433 Teams

OBSTETRICS & GYNECOLOGY

Physiology of Menstrual Cycle

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Objectives:

- Describe the hypothalamic-pituitary-ovarian axis which controls the menstrual cycle.
- Define the ovarian cycle, ovulation and identify ovarian hormones (estrogen, progestin, androgens and DHEAS)
- Define uterine cycle.
- Describe the function of corpus luteum and relate it to the symptoms of corpus luteum insufficiency.

- **Great video, I advise you to watch it:** https://www.youtube.com/watch?v=2_owp8kNMus

The Menstrual Cycle

- **The menstrual cycle:** Represents a complex interaction among the **hypothalamus, pituitary, ovaries and endometrium** (cyclic changes in gonadotropins and steroid hormones induce functional and morphologic changes in the ovaries and endometrium)

- **Hypothalamic-Pituitary axis:**
  - **Pituitary gland:** Lies below the hypothalamus at the base of the brain within a bony cavity (sella turcica), it's divided into 2 portions:

-Neurohypophysis: which consists of the posterior lobe (pars nervosa), the neural stalk (infundibulum) and the median eminence is in direct continuity with the hypothalamus and central nervous system.

-Adenohypophysis:which consist of pars distails (anterior lobe), pars intermedia (intermediate lobe), pars tuberalis which surrounds the neural stalk.

Hypothalamic-Pituitary Axis

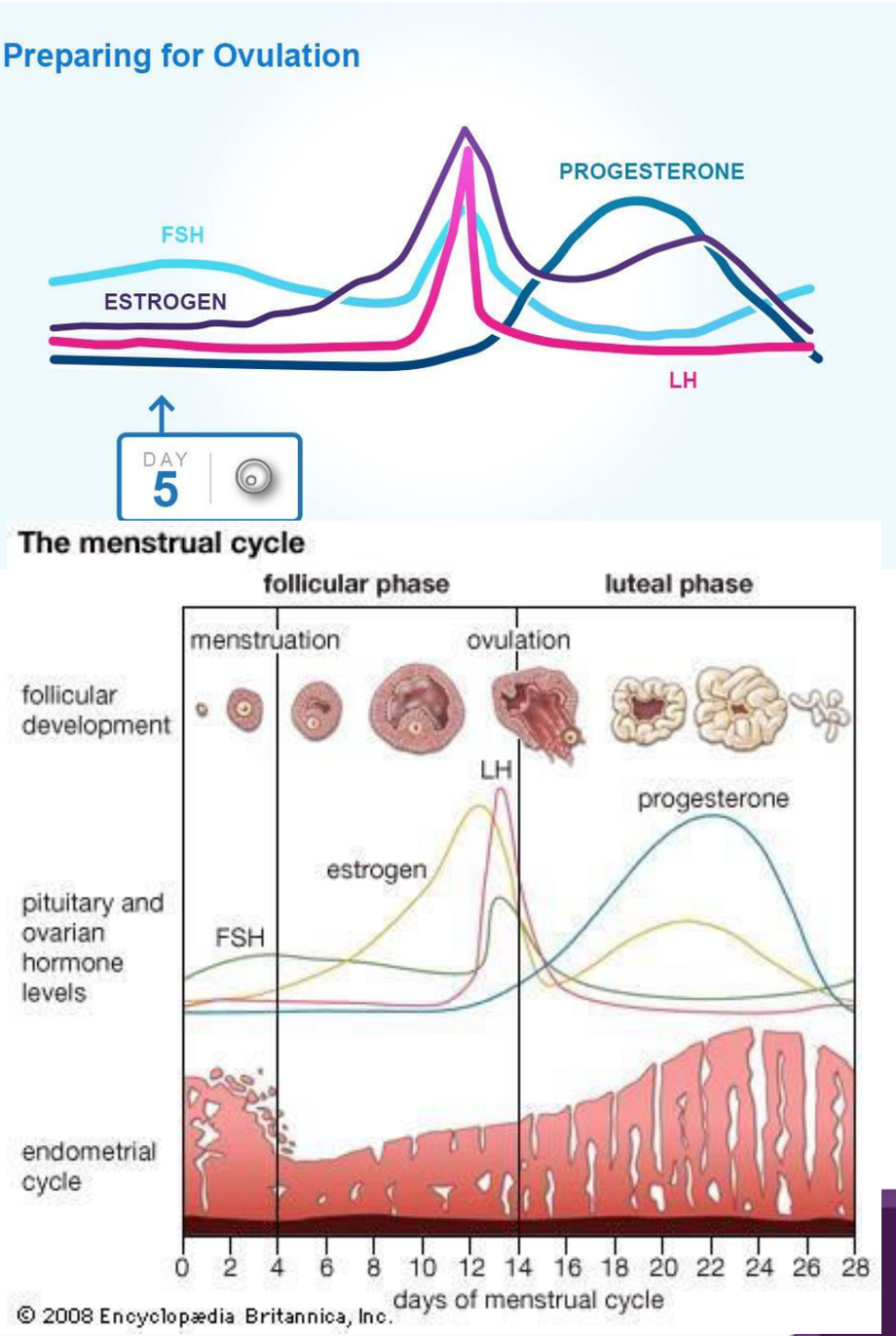
- The arterial blood supply to the median eminence and the neural stalk (pituitary portal system) represents a major avenue of transport for hypothalamic secretions to the anterior pituitary.
- The anterior pituitary contains different cell types that produce six protein hormones:

1. **Follicle – stimulating hormone (FSH)**
2. **Luteinizing hormone (LH)**
3. **Thyroid-stimulating hormone (TSH)**
4. **Prolactin**
5. **Growth hormone (GH)**
6. **Adrenocorticotropic hormone (ACTH)**

- **FSH and LH, are synthesized and stored in cells called gonadotrophs.**

Gonadotropin Secretory Patterns

- FSH, LH and TSH are glycoproteins consist of α and β subunits.
- <u>The α subunits of FSH, LH, and TSH are identical.</u> The same α subunits are also present in human chorionic gonadotrophin (hCG). The β subunits are specific for each hormone.
- **<u>Gonadotropin secretory patterns:</u>**
- Normal ovulatory cycle divided into a follicular and a Luteal phase. The follicular phase begin with the onset of menses and culminates in the pre ovulatory surge of LH.
- The Luteal phase begins with onset of the pre ovulatory LH surge and ends with first day of menses.
- Decreasing levels of estradiol and progesterone in the regressing corpus luteum of the preceding cycle initiate an increase in FSH (by a negative feedback mechanism)



Gonadotropin Secretory Patterns

- A major characteristic of follicular growth and estradiol secretion is explained by the the two-gonadotropin (LH and FSH), two-cell (theca cell and granulosa cell).
- **LH** stimulates the **theca cells** to produce androgens (androstenedione and testosterone).

- **FSH** the stimulates the **granulosa cells** to convert these androgen into estrogens (androstenedione to estrone and testosterone to estradiol).

- Initially, at lower levels of estradiol, there is a negative feedback effect on the ready-release form of LH from the pool of gonadotropins in the pituitary gonadotrophs. As estradiol levels rise later in the follicular phase, there is a positive feedback on the release of storage gondotropins, resulting in the LH surge and ovulation.

Gonadotropin Secretory Patterns

- During the luteal phase, both LH and FSH are significantly suppressed through the negative feedback effect of elevated circulating estradiol and progesterone.

- This inhibition persists until progesterone and estradiol levels decline near the end of the luteal phase as a result of corpus luteal regression, if no pregnancy occur.

- In the beginning of next cycle, there is gradual rise in serum FSH, which initiates new follicular growth.

- The duration of the corpus luteum's functional regression is **14 days** after the LH surge in the absence of pregnancy.

Hypothalamic-Pituitary Axis

- **Hypothalamus:**

- Five different small peptides that affect the reproductive cycle have released from hypothalamus.
- All exert specific effects on the hormonal secretion of the anterior pituitary gland.
- They are GnRH, thyrotropin-releasing hormone (TRH), somatotropin release-inhibiting factor (SRIF) or somatostatin, corticotropin-releasing factor (CRF), and prolactin release-inhibiting factor (PIF).

- GnRh is decapeptide that is synthesized primarily in the arcuate nucleus. It is responsible for the synthesis and release of both LH and FSH.

- GnRH reaches the anterior pituitary through the hypophyseal portal vessels and stimulates the synthesis of both FSH and LH which are stored within gonadotrophs.

Hypothalamic-Pituitary Axis

- GnRh activates and transforms these molecules into releasable forms.
- GnRH can also induce immediate release of both LH and FSH into the circulation.
- Both FSH and LH appear to be present in two different forms within the pituitary gonadotrophs. One is a releasable form and the other a storage form.
- GnRH is secreted in a pulsatile fashion throughout the menstrual cycle.
- The frequency of GnRH release, varies from about every 90 minutes in the early follicular phase to every 60 to 70 minutes in the immediate preovulatory period. During the luteal phase pulse frequency decreases while pulse amplitude increases.
- A continuous (non pulsatile) infusion of GnRH results in reversible inhibition of gonadotropin secretion through a process of “down regulation” or desensitization of pituitary gonadotrophs.

Hypothalamic-Pituitary Axis

-Several mechanism control the secretion of GnRH:

- Estradiol enhances hypothalamic release of GnRH and may help induce the midcycle LH surge by increasing GnRH release or by enhancing pituitary responsiveness to the decapeptide.
- Gonadotropins have inhibitory effect on GNRH. Dopamine has a direct inhibitory effect on GNRH. Serotonin inhibit GNRH pulsatile release. Catecholamines and endogenous opioids may play a major regularity role as well.

-Ovarian cycle:

- **Estrogens:** During early follicular development, circulating estradiol levels are relatively low.
- About 1 week before ovulation level begins to increase, at first slowly,then rapidly. The conversion of testosterone to estradiol in the granulosa cell of the follicle occurs through an enzymatic process called **aromatization.**
- The levels reach a maximum 1 day before the midcycle LH peak.

Ovarian Cycle cont.

- After this peak and before ovulation, there is a marked and precipitous fall.
- During luteal phase,estradiol rises to a maximum 5 to 7 days after ovulation and returns to baseline shortly before menstruation.
- Estrone secretion by the ovary is considerably less than secretion of estradiol but follows a similar pattern.
- Estrone is largely derived from the conversion of androstenedione through the action of the enzyme aromatase.

Ovarian Cycle cont.

-Progestins: During follicular development, the ovary secretes only very small amounts of progesterone and 17α progesterone.

- The bulk of the progesterone comes from the peripheral conversion of adrenal pregnenolone and pregnenolone sulfate.

- Just before ovulation, the unruptured but luteinizing graafian follicle begins to produce increasing amounts of progesterone. At about this time, a marked increase also occurs in serum 17α-hydroxy-progesterone.

- The elevation of basal body temperature is temporarily related to the central effect of progesterone.
- Secretion of progestins by the corpus luteum reaches a maximum 5 to 7 days after ovulation and returns to baseline shortly before mesntruation.
- Should pregnancy occur, progesterone levels and therefore basal body temperature remain elevated.

Ovarian Cycle cont.

-Androgens: Both the ovary and the adrenal glands secrete small amounts of testosterone.

- Most of the testosterone is derived from the metabolism of androstenedione, which is also secreted by both the ovary and the adrenal gland.
- Near midcycle, an increase occurs in plasma androstenedione, due to enhanced secretion from the follicle.
- During the luteal phase, a second rise occurs in androstenedione, which reflects enhanced secretion by the corpus luteum.
- The adrenal gland also secretes androstenedione in a diurnal pattern similar to that of cortisol.

- The ovary secretes small amounts of the very potent dihydrotestosterone (DHT), but the bulk of DHT is derived from the conversion of androstenedione and testosterone.
- The majority of dehydro-epiandrosterone (DHEA) and virtually all DHEA sulfate (DHEA-S), which are weak androgens, are secreted by the adrenal glands.

Serum-Binding Proteins

- Circulating estrogens and androgens are mostly bound to specific sex hormone-binding globulins (SHBG) or to serum albumin.

- The remaining fraction of sex hormones is unbound (free), and this is the biologically active fraction.

- The synthesis of SHBG in the liver is **increased by estrogens and thyroid hormones but decreased by testosterone**

Follicular Development

- Primordial follicles undergo sequential development, differentiation, and maturation until a mature graafian follicle is produced.
- The follicle then ruptures, releasing the ovum. Subsequent luteinization of the ruptured follicle produces the corpus luteum.

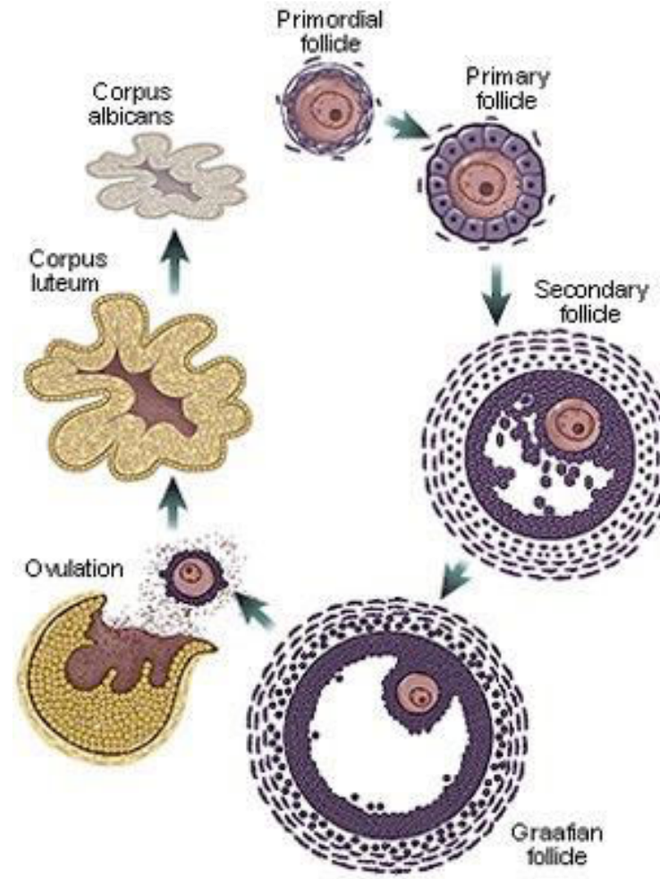
- At about 8-10 weeks of fetal development, oocytes become progressively surrounded by precursor granulosa cells, which then separate themselves from the underlying stroma by a basal lamina.
- This oocyte-granulosa cell complex is called a primordial follicle.
- Between 20-24 weeks,In response to gonadotropin and ovarian steroids, the follicular cells become cuboidal, and the stromal cells around the follicle become prominent.

- During each cycle, a cohort follicles is recruited for development.

Follicular Development

- Among the many developing follicles, only one usually continues differentiation and maturation into a follicle that ovulates. The remaining follicles undergo atresia.

- Follicles greater than 10 mm in diameter are usually estrogen predominant ,whereas smaller follicles are usually androgen predominant.
- Mature preovulatory follicles reach mean diameters of about 18 to 25 mm.
- Furthermore, in estrogen-predominant follicles, antral FSH concentrations continue to rise while serum FSH levels decline beginning at the mid-follicular phase.
- In smaller androgen- predominant follicles, antral fluid FSH values decrease while serum FSH levels decline; thus, the intrafollicular steroid milieu appears to play an important role in determining whether a follicle undergoes maturation or atresia.
- Additional follicles may be “rescued” from atresia by administration of exogenous gonadotropins.



Follicular Development

- Follicular maturation is dependent on the local development of receptors for FSH and LH.
- FSH receptors are present on granulosa cells. Under FSH stimulation, granulosa cells proliferate, and the number of FSH receptors per follicle increases proportionately.
- Thus, the growing primary follicle is increasingly more sensitive to stimulation by FSH; as a result, estradiol levels increase.
- Estrogens, particularly estradiol enhance the induction of FSH receptors and act synergistically with FSH to increase LH receptors.

- During early stages of folliculogenesis, LH receptors are present only on the theca interna layer. LH stimulation induces steroidogenesis and increases the synthesis of androgens by theca cells. In non-dominant follicles, high local androgen levels may enhance follicular atresia.
- However, in the follicle destined to reach ovulation, FSH induces aromatase enzyme and its receptor formation within the granulosa cells.

Follicular Development

- As a result, androgens produced in the theca interna of the dominant follicle diffuse into the granulosa cells and are aromatized into estrogens. FSH also enhances the induction of LH receptors on the granulosa cells of he follicle that is destined to ovulate.

-Ovulation:

- The ovulatory LH surge initiates a sequence of structural and biochemical changes that leads to ovulation.
- Before ovulation, a general dissolution of the entire follicular wall occurs, particularly the portion that is on the surface of the ovary
- This occurs as a result of the action of **proteolytic enzymes.**

- With degeneration of the cells on the surface, a stigma forms, and the follicular basement membrane finally bulges through the stigma. When this ruptures, the oocyte, together with the corona radiata and some cumulus oophora cells, is expelled into the peritoneal cavity.

Ovulation

- At birth, primary oocytes are in the prophase of first meiotic division.
- They continue in this phase until the next maturation division occurs with the midcycle LH surge.

- A few hours preceding ovulation, the chromatin resolved into distinct chromosomes and meiotic division takes place with unequal distribution of the cytoplasm to form a secondary oocyte and the first polar body.
- Each element contains 23 chromosomes each in the form of two monads.

Luteinization and Corpus Luteum Function

- After ovulation and under the influence of LH, the granulosa cells of the ruptured follicle undergo luteinization.
- These luteinized granulosa cells, plus the surrounding theca cells, capillaries, and connec- tive tissue, form the corpus luteum, which **produces copious amounts of progesterone and some estradiol.**
- **The normal functional life span of the corpus luteum is about 9 to 10 days.**
- After this time it regresses, and unless pregnancy occurs, menstruation ensues, and the corpus luteum is gradually replaced by an avascular scar called a *corpus albicans*.

Uterine Cycle

- Functionally, the endometrium is divided into two zones:

1-The outer portion, or functionalis:

That undergoes cyclic changes in morphology and function during the menstrual cycle and is sloughed off at menstruation.

2-the **inner portion,** or **basalis:**

That remains relatively unchanged during each menstrual cycle and, after menstruation, **provides stem cells for the renewal of the functionalis.**

- The cyclic changes in histophysiology of the endometrium can be divided into three stages:

1-Menstrual phase:

The first day of menstruation is taken as day 1 of the menstrual cycle. The first 4 to 5 days of the cycle are defined as the menstrual phase. During this phase, there is disruption and disintegration of the endometrial glands and stroma, leukocyte infiltration, and red blood cell extravasation. **In addition to this sloughing of the functionalis, there is a compression of the basalis due to the loss of ground substances.**

2-Proliferative phase:

It is characterized by endometrial proliferation or growth secondary to **estrogenic stimulation.**

The large increase in estrogen secretion causes marked cellular proliferation of the epithelial lining, the endometrial glands, and the connective tissue of the stroma. Numerous mitoses are present in these tissues, and there is an increase in the length of the spiral arteries, which traverse almost the entire thickness of the endometrium. By the end of the proliferative phase, cellular proliferation and endometrial growth have reached a maximum, the spiral arteries are elongated and convoluted, and the endometrial glands are straight, with narrow lumens containing some glycogen.

3-Secretory phase:

Following ovulation, **progesterone** secretion by the corpus luteum stimulates the glandular cells to secrete glycogen, mucus, and other substances.

The glands become tortuous and the lumens are dilated and filled with these substances. The stroma becomes edematous. Mitoses are rare. The spiral arteries continue to extend into the superficial layer of the endometrium and become convoluted.

If pregnancy does not occur by day 23, the corpus luteum begins to regress, secretion of progesterone and estradiol declines, and the endometrium undergoes involution.

About 1 day before the onset of menstruation, marked constriction of the spiral arterioles takes place, causing ischemia of the endometrium followed by leukocyte infiltration and red blood cell extravasation (secondary to prostaglandins production by the endometrium)

The resulting necrosis causes menstruation or sloughing of the endometrium. Thus, menstruation, which clinically marks the beginning of the menstrual cycle, is actually the terminal event of a physiologic process that enables the uterus to be prepared to receive another conceptus.

Corpus Luteum Insufficiency

- The original definition of luteal phase deficiency (LPD) was a corpus luteum defective in progesterone secretion, which in turn was a cause of infertility or early spontaneous abortion.
- Further investigation led to a broadening of this definition to include a short luteal phase interval (<12 days between ovulation and menses) with relatively normal progesterone concentrations, a normal-length luteal phase with inadequate progesterone production, or inadequate endometrial response to otherwise normal progesterone concentrations.
- Diagnosis: low serum progesterone levels.
- Treatment: Exogenous Progesterone Supplementation.

More info.:
http://www.glowm.com/section_view/heading/Luteal%20Phase%20Deficiency:%20Pathophysiology,%20Diagnosis,%20and%20Treatment/item/326

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