

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

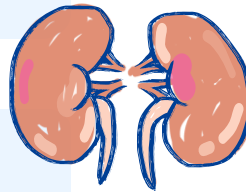


Female Physiology before Pregnancy (pt.2)

FINAL | Lecture 2

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﴿قُلْ بِفَضْلِ اللَّهِ وَبِرَحْمَتِهِ فَبِذَلِكَ فَلْيَفْرَحُوا هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾



- In the previous lecture, we discussed the hormonal regulation of the menstrual cycle, focusing on the relationship between the hypothalamus, anterior pituitary gland, and ovarian hormones. During the follicular phase, developing follicles secrete increasing amounts of estrogen, which gradually rises and reaches a peak around mid-cycle.
- At this point, a surge of LH and a smaller rise in FSH occur, accompanied by a moderate increase in progesterone. Unlike the usual negative feedback effect, high estrogen levels together with progesterone produce a positive feedback effect on the anterior pituitary, leading to a marked increase in LH secretion and a smaller increase in FSH about 12–24 hours before ovulation.
- LH is essential for ovulation. **Without the LH surge, ovulation cannot occur regardless of other hormonal fluctuations.** After ovulation, estrogen and progesterone levels continue to rise due to secretion from the corpus luteum. During the second half of the cycle, these hormones exert a negative feedback effect on the hypothalamus and anterior pituitary, reducing further LH secretion.
- Hormonal regulation is **dynamic** and not fixed. Estrogen does **not** always produce the same effect because the response depends on changes in regulatory systems, stimulatory factors, and feedback mechanisms occurring throughout the cycle. **Therefore, hormonal actions vary depending on the physiological stage.**

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.

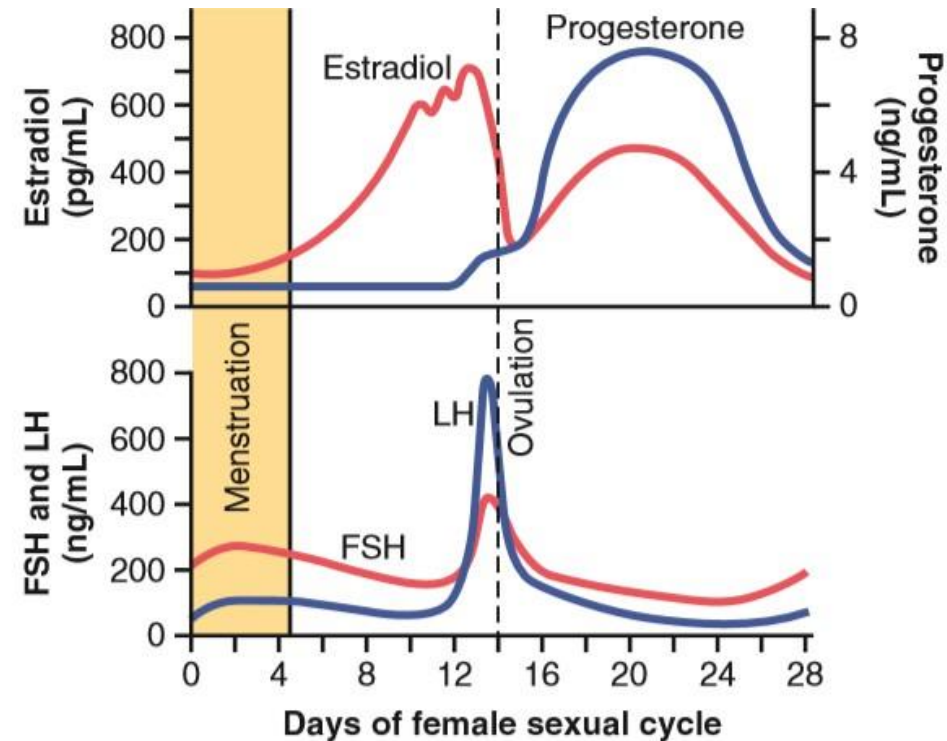


Figure 82-4. Approximate plasma concentrations of the gonadotropins and ovarian hormones during the normal female sexual cycle. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

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 ↑

Role of LH in Follicular Rupture

- LH plays an important role in the **final maturation and rupture of the follicle**, by stimulating granulosa cells and promoting enzymatic and cellular changes that prepare the follicle for ovulation. Under the influence of LH, granulosa and theca cells begin transforming into progesterone-secreting cells, a process known as **luteinization**.
- LH also activates enzymes involved in **progesterone synthesis**, shifting steroid production from predominantly estrogen toward progesterone secretion. Consequently, progesterone levels begin to rise shortly before ovulation.

Mechanism of Follicular Rupture

- The LH surge is essential for the final growth of the follicle and release of the oocyte. It stimulates the **secretion of proteolytic enzymes** within the follicle, which weaken the follicular wall, particularly at a small avascular area called the **stigma**. The stigma gradually becomes thin, swollen, and weakened prior to rupture.
- At the same time, **increased blood flow and vascular permeability** cause plasma to leak into the follicle, leading to accumulation of follicular fluid and increased intrafollicular pressure. **The combined effects of enzymatic weakening and follicular swelling eventually result in rupture of the follicular wall.**
- Following rupture, follicular fluid is expelled and carries the **secondary oocyte** outward from the ovary during ovulation.

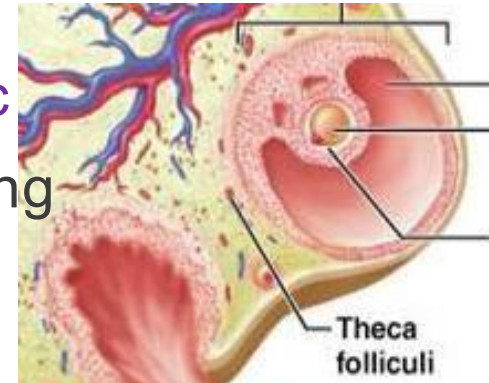
Initiation of ovulation

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

Hyperemia and vasodilation

2. Rapid growth of **new blood vessels** into the follicle wall & prostaglandins are secreted into the follicular tissue. **increased fluid transudation**



Ovulation

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

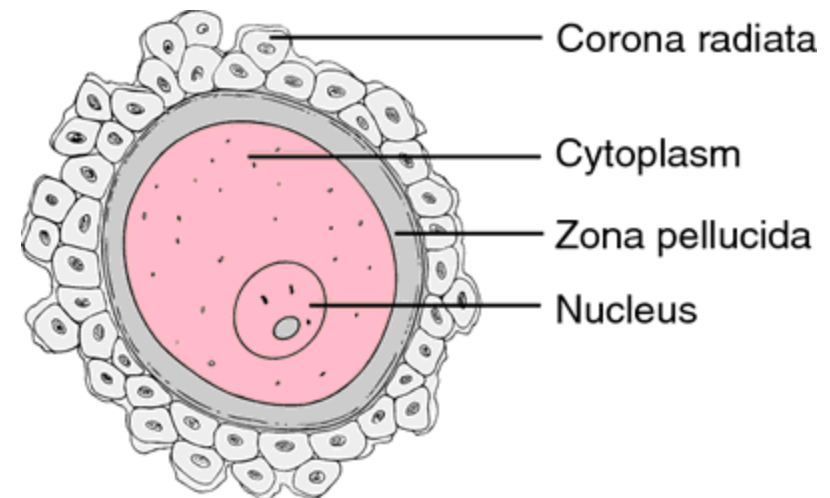
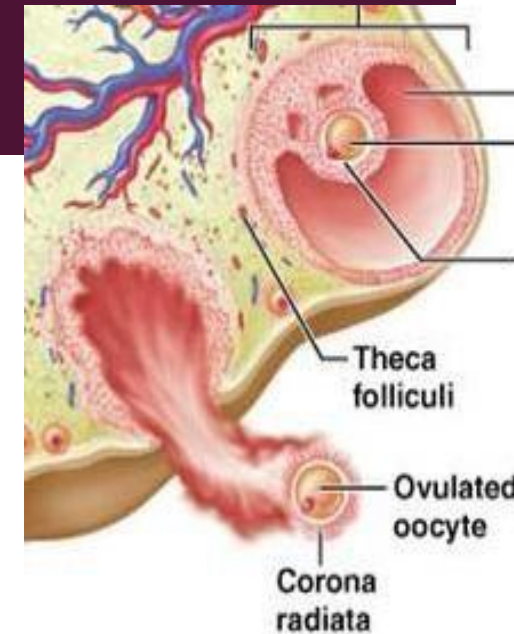
During ovulation, stigma

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

Important map!

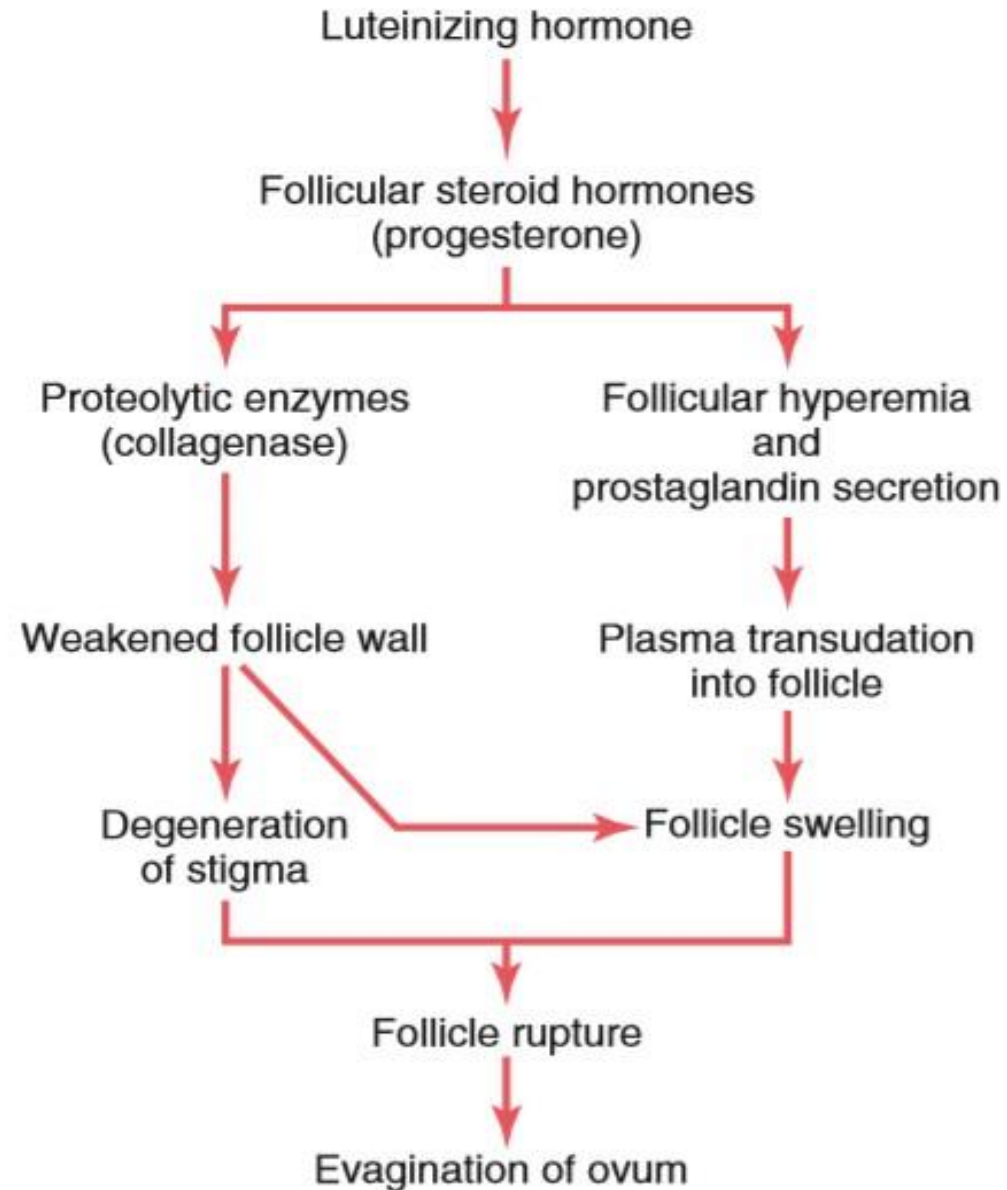
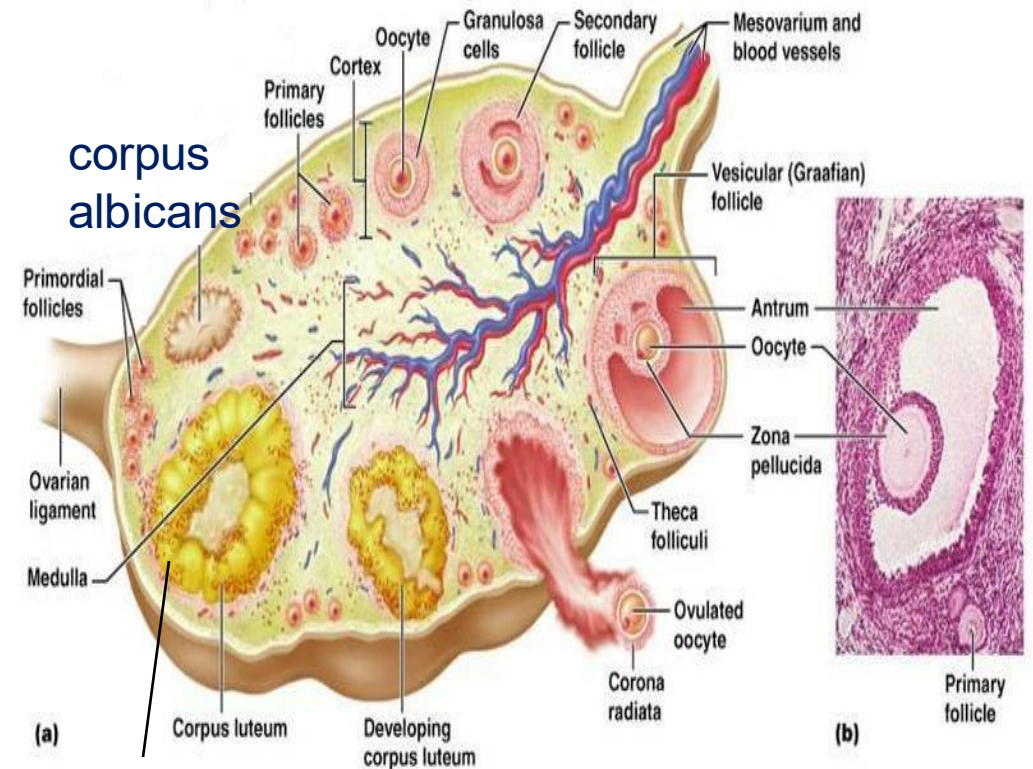


Figure 82-6. The postulated mechanism of ovulation.

Corpus Luteum

Corpus Luteum (Luteal Phase) (mentioned before...)

1. After ovulation, the ruptured follicle becomes the corpus luteum under LH influence.
2. It reaches maximum size (~1-1.5 cm) about 7-8 days after ovulation.
3. **Granulosa and theca cells undergo luteinization → become lutein cells.**
4. **Granulosa lutein cells → mainly secrete progesterone + some estrogen.**
5. **Theca lutein cells → secrete smaller amounts of progesterone + androgens.**
6. Some androgens can be converted into estrogen.
7. Corpus luteum becomes the main source of progesterone in the luteal phase.

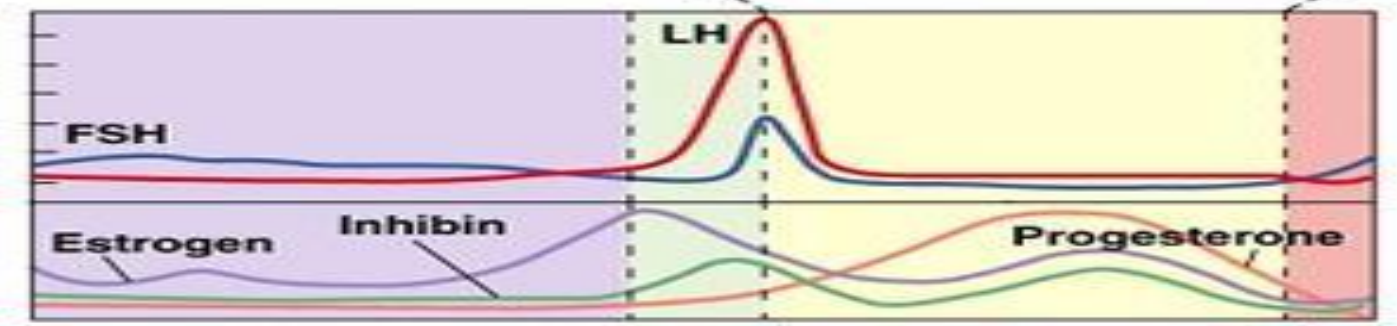
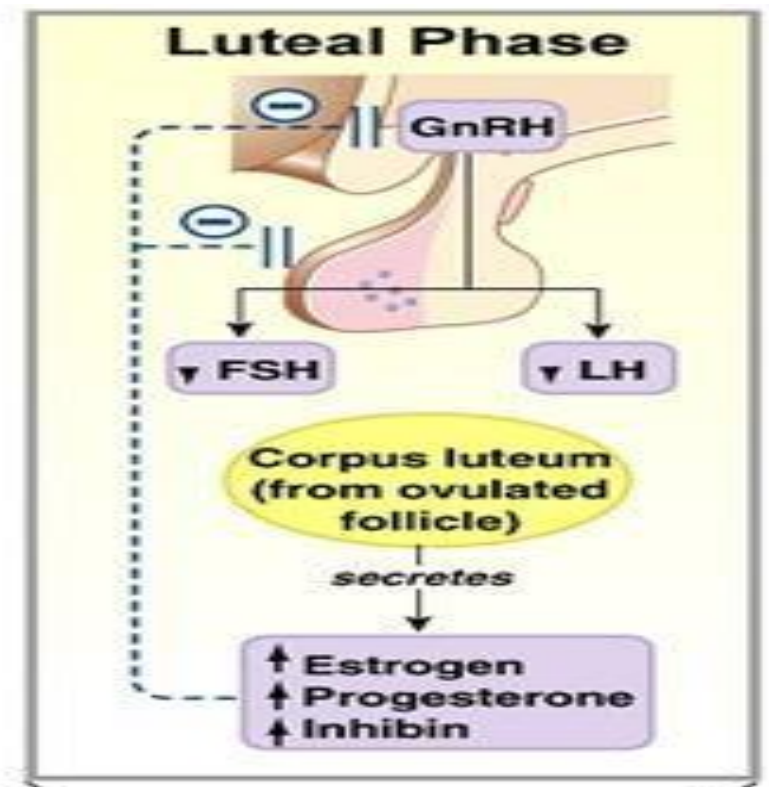


7-8 days after ovulation
~ 1.5 cm in diameter

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

The corpus luteum secretes progesterone, estrogen, and inhibin (all have inhibitory functions).

- Estrogen and progesterone exert inhibitory effects on the hypothalamus and anterior pituitary (Estrogen has a more potent negative feedback effect on gonadotropin secretion than progesterone does).
- Inhibin specifically inhibits the anterior pituitary, mainly reducing FSH secretion.



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.

Corpus Luteum

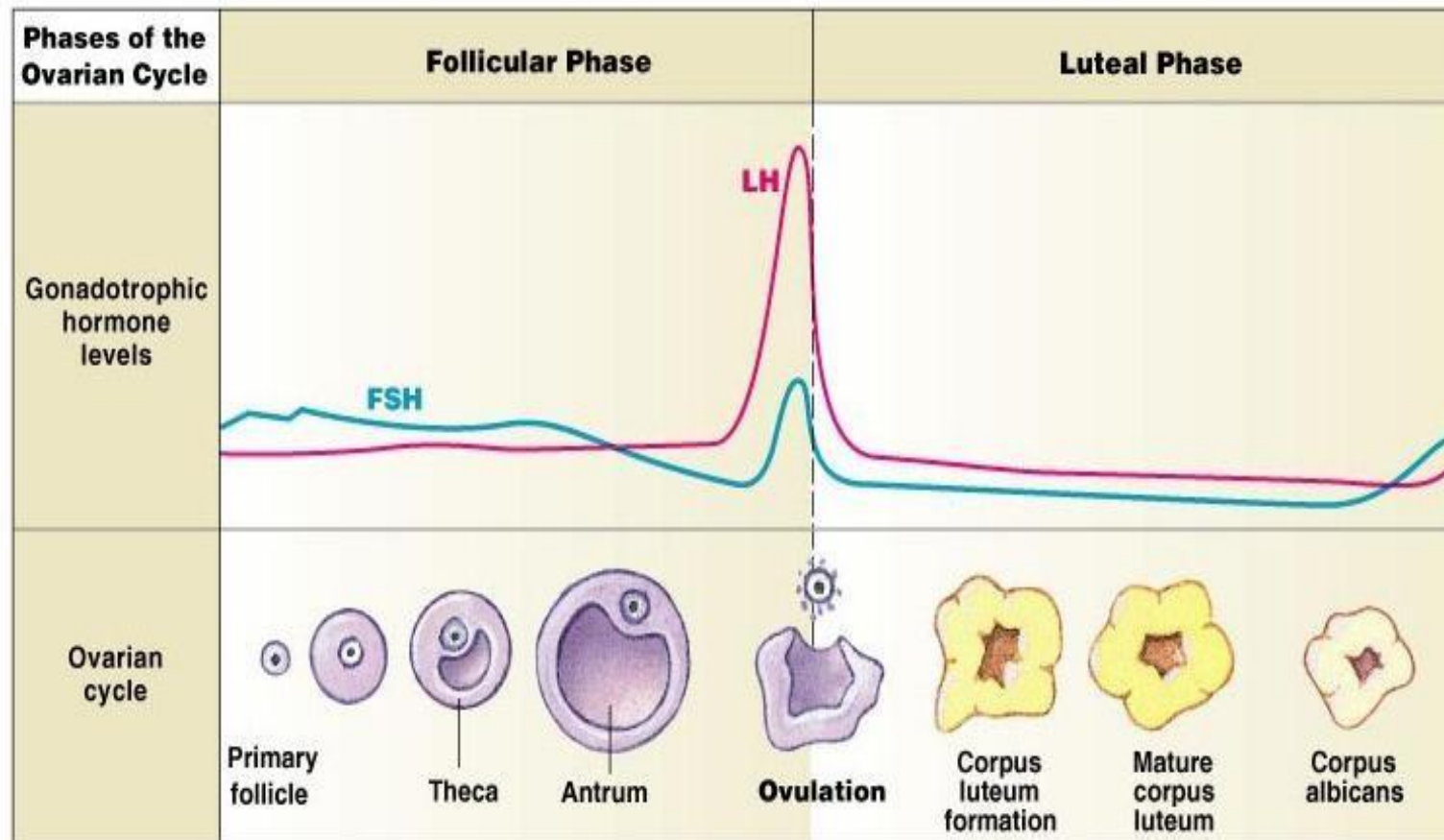
Luteinizing function of LH:

- 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
- If fertilization does **not** occur, the **corpus luteum** undergoes degeneration (involution) and becomes the **corpus albicans**.
 - If fertilization occurs, **human chorionic gonadotropin (hCG)** is secreted by the **trophoblast** of the developing embryo, maintaining the corpus luteum and preventing its degeneration. The corpus luteum therefore continues secreting **progesterone and estrogen** to support early pregnancy until the **placenta** develops and becomes the main source of these hormones.

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 inhibits FSH secretion by the anterior pituitary (AP). ↓ FSH & LH and loss of these hormones → complete degeneration of the corpus luteum **since it loses its support (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.
- **Before degeneration, lutein cells of the corpus luteum also secrete inhibin, which suppresses FSH secretion from the anterior pituitary. When the corpus luteum regresses, inhibin levels also fall, further contributing to the rise in FSH and initiation of a new cycle.**
 - **Corpus luteum involution → ↓ estrogen & progesterone → removal of negative feedback on hypothalamus & anterior pituitary → ↑ FSH (slight ↑ LH) → follicular recruitment & growth → ↑ estrogen secretion → start of new cycle.**



- Menstrual bleeding usually begins about 1–2 days after the decline in estrogen and progesterone. Around the same time, FSH and LH begin rising again to initiate the next follicular phase.
- Ovulation typically occurs about 16–36 hours after the LH surge, although the timing may vary slightly between individuals.

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. Describe effects of estrogen and progesterone
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 organs (ex. ovaries, fallopian tubes, uterus, and vagina) all increase several times in size. Estrogen is considered the primary female sex hormone. Its main role is anabolic, meaning it promotes growth and cell proliferation. Unlike testosterone, which has a more general effect on the entire body, estrogen's effect is specific to the reproductive organs.
- 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 for the facilitation of the movement of the ovum, fertilized zygote, or sperm. This prepares the uterus for possible implantation by making the lining more receptive and structurally developed.
- 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. Progesterone is necessary for the full functional maturation of the mammary glands, as it completes the development of the lobules and alveoli required for milk production. However, both estrogen and progesterone can only help the machinery of the glands; they cannot cause milk production.

EFFECTS OF ESTROGEN

- Effect of Estrogens on the Skeleton; inhibit osteoclastic activity in the bones and therefore stimulate bone growth. However, they cause (**early**) uniting of the epiphyses with the shafts of the long bones. female usually ceases earlier than growth of the male **that is why females tend to be shorter and females who reach puberty normally tend to be shorter than females who don't (Osteoporosis of the Bones Caused by Estrogen Deficiency in Old Age).**
- Estrogens Slightly Increase Protein Deposition, mainly due to growth of the sexual organs and 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 .

Estrogen has a mild effect on protein metabolism, slightly increasing protein deposition, but this effect is much weaker compared to testosterone.

It also slightly increases basal metabolic rate. Because of these metabolic effects, females generally have a higher proportion of body fat compared to males, and relatively less muscle mass.

EFFECTS OF ESTROGEN

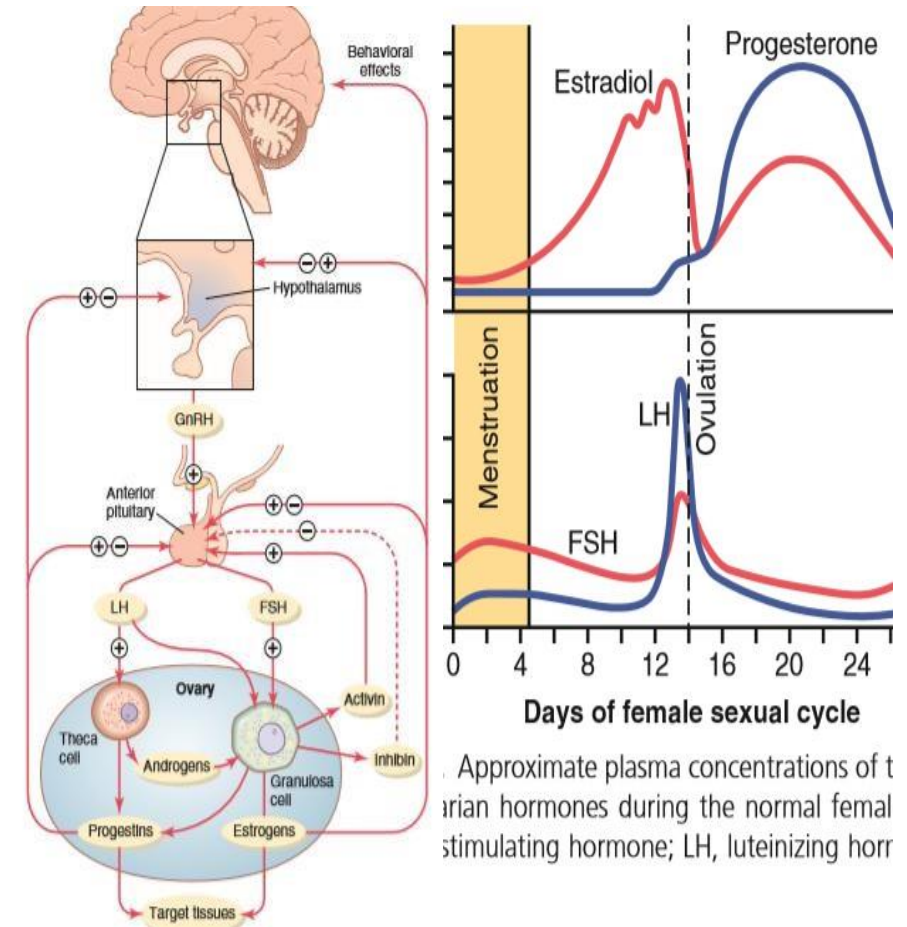
- Estrogens Have Little Effect on Hair Distribution, estrogen do not greatly affect hair distribution, adrenal androgens have greater effect on female hair, **unlike males where testosterone effect on hair is more than androgens.**
- Effect of Estrogens on the Skin. Development of a texture that is soft 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.**

Effect of progesterone

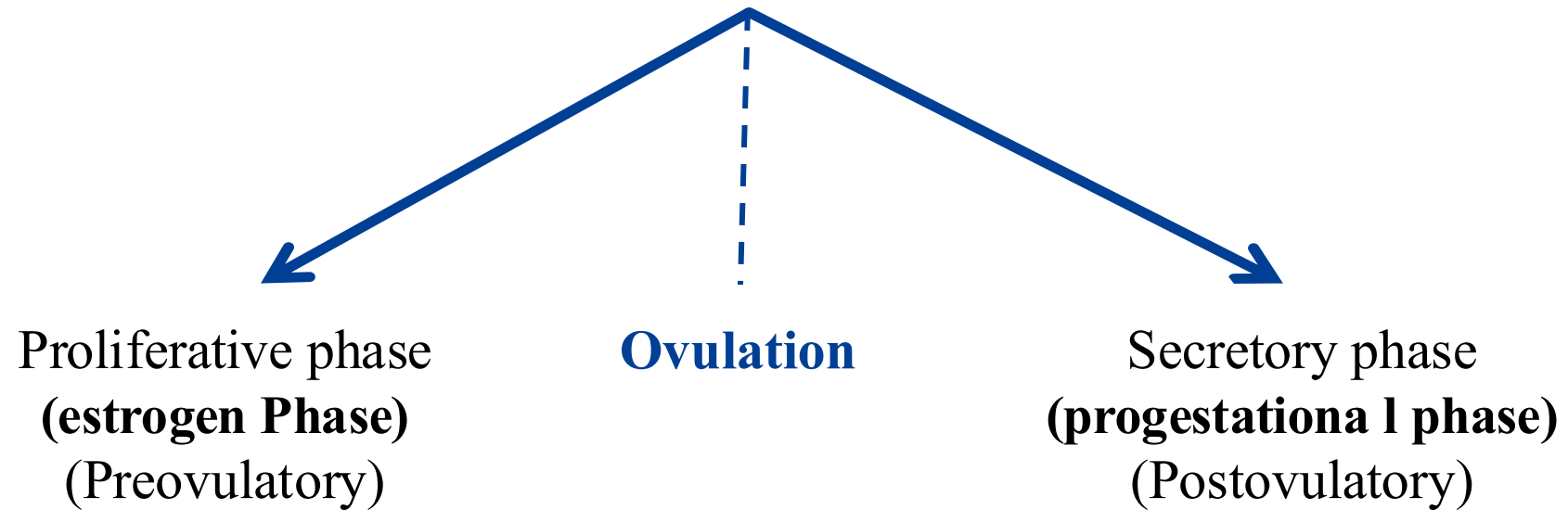
1. Progesterone Promotes Secretory Changes in the **Uterine endometrium** during the latter half of female cycle, thus preparing the uterus for implantation of the fertilized ovum. **In the uterine myometrium**, progesterone decreases the frequency and intensity of uterine contractions, thereby helping to prevent expulsion of the implanted ovum.
2. 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, **especially during division and even after implantation**. It promotes **glandular secretions and the storage of glycogen and other nutrients that can be used by the trophoblasts, which digest these cells and take the nutrients stored in the mucosal cells or glands**.
3. Progesterone Promotes Development of the Breasts. Progesterone, **especially when increases just before and after ovulation**, 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, **but NOT milk as it is induced under the effect of prolactin**).

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
- The regulation of the **endometrial cycle** can be understood through the ovarian cycle, since the **endometrial changes are influenced by the hormonal changes occurring during the ovarian cycle.**
- For example, **Estradiol stimulates proliferation of the endometrium**, producing the **proliferative phase** of the uterine cycle, which is the phase in which estradiol levels are high in the ovarian cycle. In contrast, the phase characterized by **high progesterone levels**, along with estrogen, represents the **secretory phase of the endometrial cycle after ovulation.**



Uterine (endometrial) Cycle



Please see the next slides for further details

Proliferation Phase (Estrogen Phase)

- At the beginning of each cycle, most of the endometrium has been desquamated by menstruation due to the drop of estrogen and progesterone levels. The stratum functionalis is shed, leaving only the deep layer, the stratum basalis. After menstruation only thin layer of the endometrial stroma remains & the deeper portions of the glands & crypts of the endometrium.
- As FSH increases and estrogen levels begin to rise, under the influence of **estrogens**, the stromal cells & epithelial cells proliferate rapidly increasing the thickness of the functionalis layer. That's why this phase is called the proliferative phase or the estrogen phase.
- The endometrial surface re-epithelialize 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 / Ovulation

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. **Abnormalities in this cervical mucus can make pregnancy more difficult, as cervical mucus plays an important role in the fertilization process.**

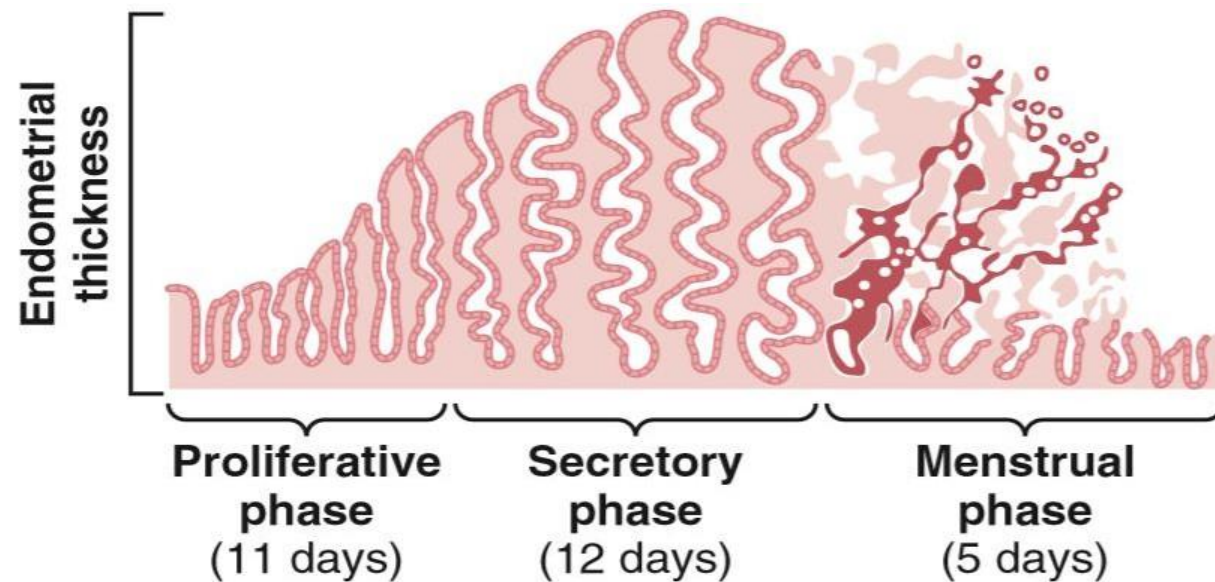
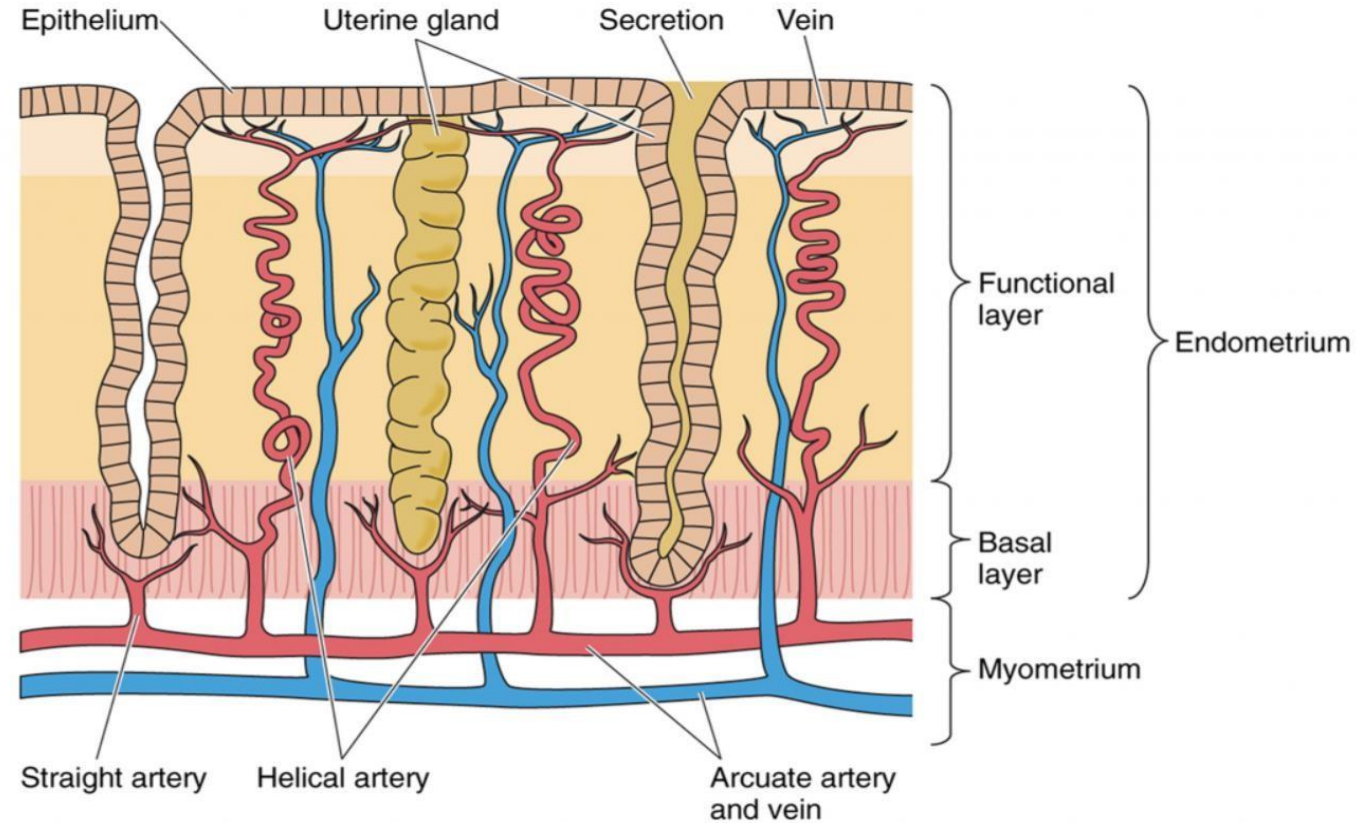


Figure 82-9. Phases of endometrial growth and menstruation during each monthly female sexual cycle.

Secretory phase (progestational phase)

- **After ovulation**, progesterone and 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 **(to support the implanted zygotes)**. 1 week after ovulation, endometrium thickness is 5-6 mm.

Uterine (endometrial) Cycle

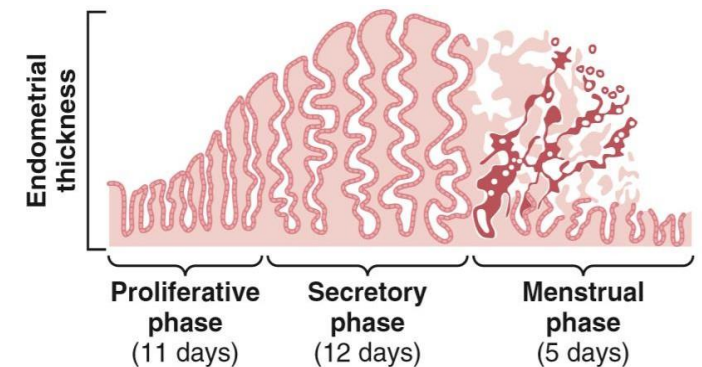


Gartner & Hiatt (2007). Color Textbook of Histology: Saunders Elsevier, p. 477

During the secretory phase, the endometrium contains well-developed secretory glands and tortuous blood vessels that support the thick mucosa.

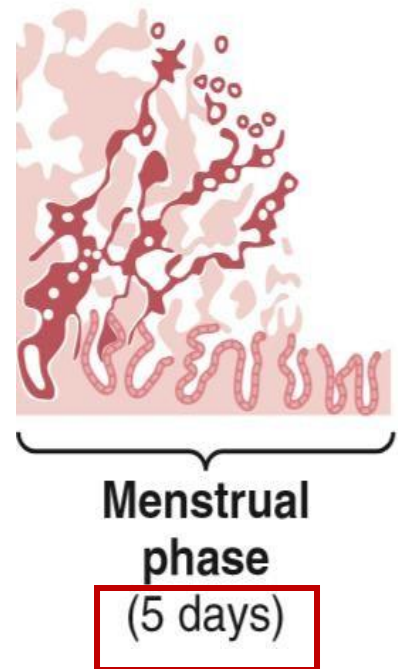
Uterine (endometrial) Cycle

- 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. Before implantation, there is no way to support the ovum except through the uterine milk.
- After implantation, The trophoblastic cells on the surface of the implanted ovum begin to digest the endometrium to implant deeper and absorb endometrial stored substances.



Menstruation

- If the ovum is not fertilized, about **(day 26)** 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
- **When there is no hormonal stimulation because of the absence of estrogen and progesterone, vasospasm or vasoconstriction occurs in the blood vessels, and prostaglandins are released, causing hypoxia, necrosis, and eventually shedding of the endometrium.**
- The mass of desquamated tissue & blood plus the contractile effects of prostaglandins all initiate contractions which expel the uterine contents.



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. **If menstrual bleeding is heavier than normal, fibrinolysin may not be sufficient to prevent clotting, so clots may appear. The presence of clots may indicate abnormal bleeding or disease and should therefore be investigated.**

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

Leukorrhoea 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.

This is important because the lining is actually more prone to infections due to the loss of blood vessels.

ANOVULATORY CYCLE

- When ovulation fails, mainly due to insufficient LH **before ovulation by about one day or 16 hours, due to any reason such as lack of stimulation from the anterior pituitary gland or insufficient GnRH stimulation**, 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 **(but it will not stop completely)**. Therefore, it is likely that progesterone is not required for maintenance of the cycle itself, but it can alter the cycle's rhythm.
- **This commonly occurs during early puberty in** 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 main cause of menopause is ovarian burnout due to an insufficient number of follicles. The number of follicles present in the ovaries is much greater than the number that actually undergo ovulation during the childbearing years, but many follicles undergo atresia and fail to continue their development.**
- **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.
 - 8) **loss of the protective effects of estrogen against stroke and its cholesterol-lowering effects.**

Menopause

menopause in the female.

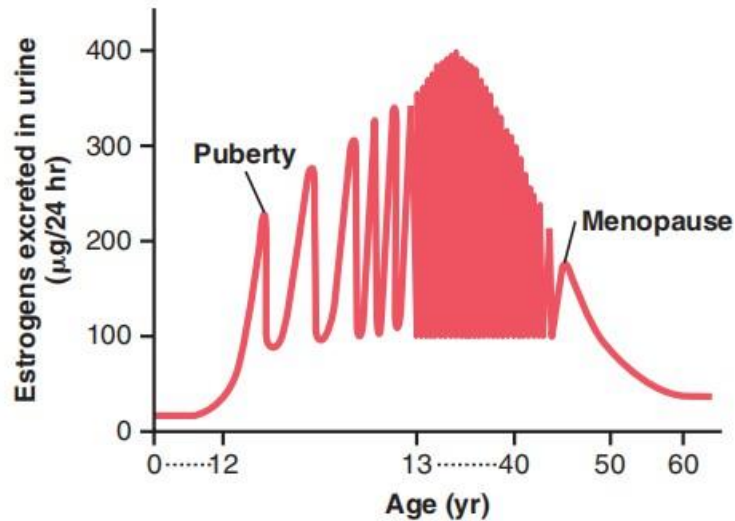


Figure 82-13. Estrogen secretion throughout the sexual life of the female human being.

This graph demonstrates estrogen levels throughout a female's life. Estrogen levels begin to rise gradually before puberty, promoting the growth of the female reproductive organs. After puberty, estrogen levels fluctuate because of the menstrual cycle, although the average levels remain relatively high and stable. Before menopause, estrogen levels gradually decline and may eventually approach zero between the ages of 50 and 60.

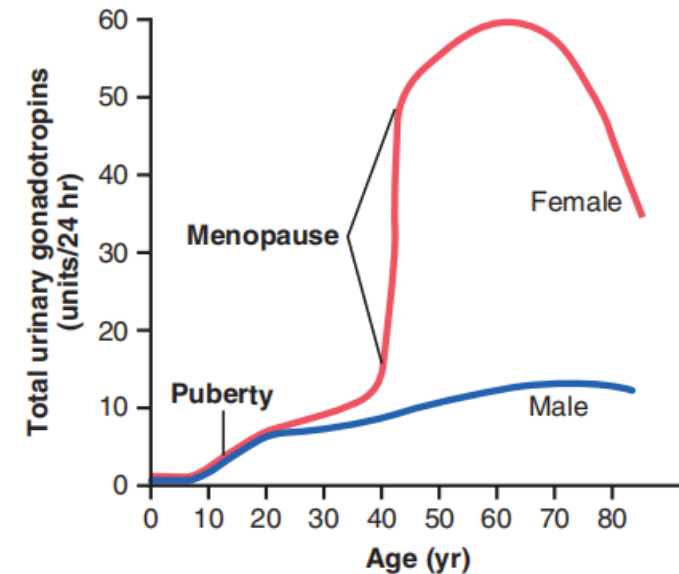
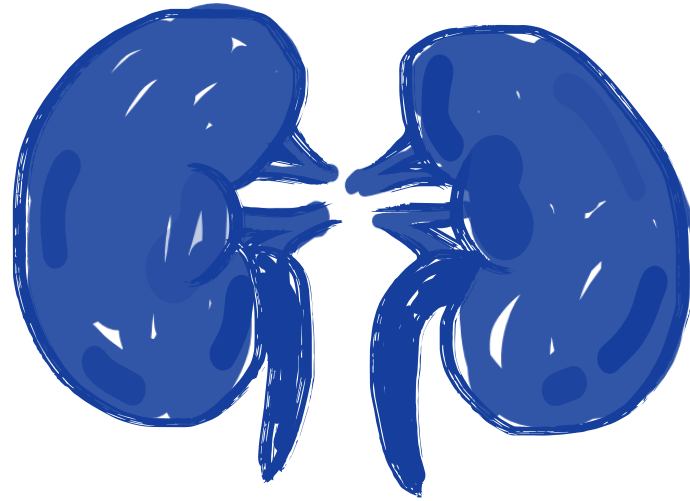


Figure 82-12. Total rates of secretion of gonadotropic hormones throughout the sexual lives of female and male human beings, showing an especially abrupt increase in gonadotropic hormones at menopause in the female.

The cessation of estrogen and progesterone production removes the negative feedback on FSH and LH secretion, causing their levels to rise markedly in females. In males, hormone levels are generally more stable because testosterone levels do not decline significantly enough to cause a major increase in gonadotropins. Testosterone levels may decrease later in life, around the ages of 80–90 years, and may reach about 50% of normal levels, but usually not lower than that.



PHYSIOLOGY
QUIZ
LECTURE #

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقه من فتنة القبر وعذاب النار،
أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.

سُورَةُ الْأَجْرَابِ

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

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