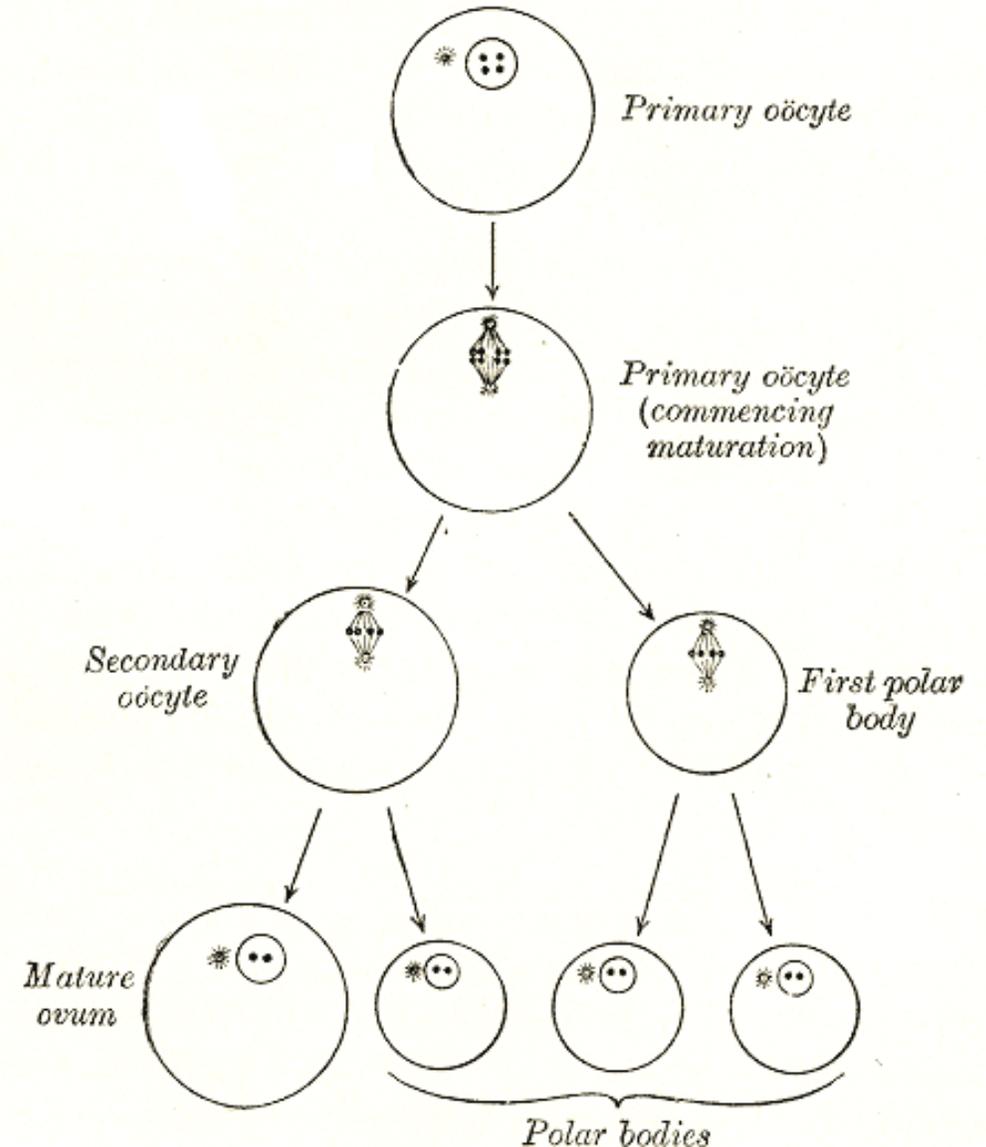
- Only those oogonia that enter meiosis will survive the atresia before birth.
- When the developing oogonia begin to enter meiotic prophase I, they are known as **primary oocyte**.
- This process begins at around 8 weeks of gestation.

# The Development of Oocyte

- The oocytes arrested in prophase ( at diplotene stage ) will remain until the time of ovulation. At ovulation, the process of meiosis resumes.
- At the diplotene stage, a single layer of 8 to 10 granulosa cells surround the oogonia to form the primordial follicles. These follicles each contain **an immature primary oocyte.**

# The development of secondary oocyte

- After the first meiotic division at ovulation, the meiosis will resume, and the oocyte is called the **secondary oocyte**.
- The secondary oocyte immediately begins the second meiotic division.
- But this division stops at metaphase and is completed only when a sperm penetrates the oocyte.

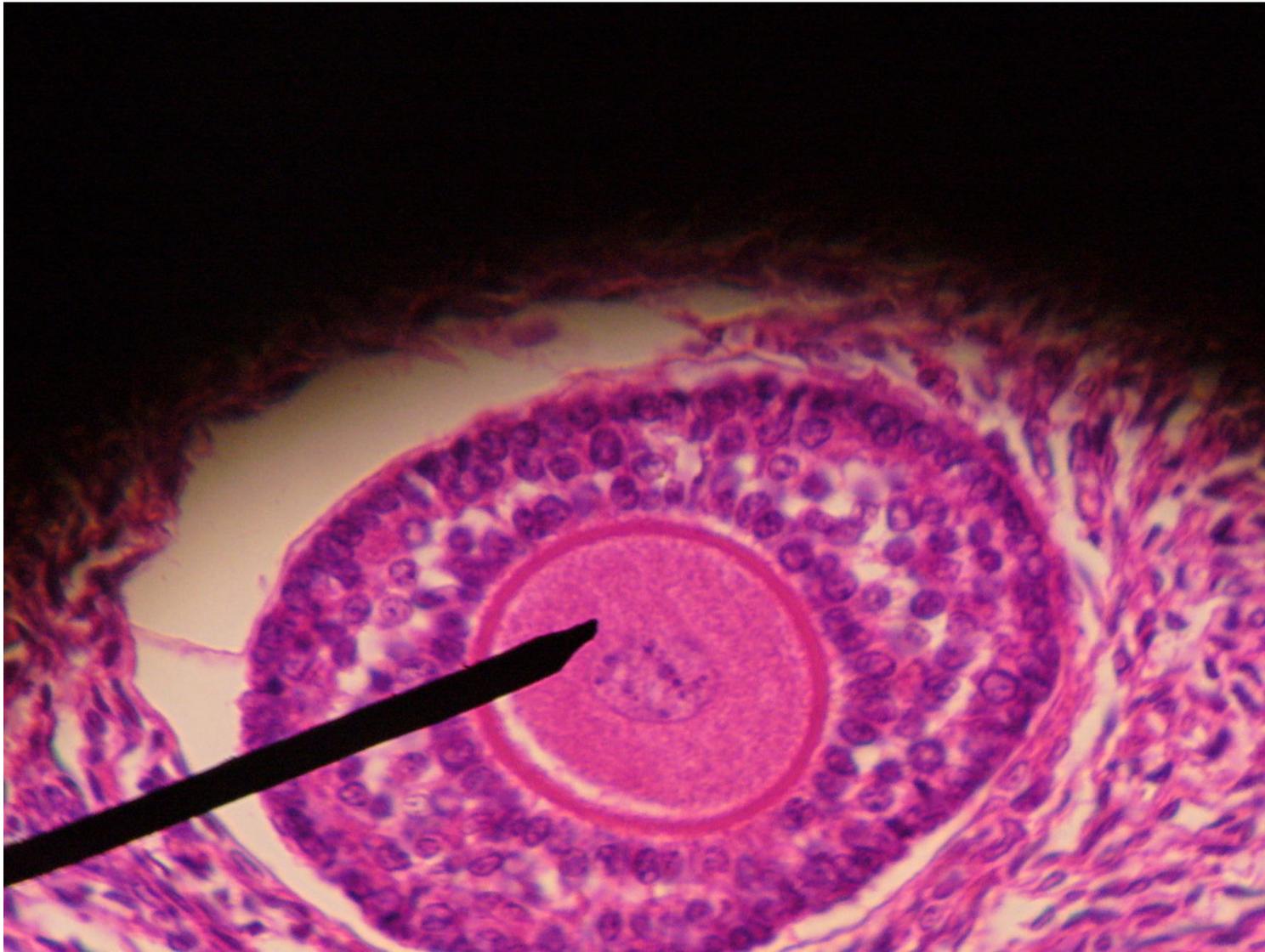


# The Development of Primordial Follicle

- When oocyte stays at diplotene stage, a single layer of 8-10 granulosa cells surround the oocyte to form the **primordial follicle**.
- The initial growth stage is **gonadotropin independent**.

# Recruitment and Growth of Primordial Follicle

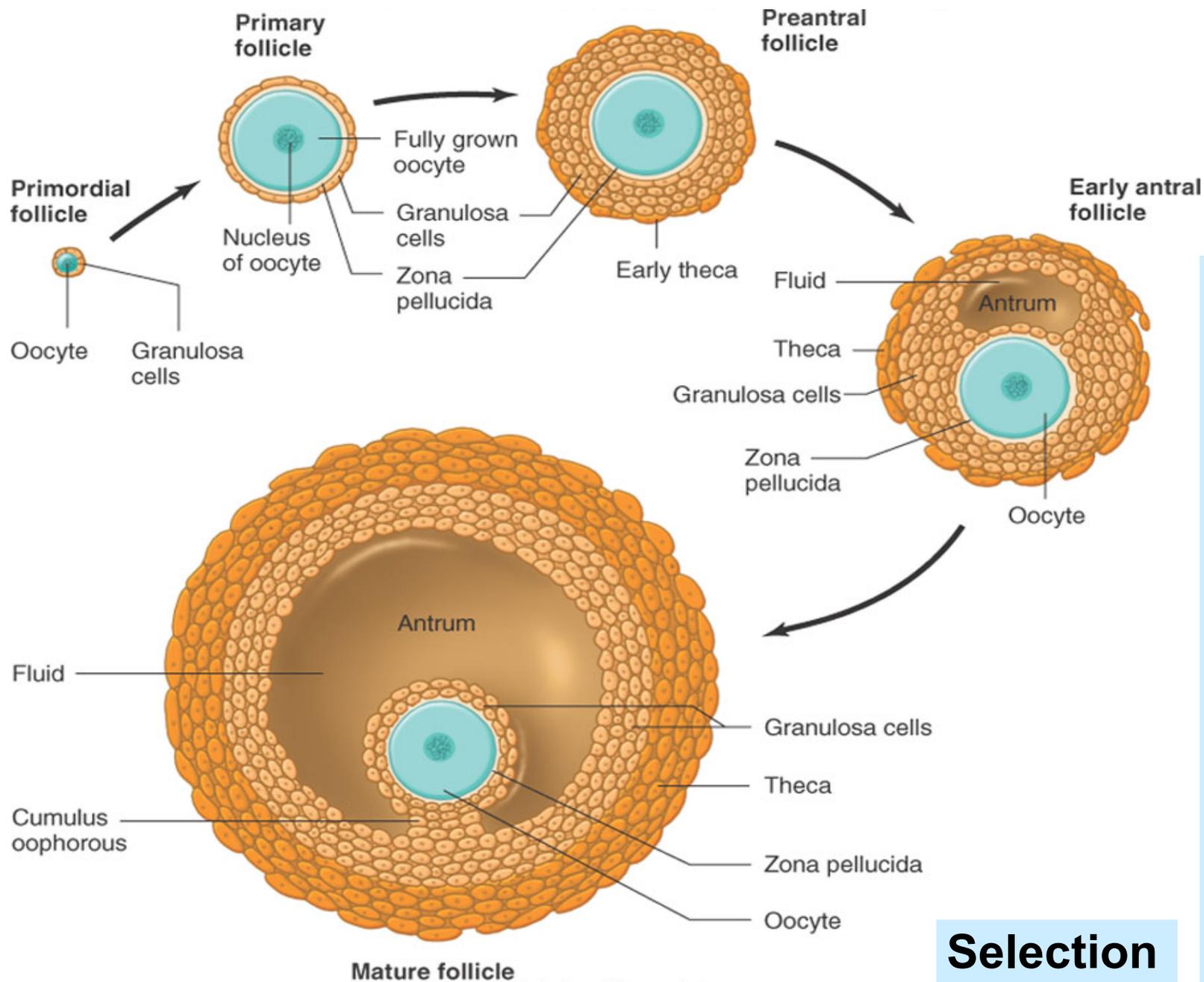
- Shortly after initial recruitment, FSH regulates follicles differentiation and growth.
- Follicular development shifts from gonadotropin independent to dependent stage.
- The first changes are growth of the oocyte and expansion of the single layer of follicular granulosa cells into a multilayer of granulosa cells.



A histological slide of a human primary ovarian follicle in greater magnification

# Preantral Follicle-selection

- The enlarging oocyte secretes----**the zona pellucida** (a glycoprotein-rich substance), which separates oocyte from the surrounding granulosa cells
- At this stage, each cohort members must either be **selected for dominance or undergo atresia.**



Adapted from Erickson et al.

Stage: gonadotropin independent to dependent growth  
 The first changes are growth of the oocyte and expansion of the single layer of follicular granulosa cells into a multilayer of granulosa cells.

**The enlarging oocyte secretes the zona pellucida to separate oocyte from the surrounding granulosa cells**

At this stage, each cohort members must either be selected for dominance or undergo atresia.<sup>15</sup>

**Selection**

# Preovulatory Follicle (Matured Follicle)

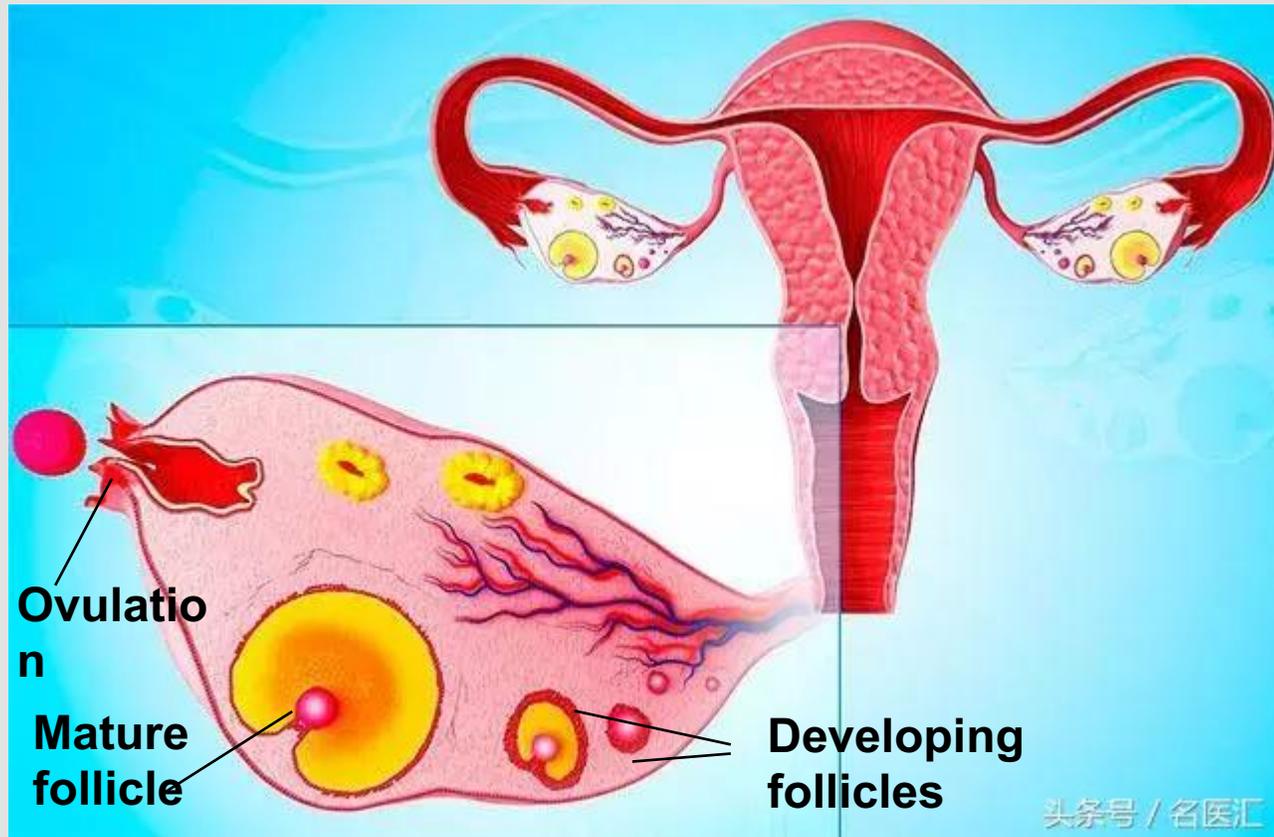
- Characterized by **antrum filled with follicular fluid.**  
The follicular fluid is composed of plasma with granulosa cells secretions.
- The oocyte remains connected to the follicle by a stalk of specialized granulosa known as the **cumulus oophorus.**
- The fully mature follicle is 1.8cm in diameter.

# Preovulatory Follicle (Matured Follicle)

- Once the rising estrogen level produce positive feedback, a substantial surge of LH occurs.
- Exposure to high level of LH results in a specific response by the dominant follicle—the result is **luteinization of the granulosa cells, production of progesterone, and initiation of ovulation.**
- Ovulation will occur in the single mature **follicle 10 to 12 hours after the LH peak or 34 to 36 hours after the initial rise of LH.**

# The Process of Ovulation

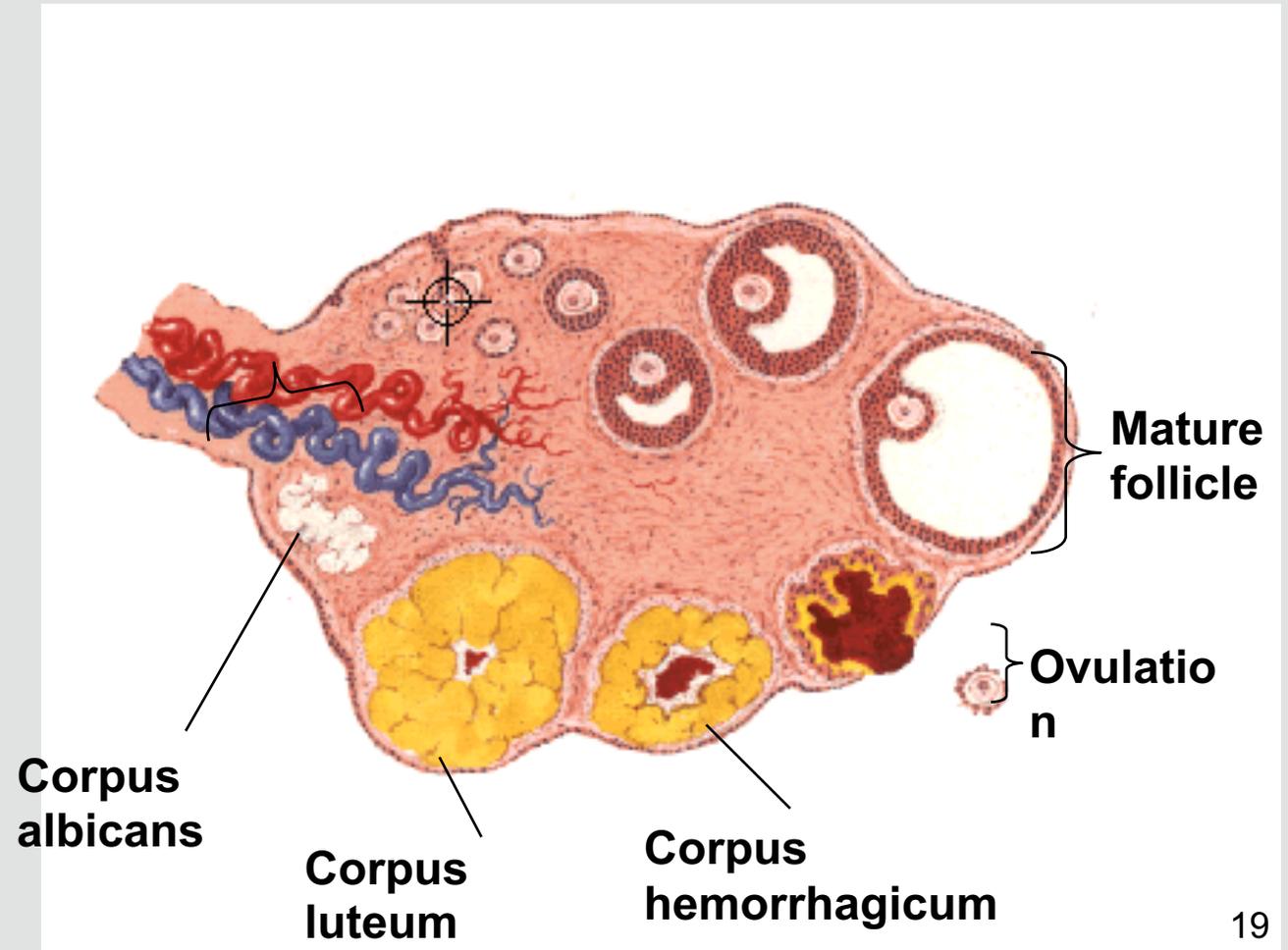
Ovulation in a woman who has a normal 28-day cycle occurs 14 days after the onset of menstruation.



- Outer wall of the follicle swells rapidly
- Wall of the follicle ruptures
- Follicular fluid flows out
- Viscous fluid carries ovum and granulosa cells (*corona radiata*) into abdominal cavity
- swept into the fallopian tube by the fimbria

# Luteal Phase

- After ovulation, the remaining follicular shell forms ----- **corpus luteum**
- Membranous granulosa cells in the follicle take up lipids and the yellow lutein pigment ----- the structure is named



# Luteal Phase

- Granulosa cells produce progesterone, which converts and supports the endometrium into secretory phase during the luteal phase.
- In addition, estrogen is also produced in significant quantities and affects the endometrium with progesterone.

- Continued corpus luteum function depends on continued LH production.
- If pregnancy occurs, placental hCG will mimic LH action and stimulate corpus luteum to secrete progesterone.
- If the absence of implantation occurs, the corpus luteum begins to regress at 6-7 days after ovulation, and estrogen and progesterone levels decrease, then the layer of endometrium is shed, and menstrual bleeding starts again.

# Ovarian sex hormones

## Two classes of ovarian sex hormones:

- Estrogens and progestins
- The most important of the estrogens is **estradiol**
- The most important progestin is **progesterone**

## Estrogens:

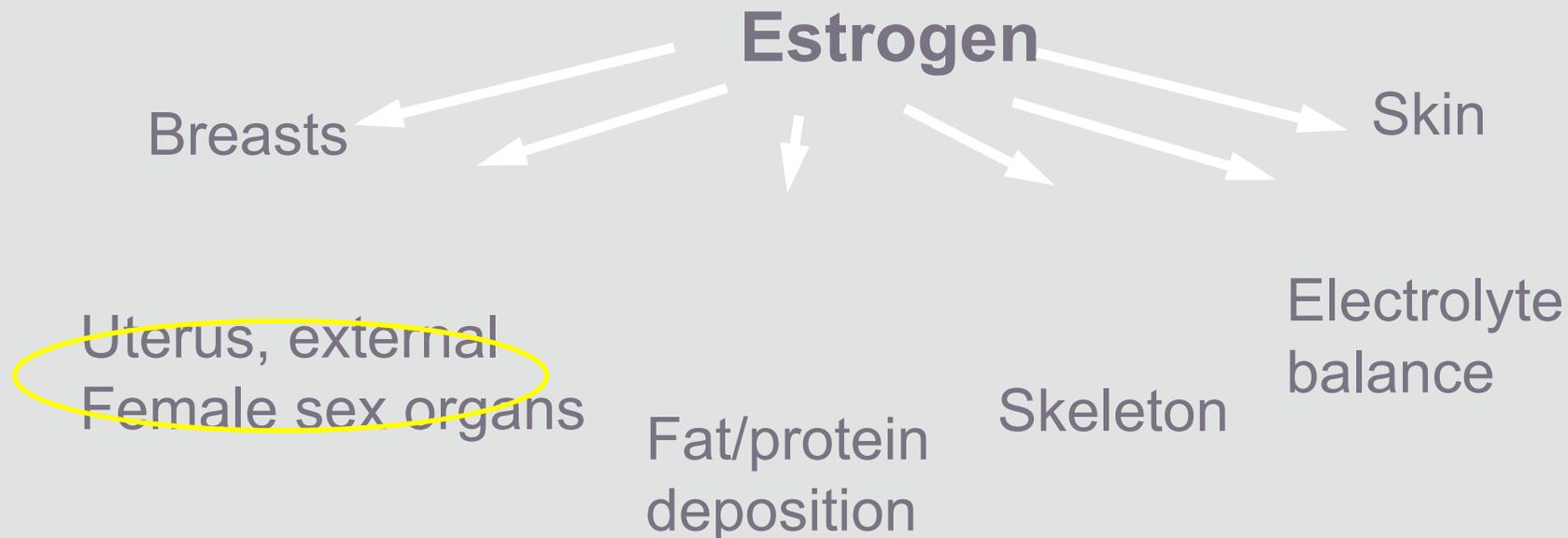
Promote proliferation and growth of sex related cells; **cause secondary sexual characteristics**

## Progestins:

Important for preparation of the uterus for **pregnancy** and the breast for **lactation**

# 1) Effects of Estrogens on Primary and Secondary Female Sexual Characteristics

**Principal Function:** cellular proliferation; growth of the tissues of sexual organs; growth of other tissues related to reproduction



## 2) Estrogen effects on the Uterus & External Female Sex Organs

- **Tissue enlargement:** fallopian tubes, uterus, vagina, and all external genitalia
- **Vaginal epithelium:** Cuboidal into stratified type; increase resistance to trauma and infection
- **Facilitate transport of fertilized ovum toward uterus:** Increase fallopian cilia number tubelocking
- **Proliferate endometrial glands in fallopian tubes and uterus:** Nourish implanting ovum

# Estrogen effects on:



## **Breast**

- development of ductile system, stroma tissues & fat deposition □ mature female breast

## **Fat/Protein deposition**

- fat deposition in subcutaneous & breast tissues; broadening of thighs/ buttocks
- protein deposition in sexual organs, bones; slight increase in total body protein

## **Skeleton**

- Increase osteoblastic activity, growth plate unit
- Post menopause: decrease osteoblast activity, bone matrix, Ca/P deposits

## **Electrolyte Balance**

- Increase sodium & water retention – effect is greater during pregnancy

## **Skin**

- Development of thick, soft & smooth skin texture
- Vascularization, increase bleeding

# Functions of Progesterone

- **Uterus**

Promotes secretory changes in uterine endometrium

Decreases uterus contraction

- **Fallopian tubes**

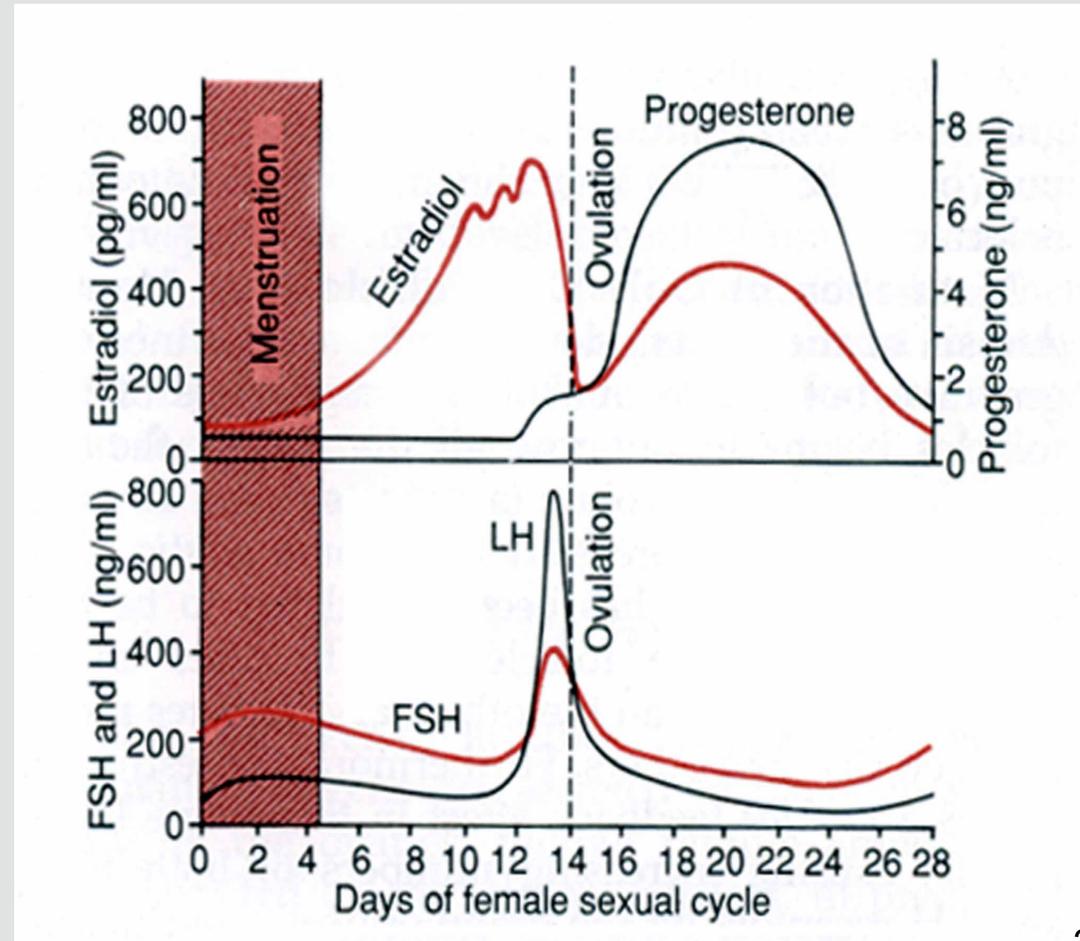
Promotes secretory changes in mucosal lining

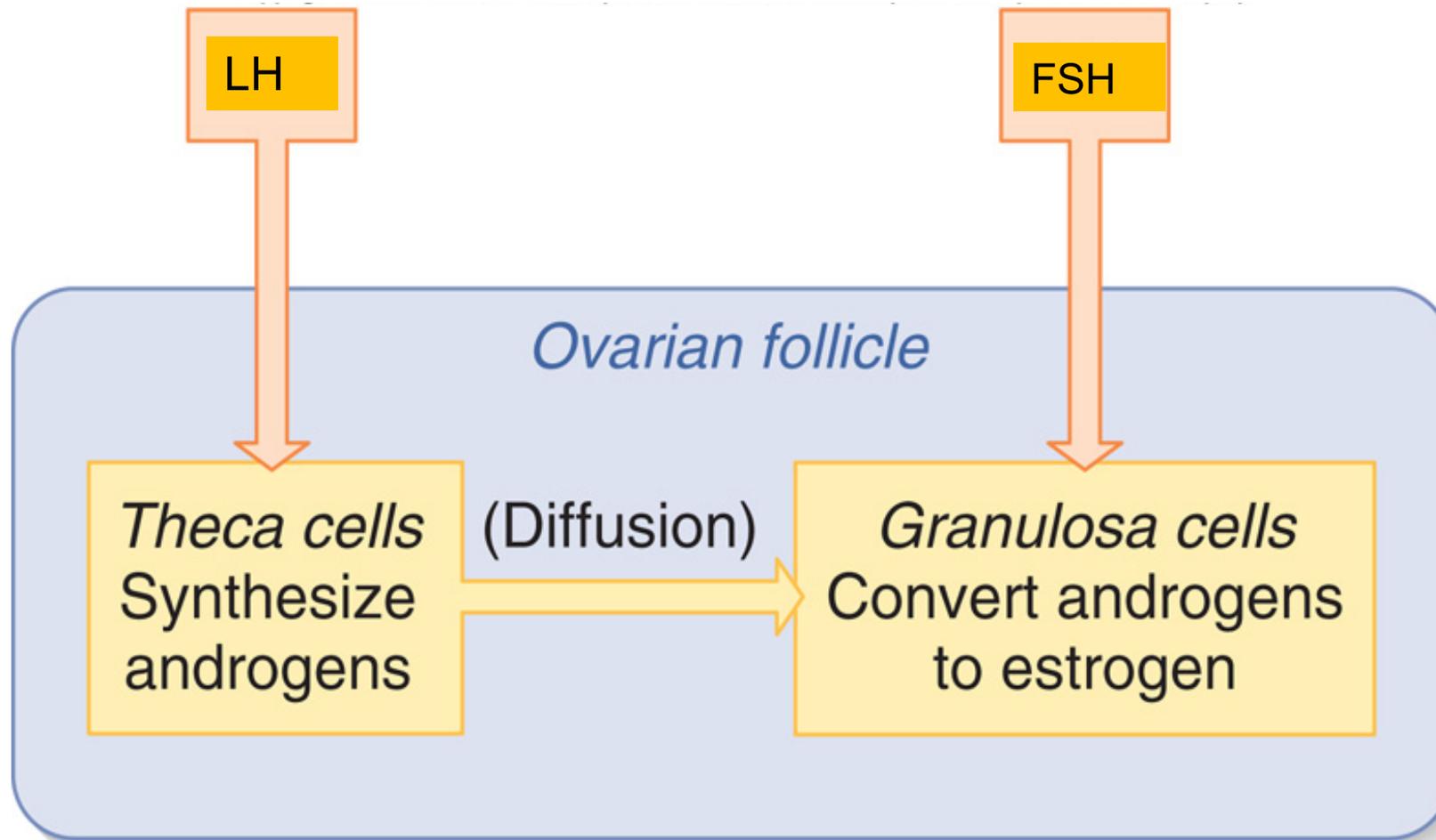
- **Breasts**

Promotes development of lobules, alveoli of breasts:  
alveolar cells proliferate, enlarge, and become secretory

# Ovarian hormones-estrogen

- There are 2 peaks of estradiol secretion: one just before ovulation and one during the midluteal phase.
- The first is secreted by dominant follicle just before ovulation, while the second is secreted by corpus luteum.





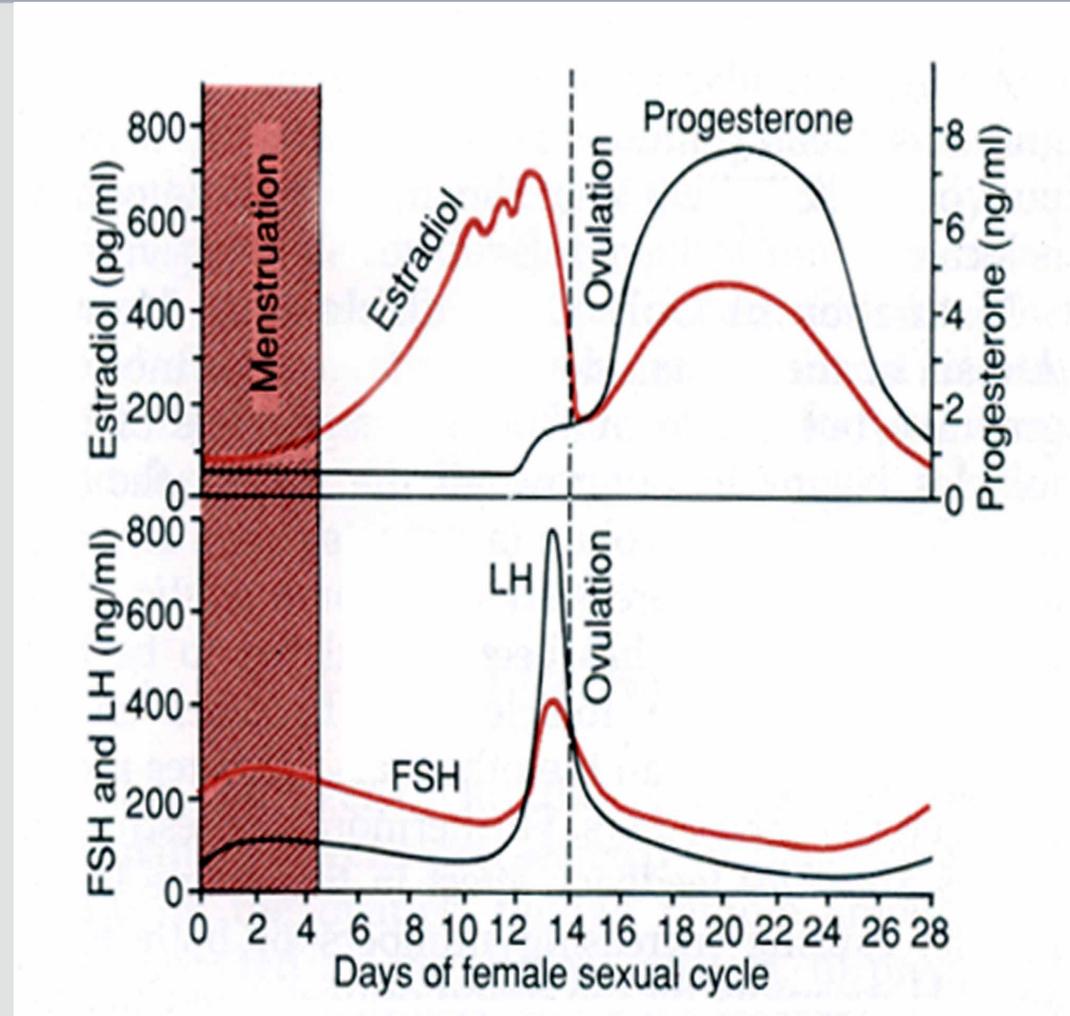
### **Two-cell Two-gonadotropin Theory**

The two-stage model of estrogen synthesis holds that androgen precursors are synthesized in the outer layer (theca cells) of the ovarian follicles and diffuse to the inner layer (granulosa cells) for conversion to estrogens; LH drives the former, FSH the latter.

# Ovarian Hormones

## Progesterone

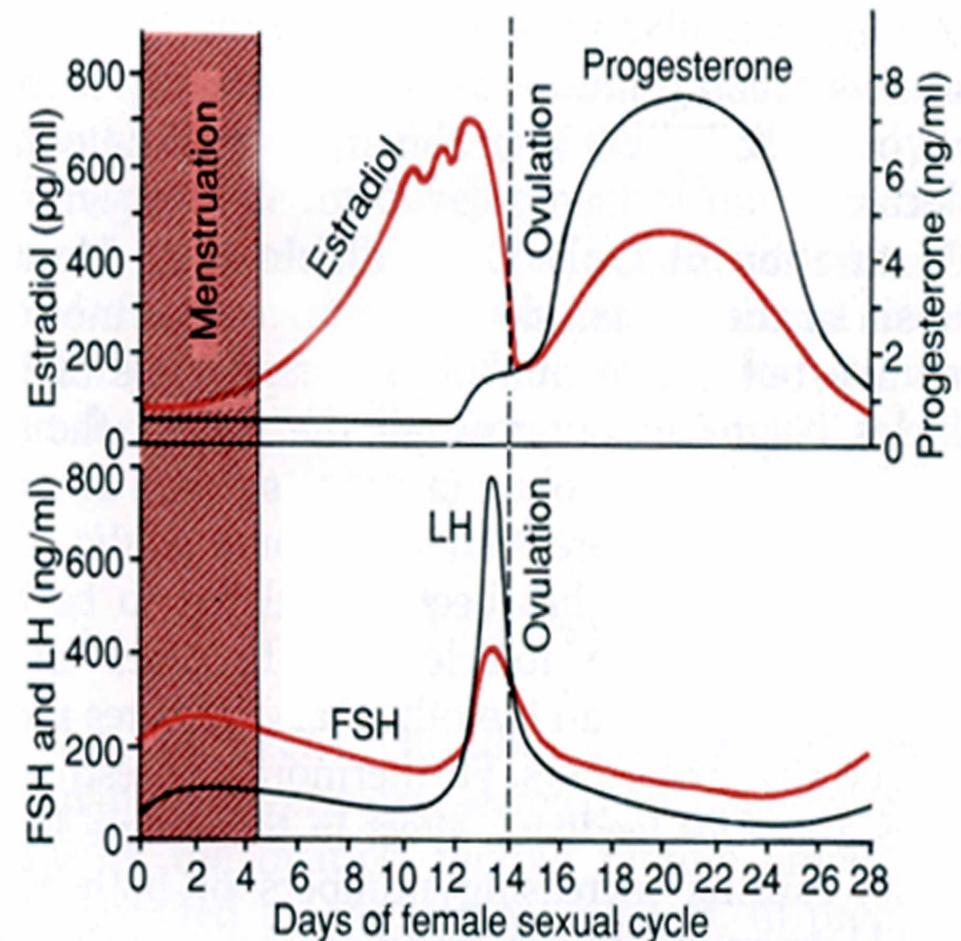
In women, the plasma progesterone level is low during follicular phase of menstrual cycle.



# Ovarian Hormones

## Progesterone

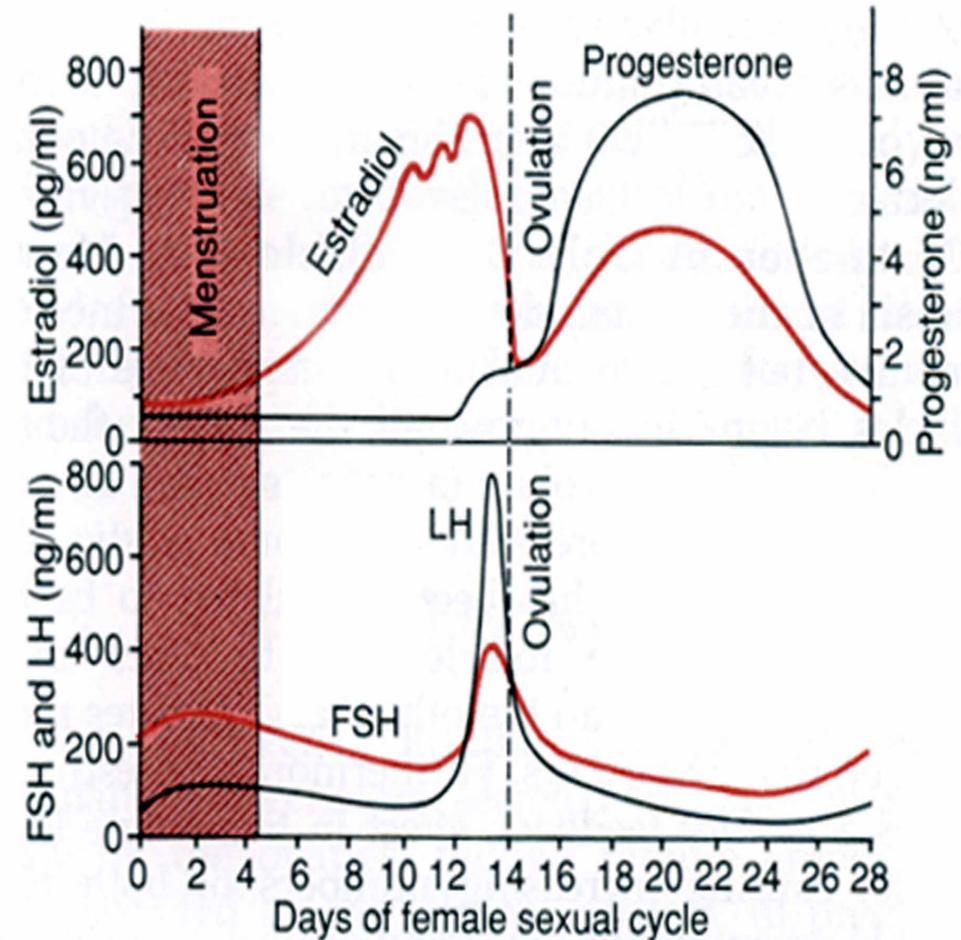
During the luteal phase, the large amounts of progesterone secreted by the corpus luteal. And the level reaches the top at the midluteal phase.



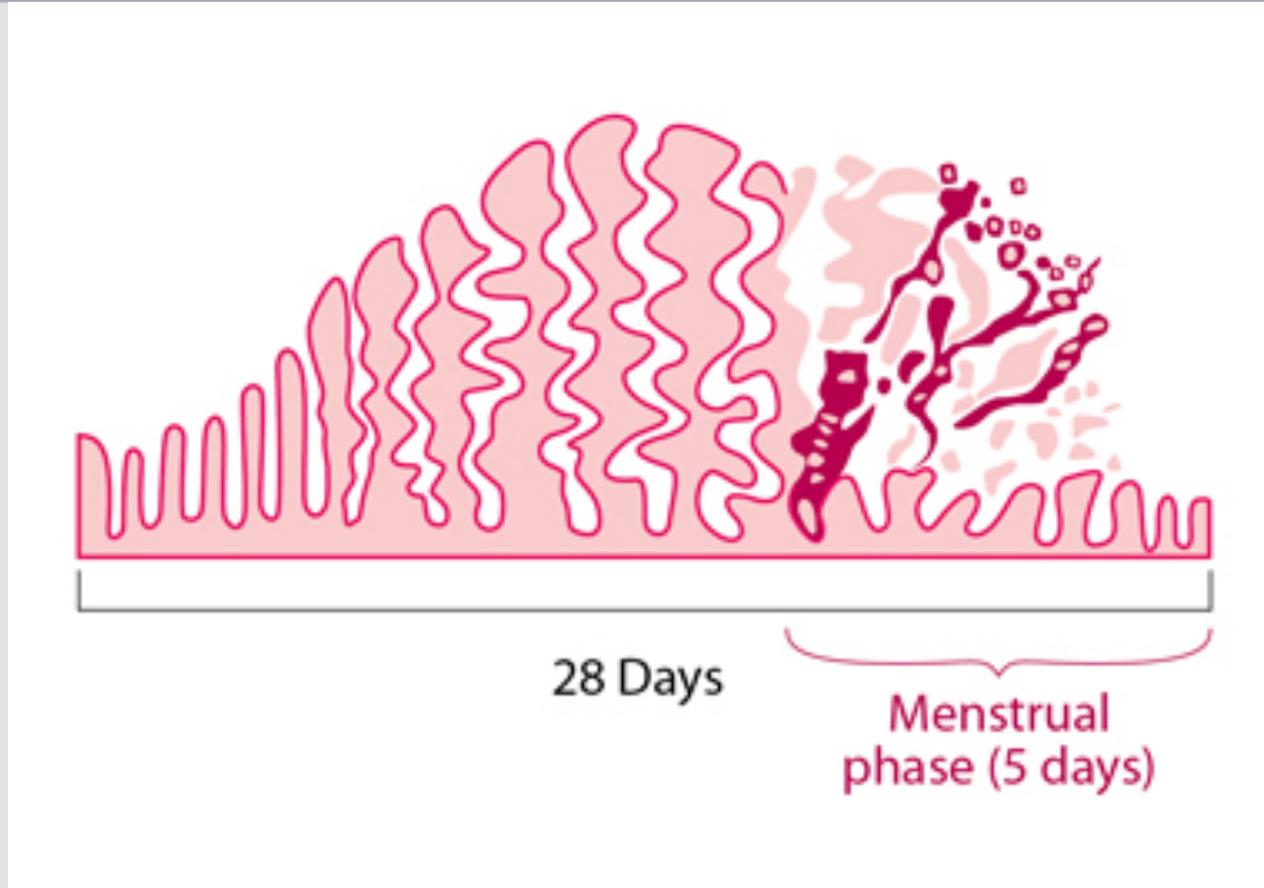
# Ovarian Hormones

## Progesterone

If no pregnancy occurs, the corpus luteal demises and stops producing estrogen and progesterone. The resulting loss of progesterone and estrogen secretion results in menstruation. Another menstrual cycle begins.



# Uterine Cycle

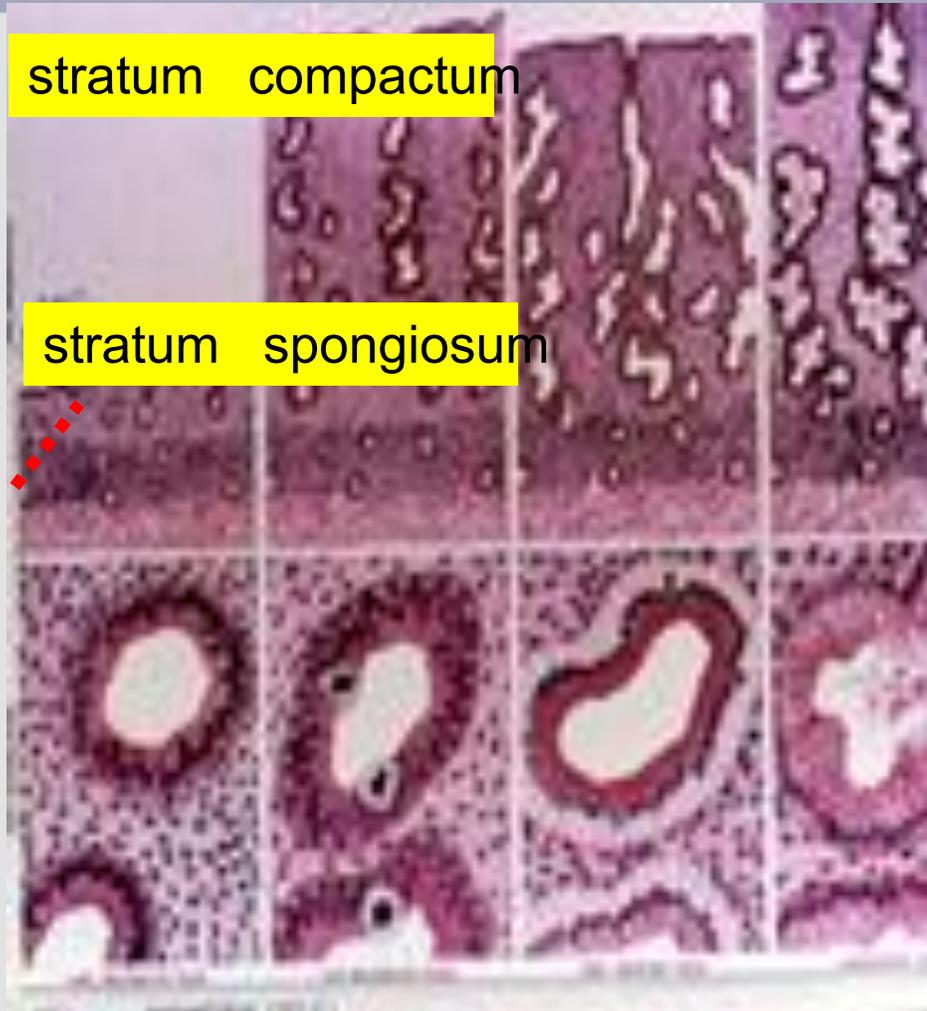


Cyclic changes of the endometrium

# Cyclic Changes of the Endometrium

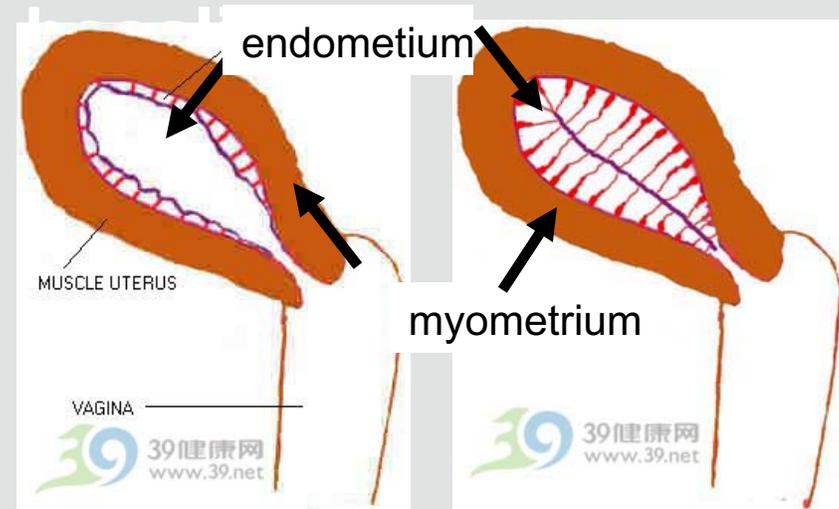
- **Decidua functionalis**: cycling portion of the endometrium and is composed of a deeply situated intermediate zone (stratum spongiosum) and a superficial compact zone (stratum compactum).
- **Decidua basalis** : deepest region of the endometrium. It does not undergo significant monthly proliferation, but, instead, is the source of endometrial regeneration after menses.

# Histologic Changes of Endometrium



decidua  
functionalis

decidua



# Proliferative Phase

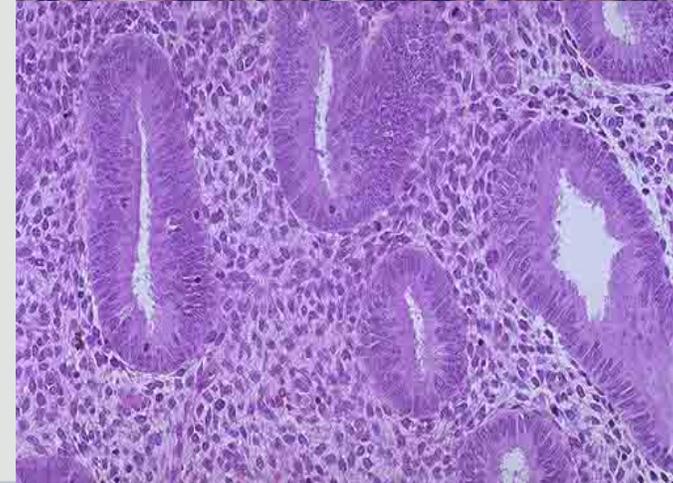
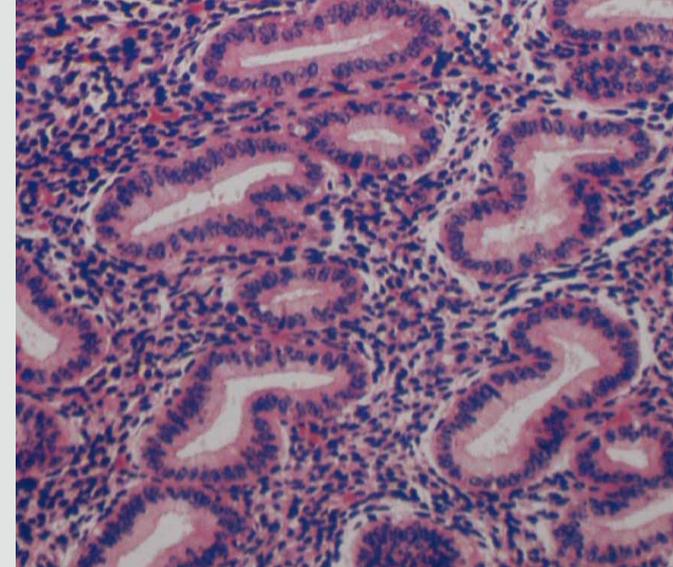
- The first day of vaginal bleeding is called day 1 of menstrual cycle.
- After menses, the decidua basalis is composed of primordial glands.
- The Proliferative Phase is characterized by progressive mitotic growth of the decidua functionalis in response to estrogen.

# Proliferative Phase

- At the beginning of the proliferative phase, the endometrium is thin, about 1-2mm.
- The predominant change during this time is evolution of the initially straight, narrow, and short endometrial glands into longer, tortuous structures.

# Proliferative Phase

- The proliferating glands have multiple mitotic cells, and their organization changes from a low columnar pattern in the early proliferative period to a pseudostratified pattern before ovulation.
- Throughout this time, the stroma is a dense compact layer, and vascular structures are rare.

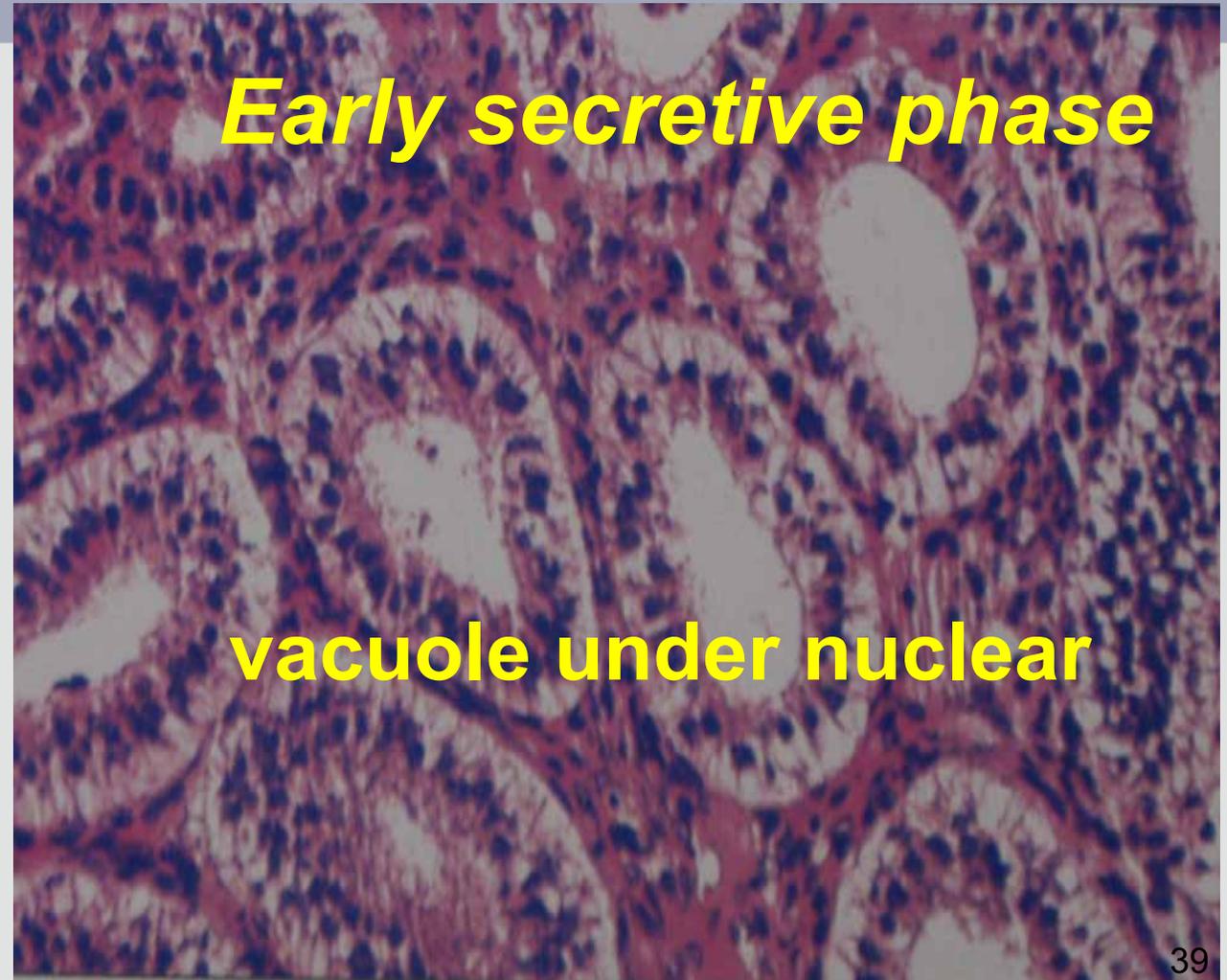


# Secretory Phase

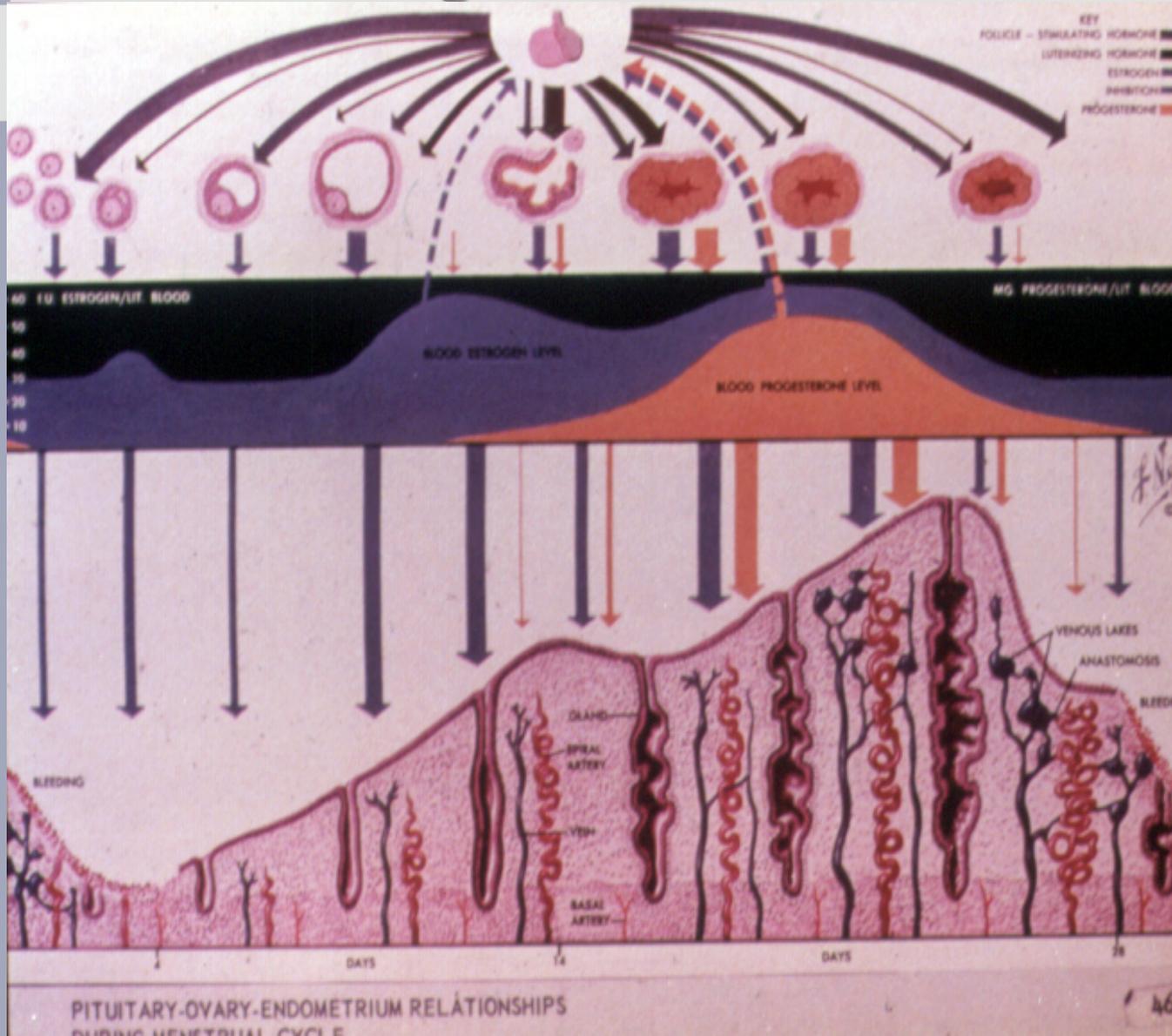
- After ovulation , the onset of progesterone secretion produces a great shift of histologic appearance of the endometrium to the secretory phase.
- In contrast to the proliferative phase, the secretory phase of the menstrual cycle is characterized by the cellular effects of progesterone in addition to estrogen.

# Secretory Phase-gland

During the secretory phase,  
the endometrial glands  
form characteristic  
vacuoles.



# Secretory Phase-stroma



In late secretory phase, the spiral arteries become clearly visible and then progressively lengthen and coil during the remainder of the secretory phase.

# Secretory Phase-stroma

- Approximately 2 days before menses, there is a dramatic **increase of lymphocytes** that migrate from the vascular system.
- This **leukocytic infiltration** heralds the collapse of the endometrial stroma and the onset of the menstrual flow.

# Menstruation

- In the absence of implantation, glandular secretion ceases, and an irregular break-down of the decidua funtionalis occurs.
- The shedding of endometrium
- Menstrual blood mainly comes from artery.
- Contains tissue debris, prostaglandins, fibrinolysin
- The degeneration of the corpus luteum and withdrawal of estrogen and progesterone is the cause of the shedding.
- The source of subsequent endometrial growth is decidua basalis.

# Menstruation

- Usually lasts for 2 to 8 days, average 2 to 7 days
- The average blood loss is 35 milliliters ( 20–60 ml )
- Menorrhagia ( abnormal uterine bleeding ) : total menstrual flow >80ml per cycle
- Why does Menstrual blood not coagulate?

# Female Hormone System (H-P-O axis)

## 1) **Hypothalamus:**

Gonadotropin-releasing hormone (GnRH)

## 2) **Anterior pituitary:**

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH)

## 3) **Ovary:**

Estrogens and progesterone

# Hypothalamus and Its Hormones

- The hypothalamus is a small neural structure situated at the base of the brain. It is connected directly to the pituitary gland.
- The major secretory products of the hypothalamus are the pituitary-releasing factors.
- Gonadotropin-releasing hormone (GnRH), which controls the secretion of Luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

# Endocrine Glands in the Human and Their Hormones

## Hypothalamus

Thyrotropin-releasing hormone  
Dopamine  
Growth hormone-releasing hormone  
Somatostatin  
**Gonadotropin-releasing hormone**  
Corticotropin-releasing hormone  
Oxytocin  
Vasopressin

## Thyroid

Triiodothyronine  
Thyroxine

## Pineal gland

Melatonin

## Pituitary Gland

### Anterior pituitary

Growth hormone  
Thyroid-stimulating hormone  
Adrenocorticotrophic hormone

**Follicle-stimulating hormone**  
**Luteinizing hormone**

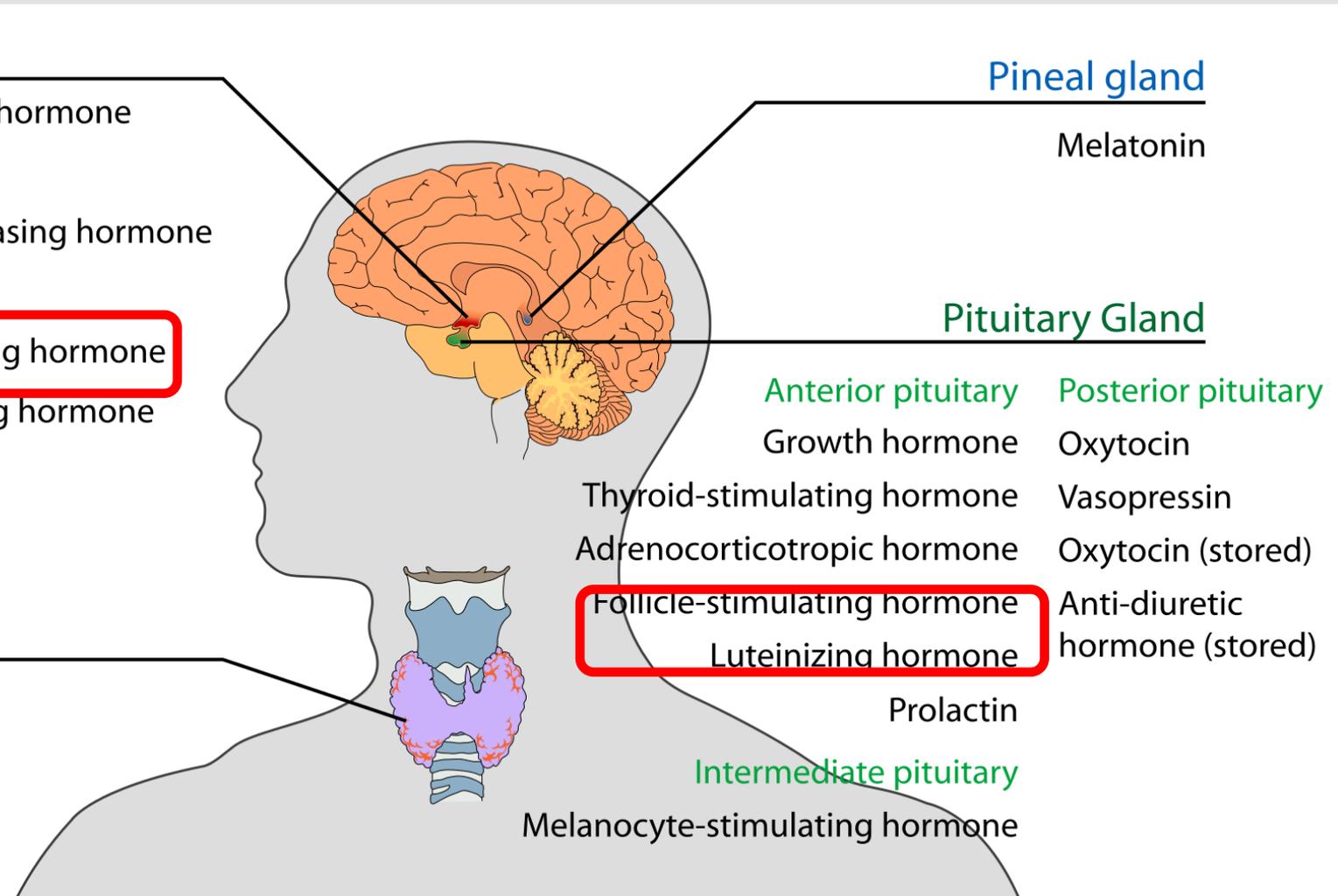
Prolactin

### Intermediate pituitary

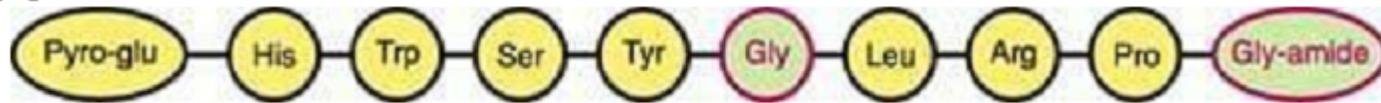
Melanocyte-stimulating hormone

### Posterior pituitary

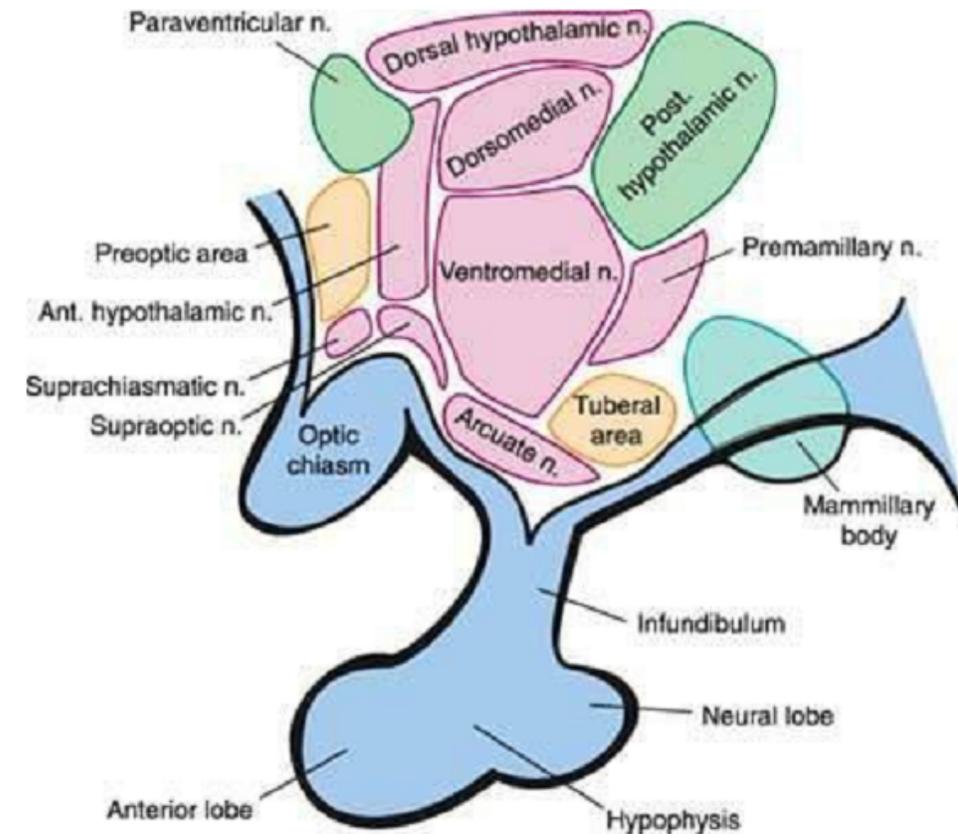
Oxytocin  
Vasopressin  
Oxytocin (stored)  
Anti-diuretic hormone (stored)



# Gonadotropin-releasing hormone-GnRH



- The controlling factor for gonadotropin secretion.
- It is a decapeptide produced by neurons in the **arcuate nucleus** of the hypothalamus



# Gonadotropin-releasing hormone-GnRH

- GnRH is unique among releasing hormones in that it simultaneously regulates the secretion of two hormones—FSH and LH.
- It is also unique among the body's hormones because it must be secreted in a pulsatile fashion to be effective, and the pulsatile release of GnRH influences the release of the two gonadotropins

# Feedbacks to the Hypothalamus

- The long feedback loop

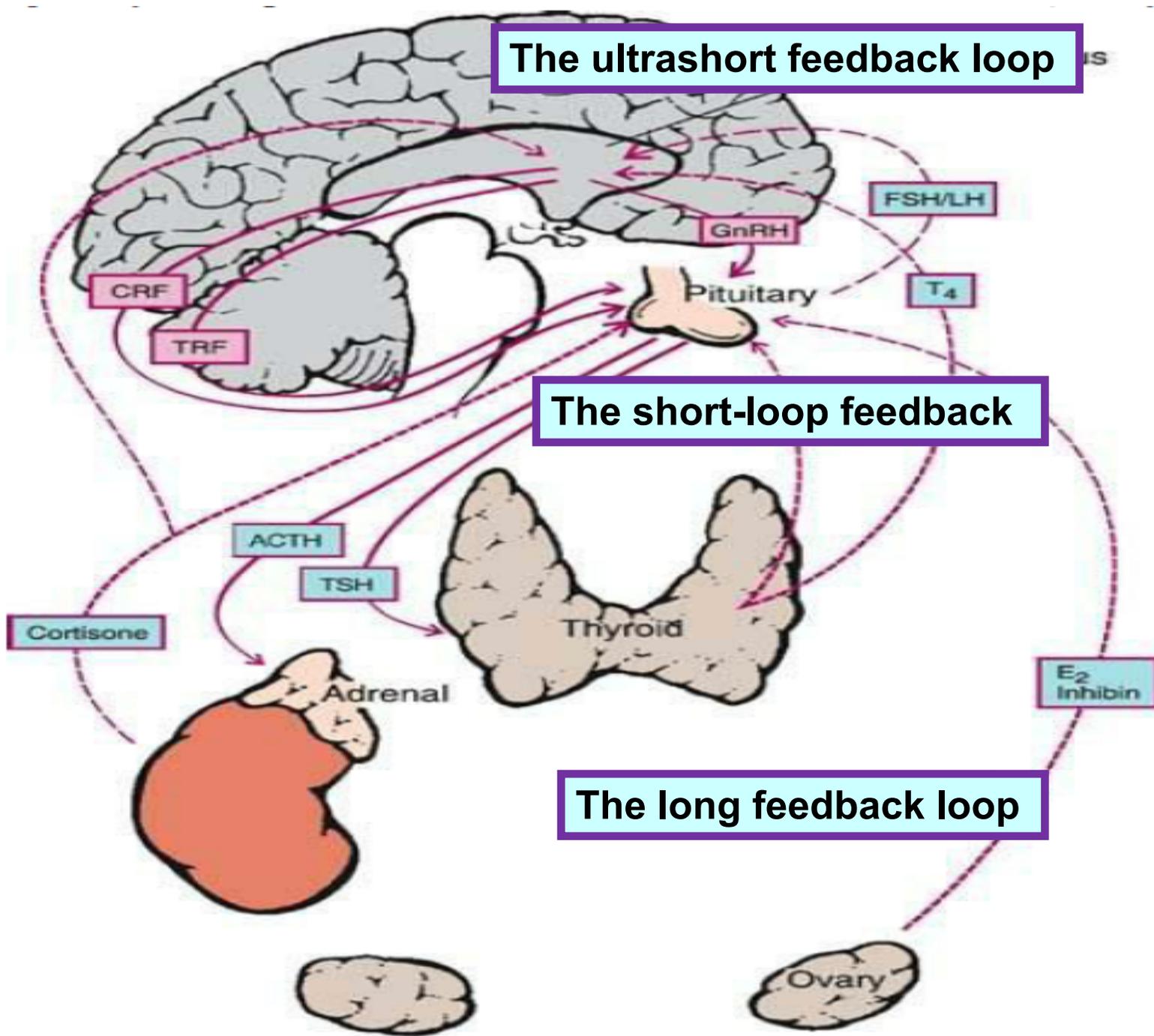
Androgens and estrogens to hypothalamus

- The short-loop feedback.

FSH and LH to hypothalamus

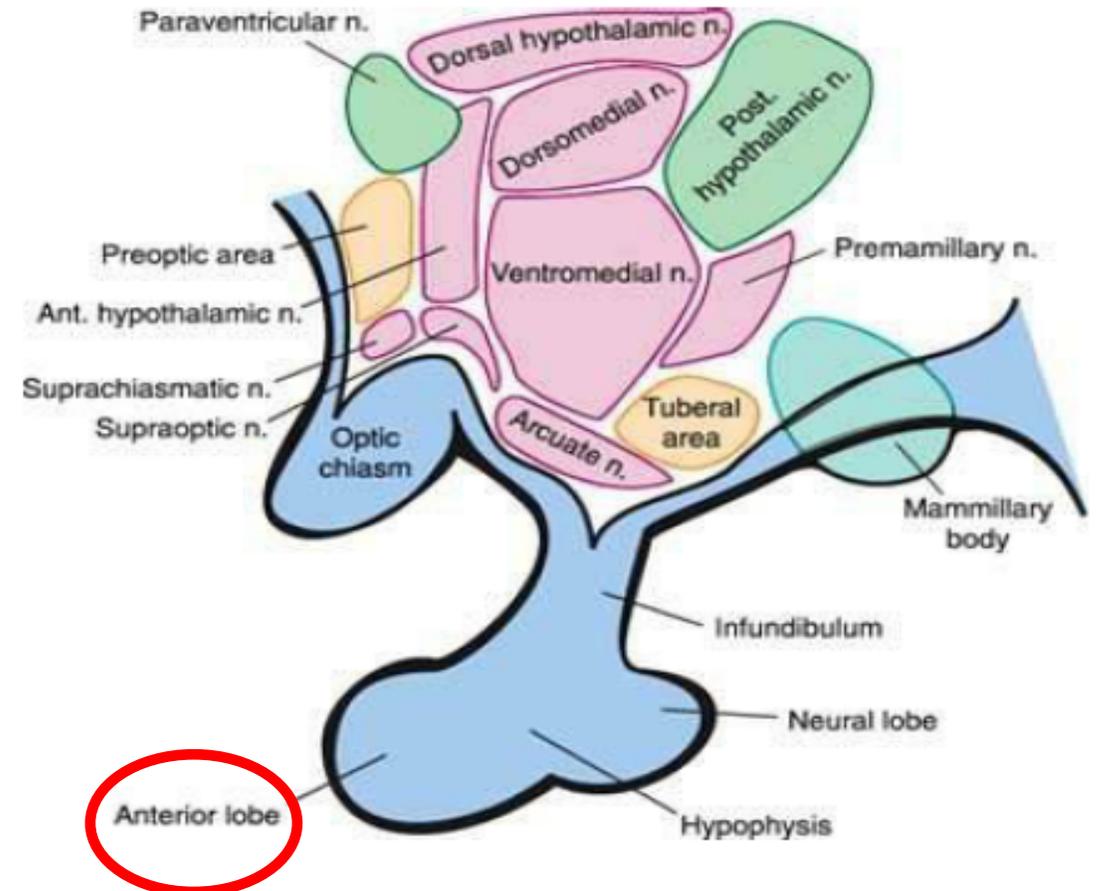
- The ultrashort feedback loop

hypothalamus secretions to itself



# Pituitary gland and its hormones secretion

- The pituitary is divided into three regions or lobes: anterior, intermediate, and posterior.
- The anterior pituitary is responsible for secretion of **gonadotropins (FSH & LH)**. Each hormone is released by a specific pituitary cell type.

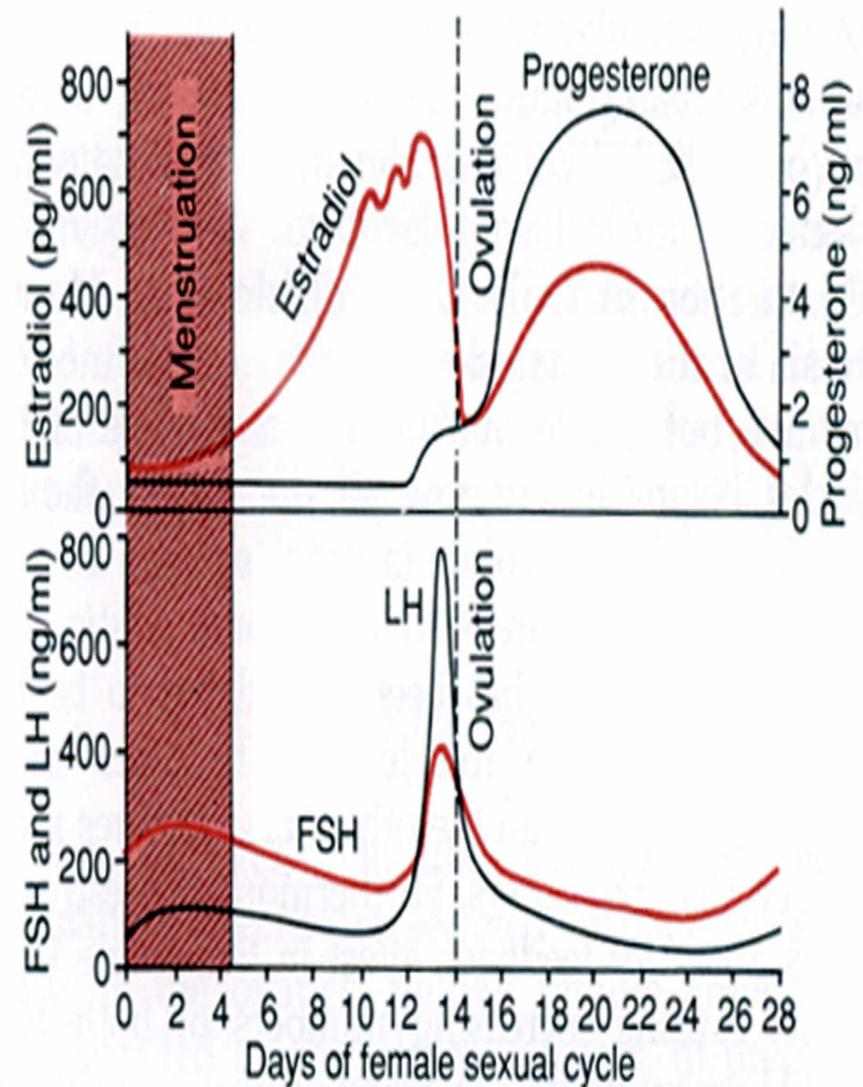


# Gonadotropins

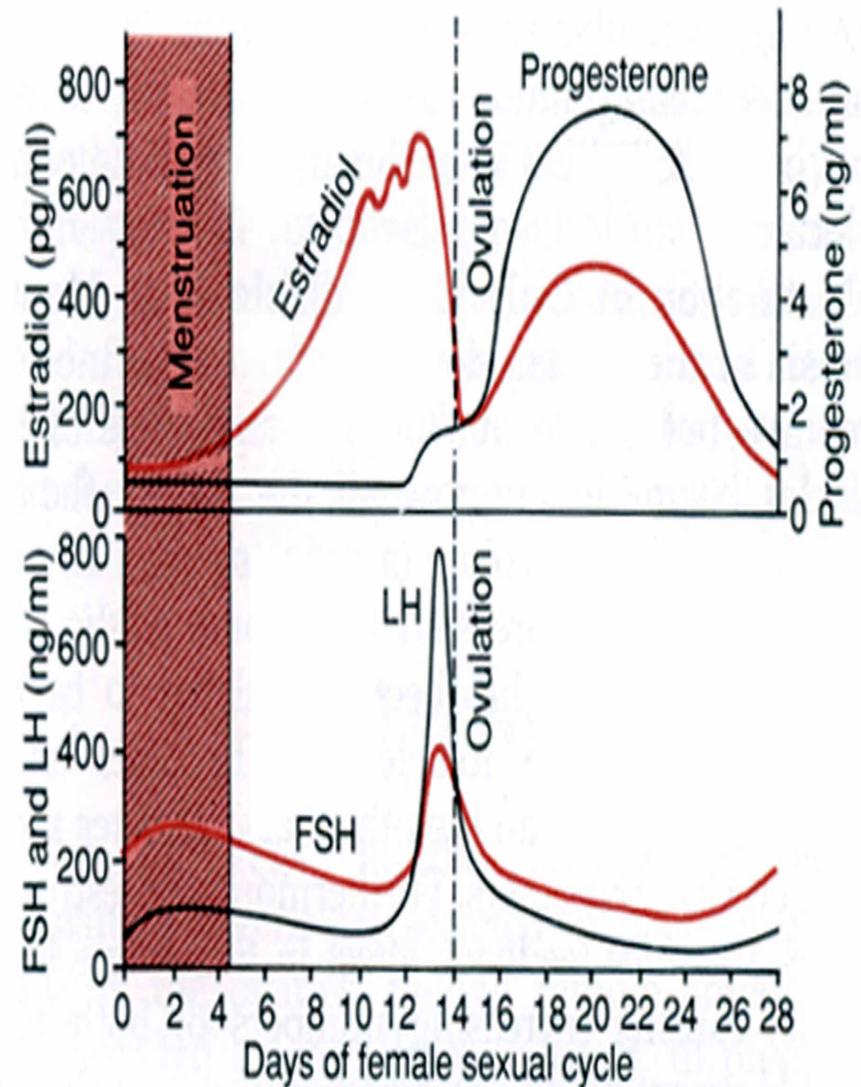
- The gonadotropins including follicle-stimulating hormone(FSH) and luteinizing hormone(LH)
- They are responsible for ovarian follicular stimulation.
- Structurally, there is great similarity between FSH and LH.
- They are both glycoproteins that share identical  $\alpha$  subunits and differ only in the structure of their  $\beta$  subunits.

# Gonadotropins-FSH

- At the beginning of each menstrual cycle, levels of gonadal steroids are low because of the demise of the corpus luteum.
- The negative feedback effect decrease which allows **the increase of FSH levels**, and a cohort of growing follicles is recruited.

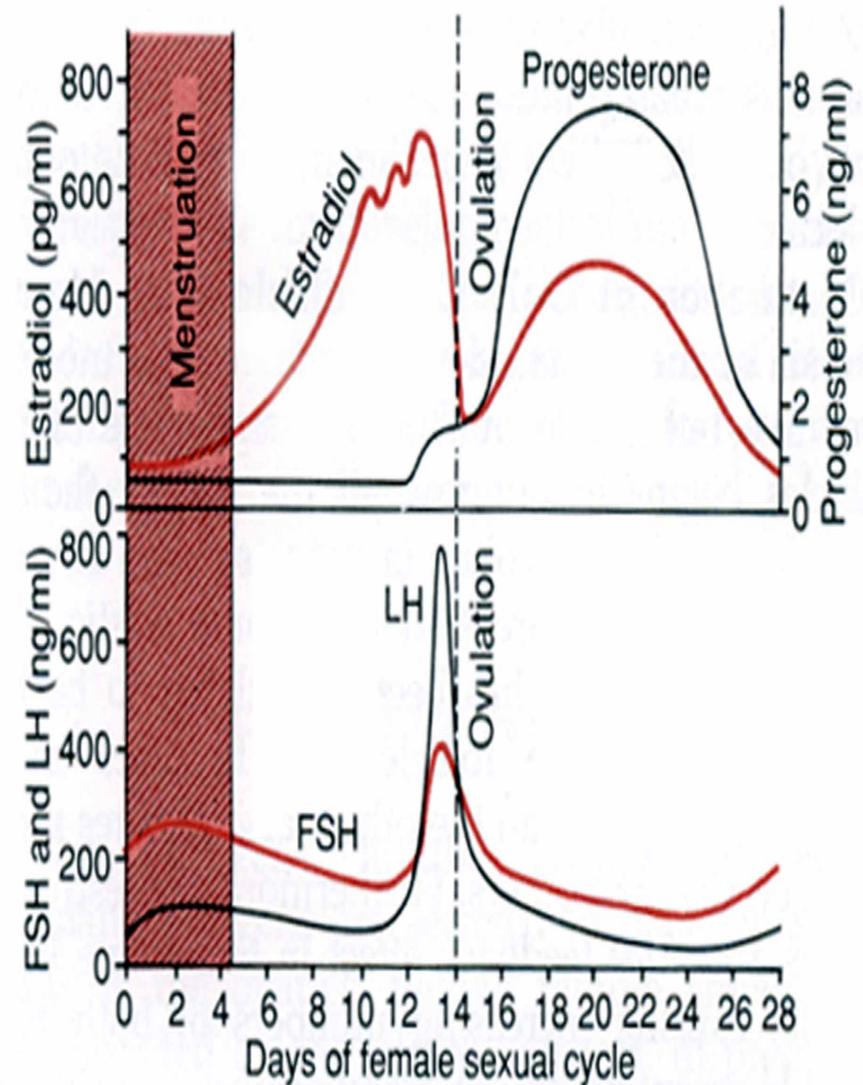


- After selection, a single, dominant follicle develops and secretes estrogen in large quantity.
- The rising estrogen level ( $> 200 \text{ pg/mL}$ ) produces positive feedback, then a substantial surge of LH occurs.



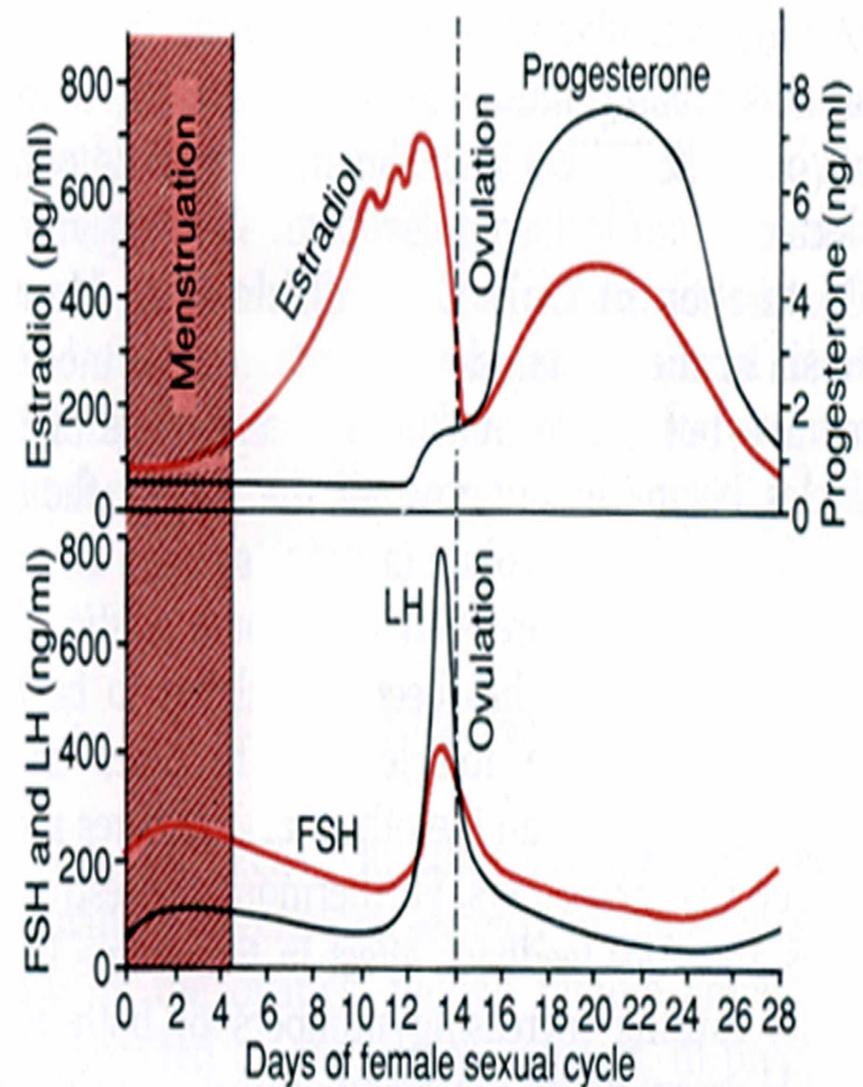
# Gonadotropins-FSH

- The LH surge results luteinization of the granulosa cells, production of progesterone, and initiation of ovulation
- Ovulation will occur 10 to 12 hours after the LH peak or 34 to 36 hours after the initial rise in midcycle LH



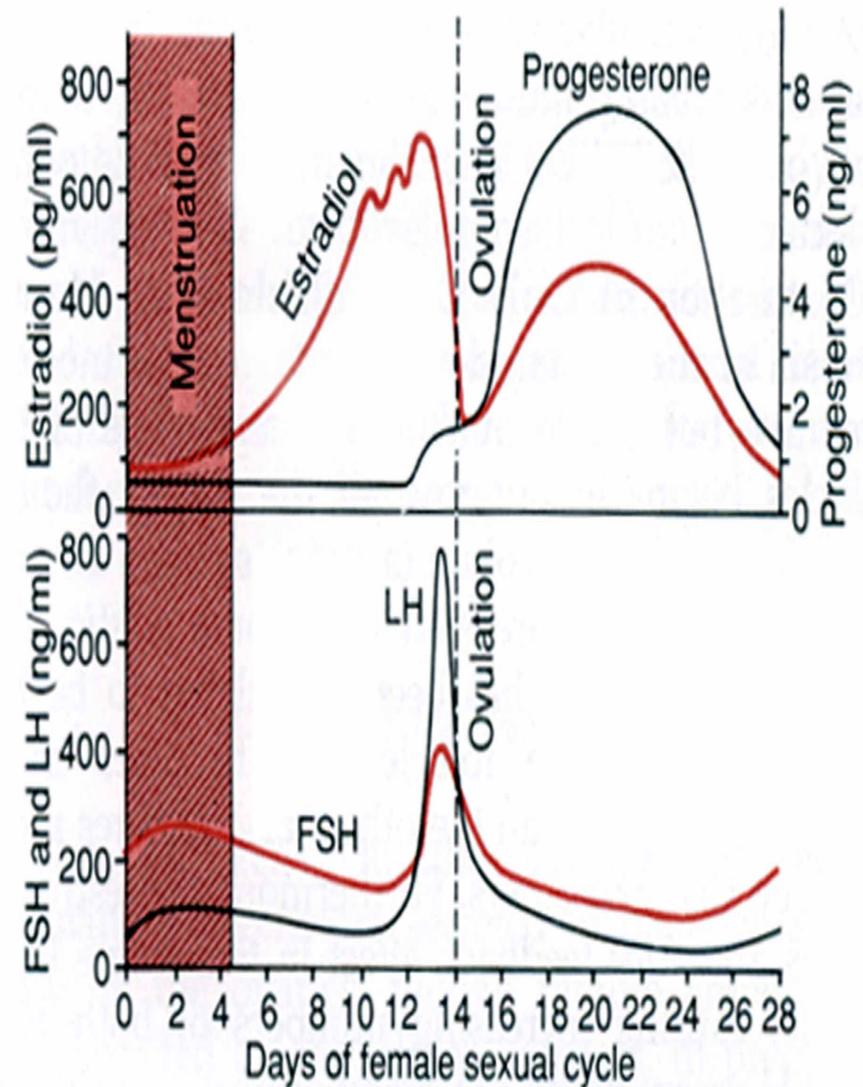
# Gonadotropins-FSH

- After ovulation, the secretion of FSH is low because of the elevated levels of estrogen, progesterone and inhibin-B.



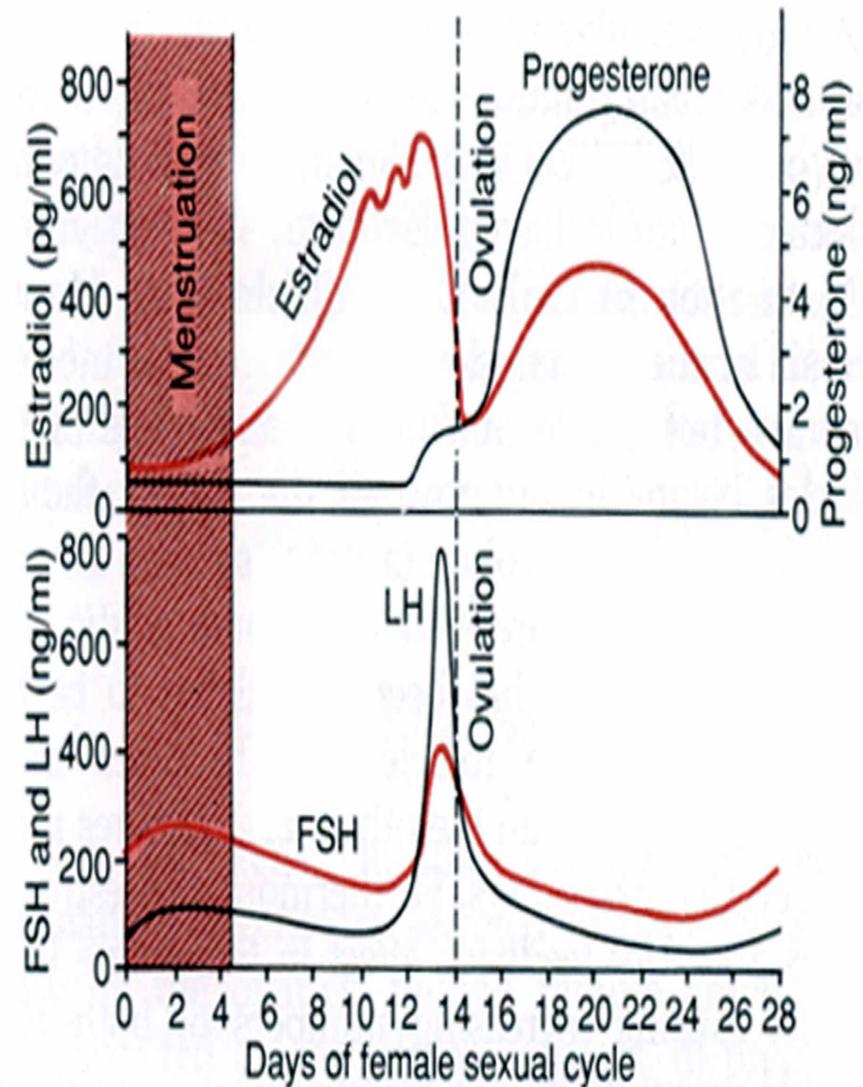
# Gonadotropins-LH

- At the beginning of each menstrual cycle, LH secretion is low and begins to rise .
- At 36-48h before ovulation, the estrogen feedback effect becomes positive, and this initiates the LH surge which produces ovulation.



# Gonadotropins-LH

- After ovulation, the secretion LH is low because of the elevated levels of estrogen, progesterone and inhibin-B.



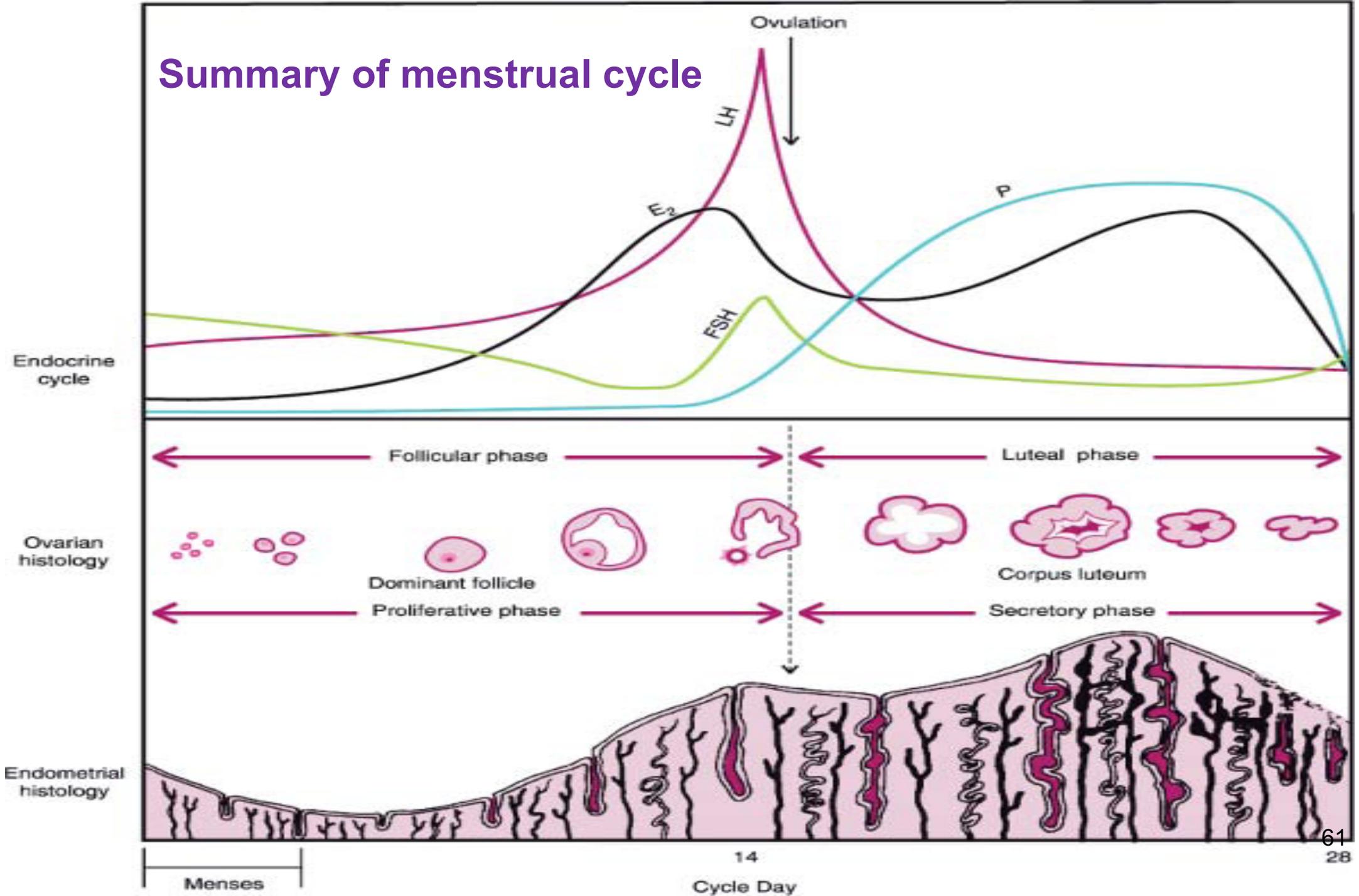
# Negative Feedback

- Rising levels of gonadal steroids, including estrogen , progesterone, inhibins suppress FSH, LH secretion by the pituitary.
- A moderate ,constant level of circulating estrogen exerts a negative feedback effect on LH secretion.

# Positive Feedback

- An elevated estrogen level ( $> 200$  pg/mL ) exerts a positive feedback effect and stimulates LH secretion.
- When circulating levels of progesterone were high ,the positive feedback effect of estrogen was inhibited.

# Summary of menstrual cycle



# KEYPOINTS

- The female reproductive process involves **four organs** : *the hypothalamus , the pituitary gland, the ovary, and the uterus*
- **Five hormones** play key role in the female reproductive process: *hypothalamic gonadotropin-releasing hormone (GnRH), luteinizing hormone(LH), follicle-stimulating hormone(FSH), estrogen and progesterone*
- The most important event after sexual maturity is menstrual cycle: **ovarian cycle** and **uterine cycle**.

*Thanks for your attention*