OB/GYN

MEDICINE
KING SAUD UNIVERSITY

Physiology of Menstrual Cycle & Ovulation

Done by: Lina alwakeel , Nouf AlAmari , Laila Mathkour , Rema Albarrak , Alanoud binmethem

Revised by: Allulu Alsulayhim , Dina Aldussary , Sondos Alhawamdeh

References: 437 Lectures And Notes , 436 teamwork

Color code: 437 Notes , 436 Notes | Important | Extra | Kaplan

Editing file: https://docs.google.com/presentation/d/1C-lJHwIqf6tV5j8V9UIMv8PKAH4i4zLbfK6GOFB2PA4/edit?usp=sharing

Objectives:

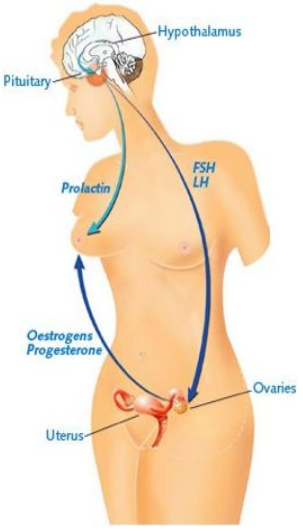
Not given by the doctor

What is menstrual cycle?

- cyclic pattern of activity of hypothalamus, pituitary, ovary, and uterus that produces rhythmical series of physiological changes that occur in females between menarche to menopause.
- **Menarche:** first menstruation in a female that signifies potential reproductivity, commonly occurs around age 12
- **Menopause:** end of a woman's reproductive phase which signifies diminished ovarian function, commonly occurs between ages 45 and 55. It is only going to happen during reproductive age, which can be as early as age 8 (still acceptable as normal), till menopausal age which is الله أعلم كم مافي عمر معين ممكن تستمر له ونقول هذا مو طبيعي

- menstruation (bleeding) is the end of the previous cycle.

Hormones in Menstrual cycle



- Menstrual cycle occurs with the maturation of the hypothalamic–pituitary–ovarian axis. The hormones produced include gonadotropin-releasing hormone (GnRH) from the hypothalamus, which stimulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary, which stimulates estrogen and progesterone from the ovarian follicle.
- Complex interactions among the hypothalamus, pituitary gland , ovaries & endometrium
- **Ovary:** functional & morphologic changes resulting in follicular maturation, ovulation and corpus luteum formation.
  -First half of the cycle (Days 1–14) : FSH stimulate growing several follicles (maybe 20–35 follicles) ⟶ growing follicles produce estradiol , when estradiol levels peak ⟶LH levels increase
  -Second half of the cycle (Days 14–28) : at the mid cycle there will be an increase in LH levels. LH surge occurs causing maturation of the follicle and releasing of the oocyte and the corpus luteum produces progesterone which is a very important hormone in pregnancy.
  - the growing follicle releases estrogen which has **(proliferative effect : cells show high mitotic activity)** and progesterone **(secretory effect: Increased endometrial tortuosity)** on the endometrium.

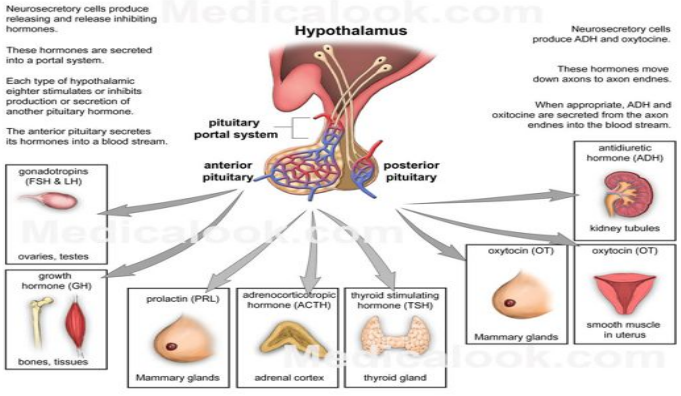
- **Endometrium :** functional and morphologic changes, either to prepare it for conception or shedding of the menstrual endometrium

    - There is a big misconception worldwide between women ' if I don't have menses every month it will affect my body' and that is not true, what will affect your body is hormonal abnormalities specially **estrogen**.
    - Estrogen is very imp and has systemic effect mainly cardiovascular protection, bone protection, and psychological effect (it may protect from alzheimer)

- Physiological changes during the menstrual cycle can be observed at three different levels:
    - neuroendocrine level (hormones)
    - ovaries
    - uterus
- Menstrual cycle can be divided into 3 phases:
    - Menstrual phase
    - Proliferative / Follicular (estrogen) phase
    - Secretory / Luteal phase (progesterone) phase

Hypothalamus

- Located in the arcuate nucleus location is not imp clinically but may come as MCQs question.
- Secretes Gonadotropins Releasing Hormone (GnRH: decapeptide)
- It reaches Anterior Pituitary via hypophyseal portal vessels to synthesize and release FSH & LH hormones
- Its receptors are present in other sites beside pituitary gland e.g. ovary



GnRh secreted as a pulsatile fashion in order to have ovulation. Another imp info is that if GnRh is released continuously it will inhibit pituitary, that is why in clinical site we are using GnRh agonist to inhibit production of LH or FSH in some cases such as abnormal uterine bleeding, endometriosis, fibroids, hirsutism

- Secreted in a pulsatile fashion
  - early follicular phase: Q 90 mins
  - preovulatory: Q 60-70 mins
  - luteal: variable
- Continuous → downregulation/desensitization
  - GnRh agonist can be used as a treatment for: abnormal uterine bleeding, endometriosis, fibroids, etc.

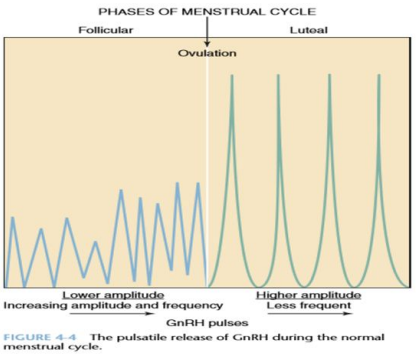
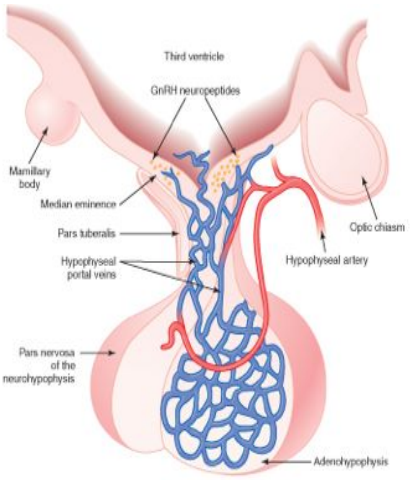


FIGURE 4-4 The pulsatile release of GnRH during the normal menstrual cycle.

Pituitary Gland imp

- Located below the hypothalamus and within a bony cavity (sella turcica)
- Divided into 2 portions (Anterior & Posterior)
- Anterior portion secretes many hormones including: Folllicular Stimulating Hormone (FSH) and Luteal Stimulating Hormone (LH)
- **FSH and LH :** synthesized and stored in gonadotrophs
- Glycoproteins: alpha and beta subunits
  - alpha: similar (FSH, LH and TSH)
  - beta: variable (hormone specific)
- Half-life: LH: 30 min, FSH: several hrs



- **FSH:** stimulates the growth of granulosa cells and induces the **aromatase** enzyme that converts androgens to estrogens. It raises the concentration of its own receptors on the granulosa cells. It stimulates the secretion of inhibin from the granulosa cells and is suppressed by inhibin.
- **LH:** stimulates the production of androgens by the theca cells, which then get converted to estrogens in the granulosa cells by the aromatase enzyme (two-cell theory). It raises the concentration of its own receptors in FSH-primed granulosa cells. The LH surge, which is dependent on a rapid rise in estrogen levels, stimulates synthesis of prostaglandins to enhance follicle rupture and ovulation. The LH surge also promotes luteinization of the granulosa cells in the dominant follicle, resulting in progesterone production as early as the 10th day of the cycle. LH increases in the pre-ovulatory period.

It's imp to know that almost all hormones are made of two subunits alpha and beta. Alpha is similar in all these hormones, beta subunit is different. So if we are going to do hormonal profile we test Beta subunits, if we didn't do that it will appear too high (false positive).

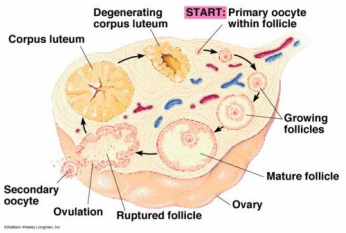
HCG hormone has the same structure. is only secreted when there are trophoblasts in the body (during pregnancy, some tumors). So if we want to test for pregnancy we always test for beta subunits of HCG.

Menstrual cycle

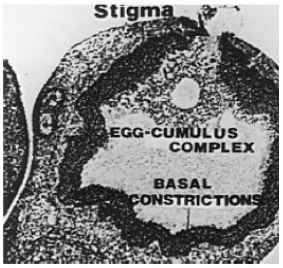
On average 28 days, can be as short as 21 days and as long as 40 days. (17-35)
You need to know that each phase will happen at a different organ levels.

Phase	Menstrual phase	Proliferative phase	Ovulation	Secretory phase
Average start & end day (assuming a 28 day cycle)	1-4 days	5-13 days	13-16 days	16-28 days

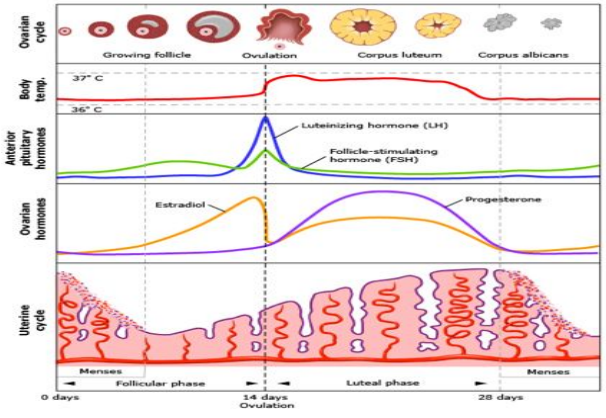
Pls remember something imp when I say day 3 it means 3rd day of bleeding, we start counting from the 1st day of blood coming out (whatever the color or amount), has nothing to do with the cramps or other symptoms.

Phases of menstrual cycle	
Menstrual phase	• Menstrual bleeding, menses, period • Lasts 3 -5 days on average can be 2-8 • Discharge of bloody fluid containing endometrial cells, glandular secretions and blood cells • Due to strong vasoconstriction and proteolytic activity, functional stratum of endometrial tissue dies and is discharged during menstrual bleeding • Changes in color or smell of the blood usually is not significant clinically • in the absence of a pregnancy →drop of estrogen and progesterone levels after the luteal phase →tortuous blood vessels contraction → ischemia → shedding of the endometrium →menstruation and stimulates the hypothalamus to produce GnRH starting the next cycle.
Follicular phase	• Due to the rise of follicle stimulating hormone (FSH) during the first days of the cycle, several ovarian follicles are stimulated • Follicles compete with each other for dominance • The follicle that reaches maturity is called a **Graafian follicle** the only one which has egg in it. ❖ **Follicular development** ○ Primordial follicle ○ Primary follicle ○ Secondary follicle ○ Cohort of follicles is recruited each cycle ○ Only one continues differentiation and maturation ○ Others: atresia 

	○ Maturation depends on: FSH and LH receptors.
Ovulation	• Most important event: LH surge surge=sudden increase. LH increases in the preovulatory stage. (mid cycle usually day 14) • Proteolytic enzymes → dissolution of follicular wall • Stigma formation not imp • Ovulation: rupture of the stigma • During the follicular phase, estrogen suppresses production of luteinizing hormone (LH) from the pituitary gland • When the ovum has nearly matured, levels of estrogen reach a threshold above which they stimulate production of LH (positive feedback loop) • The release of LH matures the ovum and weakens the wall of the follicle in the ovary, causing the fully developed follicle to release its secondary oocyte • Oocyte + corona radiata + cumulus cells • <u>It is a Gradual:</u> several minutes → an hour • After being released from the ovary, the ovum is swept into the fallopian tube. • Lifespan of the eggs is 12-24hrs, it has to be fertilized during this period otherwise it will undergo degeneration. • LH can be tested by urine test (ovulation test or LH test). • If we induced LH surge or test was + we tell the couple that they have 36 hrs period, sexual intercourse should happen during this period.
Luteal phase	• **Corpus luteum:** solid body formed in an ovary after the ovum has been released into the fallopian tube • Produces significant amounts of progesterone, which plays a vital role in making the endometrium receptive to implantation of the blastocyst. • High levels of Estrogen and Progesterone suppress production of FSH and LH that the corpus luteum needs to maintain itself. ❖ Corpus luteum formation ○ Luteinization of granulosa cells (LH) ○ CL: luteinized GC + theca cells + capillaries + connective tissue ○ Major source of ovarian progesterone ○ Lives 9-10 days if no pregnancy ○ It gradually regresses → corpus albicans



Gonadotropin secretory pattern



Hormones in Ovarian cycle

1. **Estrogen :**
    a. gradually increase during follicular phase
    b. remember: Two gonadotropin-two cell theory you need to go through it

It is produced in the granulosa cells in response to even low FSH concentrations and stimulates proliferative changes in the endometrium. It has a negative feedback to FSH at the hypothalamic–pituitary level, but has a positive feedback to increase GnRH receptor concentrations. At low estrogen levels there is negative inhibitory feedback for LH release, but as the level of estradiol increase is sustained for 50 hours, there is a transition to a positive stimulatory feedback, leading to the LH surge.

1

Two Gonadotropin two- cell theory

know that the granulosa cell is affected by FSH, and the thecal cell is affected by LH

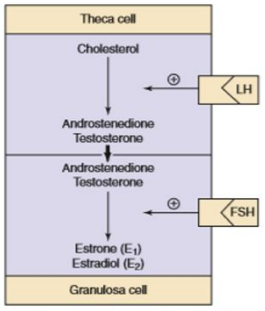
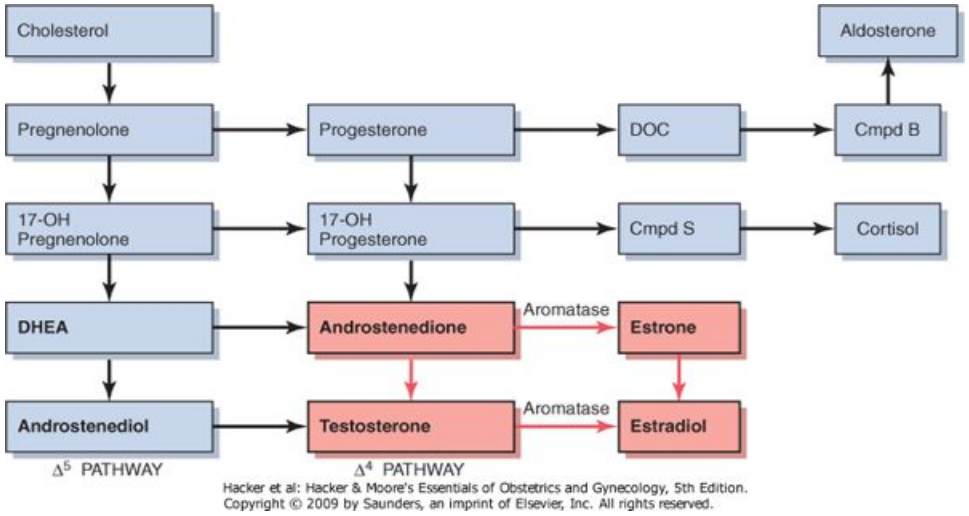


FIGURE 4-3 The two-gonadotropin (LH and FSH), two-cell (theca cell on top and granulosa cell below) theory of follicular development. Each cell is theorized to perform separate functions; LH stimulates the production of androgens (androstenedione and testosterone) in the theca cell, and FSH stimulates the aromatization of these androgens to estrogens, estrone, and estradiol in the granulosa cell.

2

Steriodogenic pathways in the ovary



Hacker et al: Hacker & Moore's Essentials of Obstetrics and Gynecology, 5th Edition.

There are three types of estrogen in the body: 1-estrone (post menopausal years, does not cause ovulation) 2- estradiol (causing ovulation) 3- estriol (during pregnancy)

2. **Progestin :** only produced by ovaries, no other source
   - produced by the corpus luteum and stimulates secretory changes in the endometrium in preparation for blastocyst implantation.
   - Follicular phase: very little from the ovary
   - The bulk: peripheral conversion of adrenal pregnenolone and P sulfate
   - High production: after ovulation/ CL
   - Corresponds with ↑ basal body temperature
   - Max: 5-7 days after ovulation

   To know if ovulation happened at the second phase of the cycle (between day 20 and 22)
   We test progesterone level (called post ovulation test)

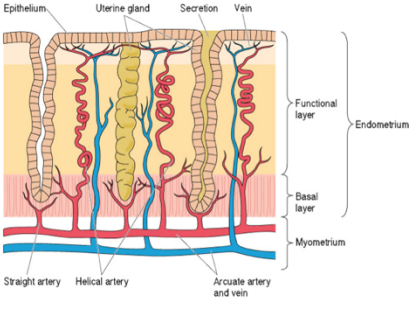
3. **Androgens :**
   include androstenedione and testosterone. They are precursors of estrogen and are produced in the theca cells. In lower concentrations they stimulate aromatase enzyme activity, whereas at high levels they inhibit it. Androgens inhibit FSH induction of LH receptors.

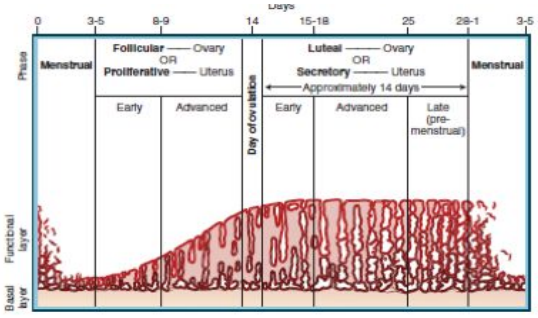
Endometrial physiology

- Responsive to Estrogen, Progesterone and Androgens.
- Results in: menstruation,Implantation/pregnancy
- **2 zones:**

1. Functional layer (outer): is the superficial layer that undergoes cyclic changes during the menstrual cycle and is sloughed off during menstruation. It contains the spiral arterioles that undergo spasm with progesterone withdrawal.
2. Basal layer (inner): is the deeper layer that remains relatively unchanged during the menstrual cycle and contains stem cells that function to renew the functionalis. It contains the basal arteries. in curettage surgery after abortion we only remove the funtional area If a female had her basal layer removed she may end up with amenorrhea (premature menopause) !! The basal layer is very imp

Histophysiology of the Endometrium





1. Menstrual phase: defined as the first four days of the menstrual cycle, with the first day of menses taken as day 1. It is characterized by disruption of endometrial tissues, WBC infiltration, RBCs extravasation. Sloughing of the functionalis and compression of the basalis occurs.
2. Proliferative phase: follows the menstrual phase and is characterized by Estrogen-induced endometrial growth, including division of stem cells that migrate through the stroma to form new epithelial lining of the endometrium and new endometrial glands. The length of the spiral arteries also increases. An **estrogen-dominant endometrium is unstable** and, in the presence of **prolonged anovulation**, will u**ndergo hyperplasia with irregular shedding over time.**
3. Secretory phase: follows the proliferative phase and is characterized by progesterone (from the corpus luteum)-induced glandular secretion of glycogen, mucus & other substance. Endometrial stroma becomes edematous, and spiral arteries become convoluted. **A progesterone-dominant endometrium is stable and will not undergo irregular shedding.** Regression of the corpus luteum occurs by day 23 if there is no pregnancy, causing decreased levels of progesterone and estradiol and endometrial involution. Constriction of the spiral arteries occurs one day before menstruation, causing endometrial ischemia and release of prostaglandins, followed by leukocyte infiltration and RBC extravasation. The resulting necrosis leads to painful cramps and menstruation. When a pregnancy occurs, the serum β-human chorionic gonadotropin (β-hCG) becomes positive at day 22–23 of the cycle. The β-hCG becomes positive when the zygote implants into the endometrium, usually 7–8 days after ovulation. Therefore, the serum β-hCG becomes positive before the missed period.

Summary

Hormones involved in menstruation:

1. GnRH from hypothalamus which released in pulsatile pattern
2. FSH and LH from pituitary
3. ESTROGEN and PROGESTERONE from ovaries

Phases of menstrual cycle	
Menstrual phase	• Bleeding phase • Lasts 3 -5 days on average • Discharge of bloody fluid containing endometrial cells, glandular secretions and blood cells
Follicular phase	• rise of FSH stimulate several ovarian follicles • mature follicle is called a **Graafian follicle.** • Average start & end day 5-13 days

Ovulation	• Most important event: LH surge surge=sudden increase • Ovulation mean rupture of the mature follicle or stigma • Usually estrogen suppress LH but levels of estrogen reach a threshold above which they stimulate production of LH • After being released from the ovary, the ovum is swept into the fallopian tube. • Average start & end day 13-16 days
Luteal phase	• **Corpus luteum:** solid body formed in an ovary after the ovum has been released • Produces progesterone, which make the endometrium receptive to implantation of the blastocyst. • High levels of Estrogen and Progesterone suppress production of FSH and LH • Average start & end day 16-28 days

MCQs

1) Which hormone surge 24-36 hours before ovulation?

A- LH B- Cortisol C- Progesterone D- Testosterone

2) In the normal physiological menstrual cycle which one of the following is true regarding the luteal phase?

A- High Prolactin Level. B- High progesterone level.

C- Low basal body temperature. D-Proliferative endometrium

3) which hormone is accurate to test in pregnancy

A- progesterone B- alpha HCG C- beta HCG D- GnRH

4) what is the name of mature follicle

A- stigma B- Graafian follicle C- corpus luteum D- primordial follicle

5) continuous release of GnRH lead to upregulation of the gonadotropin

A. true

B. false

Answers: 1- A. 2- B. 3- C. 4- B. 5- B.