



Physiology Team 431
Reproductive Block

Lecture 4

Physiology of Uterine Cycle

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Monthly endometrial cycle and menstruation

Associated with monthly cyclical production of estrogens & progesterone by the ovaries, **the endometrial lining of the uterus pass through the following stages:**

1- **Proliferative phase (Estrogen Phase) of the endometrial cycle, occurring before ovulation:**

(The proliferative phase happens before ovulation and after menstruation; it's a phase where the stromal and epithelial cells of the endometrium proliferate under the influence of estrogen from the ovaries) (Menstruation is the shedding of the superficial layer of the endometrium so the deeper layer is intact)

- At the beginning of each cycle, most of the endometrium has been desquamated by menstruation. After menstruation only thin layer of the endometrial stroma remains & the deeper portions of the glands & crypts of the endometrium **under the influence of estrogens, secreted in large quantities by the ovaries**, the stromal cells & epithelial cells proliferate rapidly.
- The endometrial surface re-epithelialized 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**.
- At the time of ovulation, the endometrium is 3-5 mm thick. The endometrial glands, cervical region secrete thin, stringy mucus which help to guide sperm in the proper direction from the vagina into the uterus.

2- **Secretory phase (Progesterational Phase) of the endometrial cycle, occurring after ovulation:**

(Secretory phase happens after ovulation and before menstruation; it's a phase where the endometrium is further increased in thickness and it has the many glands under the influence of mainly progesterone from the corpus luteum)

- After ovulation, estrogen & progesterone are secreted in the later part of the monthly cycle by the **corpus luteum**. Estrogen cause slight proliferation in the endometrium & **progesterone causes marked swelling & Secretory development of the endometrium**. The glands increase in tortuosity; excess Secretory substances accumulate in the glands.
- Stromal cells cytoplasm increase lipid & glycogen deposits in the cells & blood supply to the endometrium increases and become more tortuous. 1 week after ovulation, endometrium thickness is 5-6 mm.
- **The Secretory changes prepared the endometrium (stored nutrients) for implantation of the fertilized ovum. Uterine secretions called "uterine milk" provide nutrition for the diving ovum**. The trophoblastic cells on the surface of the implanted ovum begin to digest the endometrium & absorbed endometrial stored substances.

Menstruation:

- If the ovum is not fertilized, about 2 days before the end of the monthly cycle, **the corpus luteum involutes & estrogens & progesterone decrease to low levels of secretion.** Due to decrease estrogen & progesterone at the end of the monthly cycle, there is decrease stimulation of the endometrium, **followed by involution of the endometrium about 65% of its previous thickness.**
- During the 24 hrs preceding the menstruation, there is **vasospasm of the tortuous blood vessels & release of vasoconstrictor prostaglandins.**

There is:

1) Vasospasm

2) Decrease nutrients to the endometrium

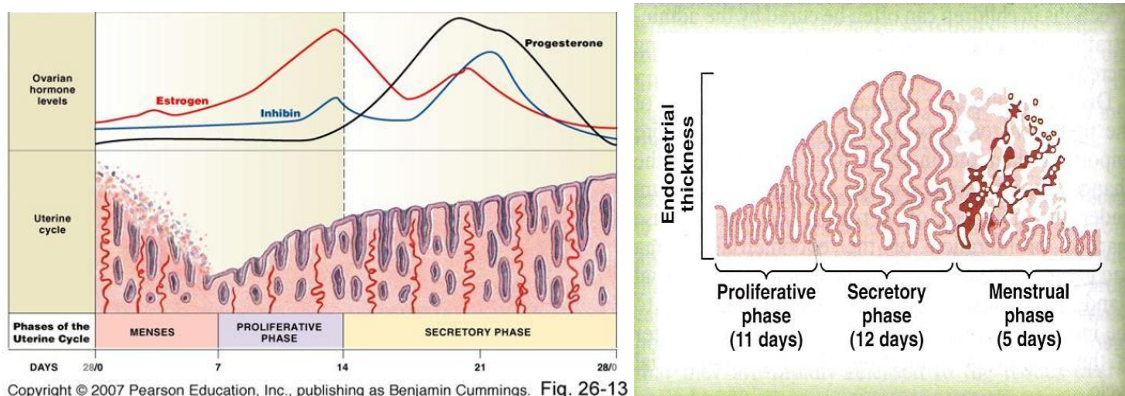
3) Loss of the hormonal stimulation, **all initiate necrosis in the endometrium blood vessels.** There is gradual necrosis of the **outer layer of the endometrium** separate from the uterus at the site of the hemorrhages within 48 hrs, **all the superficial layers of the endometrium desquamated in the uterine cavity.**

- The mass of desquamated tissue & blood plus the contractile effects of prostaglandins **all initiate contractions which expel the uterine contents.**
- In normal menstruation, about 40 ml of blood +35 ml of serous fluid are lost. (Serous fluid=PLASMA)
- The menstrual blood is **normally non-clotting due to the presence of fibrinolysin.**

Within 4 to 7 days after menstruation, the loss of blood ceases & the endometrium become re- epithelialized. (The beginning of a new cycle; proliferative phase)

Leukorrhea during menstruation:

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



Positive feedback effect of estrogen before ovulation – the pre-ovulatory LH surge:

AP secretes increased amount of LH beginning 24 to 48 hrs before ovulation. FSH surge is much smaller in the pre-ovulatory than LH surge.

- The possible causes of LH secretion could be:
- **Estrogen has special positive feedback** effect of stimulating pituitary secretion of LH & to a lesser extent FSH
- The granulosa cells of the follicle begin to secrete small increasing amount of progesterone about 1 day before ovulation which stimulate LH secretion

Feedback oscillation of the hypothalamic-pituitary-ovarian system:

Postovulatory secretion of the ovarian hormones, and depression of the pituitary gonadotropins:

During the postovulatory phase (between ovulation & beginning of menstruation) **the corpus luteum secrete large quantities of both progesterone & estrogen & inhibin which all together cause negative feedback effect on AP & hypothalamus to inhibit both FSH & LH secretion.** (Lowest level 3-4 days before the onset of menstruation)

Follicular growth phase:

2 to 3 days before menstruation, **corpus luteum regress & secretion of estrogen, progesterone & inhibin decrease.**

This decrease removes the negative feedback effect on AP hormones. Therefore a day after menstruation FSH secretion begins to increase (2 folds) while LH secretion is slightly. These hormones cause growth of the follicle. During the first 11 to 12 days of this follicle growth the rate of secretion of FSH & LH decrease slightly because of the negative feedback effect of estrogen on the AP.

Pre ovulatory surge of LH & FSH causes ovulation:

About 12 days of the monthly cycle, the high secretion of FSH & LH start to increase due to high level of estrogens causes positive feedback on the anterior pituitary which leads to pre-ovulatory LH surge & FSH surge.

Menopause:

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

- **With advanced age the ovaries become unresponsive (decline in the number of primordial follicles)** to gonadotropins and their function declines so that sexual cycles disappear (menopause).
- **The ovaries no longer secrete estrogen and progesterone. The uterus and vagina atrophy.** Due to removal of the negative feedback effect there is **increased secretion of FSH and LH.**

Definition of menopause:

- **The period during which the cycle ceases & the female sex hormones diminish to almost none.** When estrogens production falls below the critical value, estrogens no longer inhibit the production of gonadotropins FSH & LH. The production of FSH & LH after menopause in large amount.

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.**

Amenorrhea: Is **absence of menstrual period** either

- Primary amenorrhea in which menstrual **bleeding has never occurred**
- Secondary amenorrhea **cessation of cycles** in a woman (she used to have them) **with previously normal periods**, causes:

1. **Pregnancy (is the most common cause)**
2. Emotional stimuli and changes in the environment.
3. Hypothalamic diseases (decrease GnRH pulses)
4. Pituitary disorders
5. Primary ovarian disorders and various systemic diseases (like the thyroid dysfunction either hypo or hyper)

Menorrhagia: Refer to abnormally profuse flow during regular periods.

Hypomenorrhea: Refer to scanty flow.

Dysmenorrhea: Painful menstruation (cramps due to accumulation of prostaglandins in the uterus and treatment with inhibitors of prostaglandin synthesis).

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

1. Describe the normal menstrual cycle
2. Discuss the structural changes that occur in the endometrium during the menstrual cycle and explain how these changes are hormonally controlled
3. **Describe phases of the menstrual cycle**
4. **Describe the hormonal control of the menstrual cycle**
5. Describe the major disorders of the menstrual cycle
6. Describe the physiology of menopause

Keywords: Proliferative Phase, Secretory Phase, Amenorrhea, Menorrhagia, Menopause

Summary:

- *Endometrial lining of the uterus pass through proliferative and secretory phases.*
- *Proliferative phase occur before ovulation while secretory phase occur after ovulation.*
- *Stromal cells & epithelial cells proliferate rapidly under the influence of estrogen that is secreted by the ovaries in large quantities.*
- *Endometrium is prepared for implantation during secretory phase.*
- *Uterine milk is uterine secretion provide nutrition for the diving ovum.*
- *If the ovum is not fertilized, endometrium will be involute about 65% of its previous thickness.*
- *The menstrual blood is normally non-clotting due to the presence of fibrinolysin.*
- *Uterus is highly resistant to infection during menstruation due to leukocyte release.*

Q1:

A 45-year-old woman comes to the physician because of decreased libido and hot flushes. She states that her menstrual cycles are sporadic and irregular, and she suspects she is at the initial stages of menopause. Laboratory studies show elevated LH and FSH, and normal Prolactin levels. Which of the following best explains these findings?

- A. Decreased estrogens
- B. Decreased GnRH
- C. Increased androgens
- D. Increased estrogens
- E. Increased inhibin

Q2:

A 55-year-old woman comes to the physician because of a feeling of intense heat over her trunk and face with an accompanying flushing of the skin. She says that this has been occurring more frequently over the last past 3 months. The episodes last a couple of minutes and then subside. She states that she has also has reduced vaginal lubrication and dyspareunia that makes having sex very uncomfortable. Which of the following is most likely to be seen in this patient?

- A. Decreased FSH, decreased LH, increased estrogen
- B. Increased FSH, no change in LH, decreased estrogen
- C. Increased LH, increased progesterone, increased estrogen
- D. Increased LH, Increased FSH, Increased GnRH
- E. Increased hCG, Increased estrogen, Increased progesterone

Q1 Explanation:

The correct answer is A. Menopause usually occurs between the ages of 48 and 52, but the associated hormonal changes usually begin near age 45. Ovulation frequency begins to decline, and menses and fertility are reduced. Estrogen production is reduced, resulting in the characteristic hot flushes, as well as changes in secondary sex characteristics and bone density. The reduction in estrogens results in an increase in hypothalamic and pituitary hormones. Estrogen normally feeds back to reduce the production of GnRH from the hypothalamus and LH and FSH from the pituitary. Therefore, GnRH, FSH, and LH levels would be increased in the absence of estrogen feedback regulation. Also, decreased libido occurs in women with ovarian failure due to a reduction in circulating testosterone.

While decreased GnRH (choice B) would result in secondary hypogonadism, LH and FSH would also be reduced. In this patient, LH and FSH are increased, and her complaints are caused by estrogen deficiency. This would suggest that the disorder is a loss of inhibitory feedback by estrogens.

Androgens are produced in the theca cells in response to LH stimulation, then converted to estrogen in the granulosa cells. While increased LH levels could stimulate the production of androgens (choice C), the androgens would then be converted to estrogen. The estrogen would then feedback to decrease LH and FSH secretion.

An increase in estrogen (choice D) would feedback to decrease LH and FSH.

An increase in inhibin (choice E) would decrease FSH rather than increase it, as seen in this patient.

Q2 Explanation:

The correct answer is D. Around the age of 45-50 (varies individually), the sexual cycle becomes irregular and anovulatory, and eventually the cycle ceases altogether. This is the menopause, which by definition begins 12 months after the final menses. The features include vasomotor symptoms and urogenital symptoms such as vaginal dryness and dyspareunia. During female reproductive life, about 400 primordial follicles develop into mature follicles and ovulate. Approaching menopause, only a few primordial follicles remain to be stimulated by FSH and LH. This leads to the reduced production of estrogen by the ovaries. At the point when estrogen synthesis falls below a critical level, the hormone can no longer exert negative feedback effect on gonadotropin (FSH and LH) production. Instead, high levels of gonadotropins are produced in large and continuous quantities. The high hormonal levels, particularly those of LH, may be related to occurrence of hot flushes in menopause. Hypothalamic GnRH continues to be produced by the arcuate nucleus, which lies close to neurons involved in the thermoregulation. Without follicular production, the postmenopausal estrogen is derived from the aromatization of androgens in the ovarian stroma and adrenal secretion of androstenedione, which is aromatized to estrone, the major source of circulating estrogen in the postmenopausal female. Long-term exposure to estrone unopposed by progesterone production (corpus luteum) can lead to endometrial hyperplasia, a precursor of endometrial cancer.

Precocious puberty in McCune-Albright syndrome is gonadotropin-independent. Estradiol levels are increased and gonadotropins are suppressed (choice A). An LHRH-stimulation test can help to differentiate between gonadotropin-dependent and independent disorders.

Since high levels of estrogen suppress the secretion of FSH, the fall of estrogen levels prior to day 1 of menstrual bleeding permits the level of FSH to rise, leading to stimulation of follicular development. LH levels do not show significant changes during this period (choice B). By day 5-7 of the cycle, one of the follicles responds to FSH action more than the others, becomes dominant, and starts secreting large amount of estrogen.

At about mid cycle, the increased estrogen helps stimulate a large and sudden LH surge (positive feedback) which causes the follicle to rupture and expel the egg into the fallopian tube (ovulation). Immediately after ovulation, the corpus luteum begins secreting large amounts of progesterone (choice C).

In early pregnancy, the syncytiotrophoblast secretes hCG, which binds to LH receptors on the corpus luteum to rescue it and stimulates estrogen and progesterone production. The placenta takes over at 7 weeks gestation and secretes large quantities of sexual hormones (choice E).