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Physiology of the menstrual cycle

Objectives:

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

Highly recommended ! : https://www.youtube.com/watch?v=2_owp8kNMus
https://drive.google.com/file/d/1O4zeQQWHwoQFiUFfedKSNZbLToW8tXzD/view

المحاضره جدا سهله و هي مراجعة لمحاضرة الفسيولوجي سنه ثاني
لذلك " أرجوكم بلا صياح الوضع ريلاكس "

References: 435 lecture and notes, team 433

Done by : , Noura Alkharraz, Mai alageel.

Revised by: Haifa Almohsen, lina alshehri,

Khaled Al Jedia.

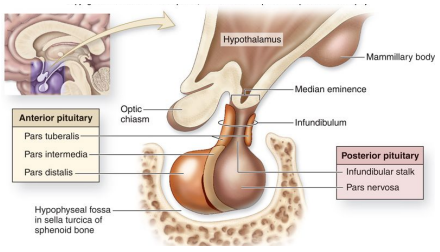
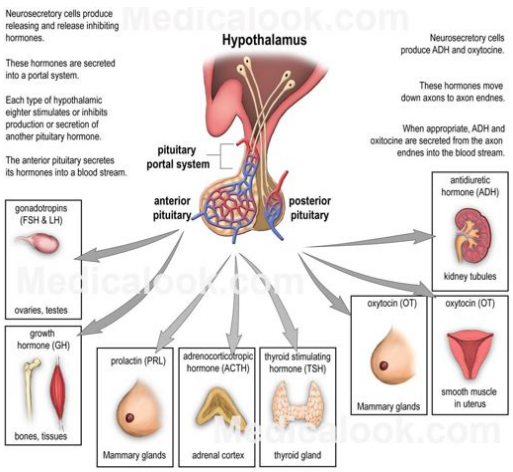
Menstrual Cycle:

It's a Complex interactions among hypothalamus, pituitary gland , ovaries & endometrium. (cyclic changes in gonadotropins and steroid hormones induce functional and morphologic changes in the ovaries and endometrium) If you have any problem in these stations the bleeding will be affected either by the amount or duration or both depending on the site of the pathology.

The Hypothalamus releases GnRH that will go to the pituitary that will release two hormones FSH and LH.They will go to the ovaries and estrogen and progesterone will be released and will affect the uterus.

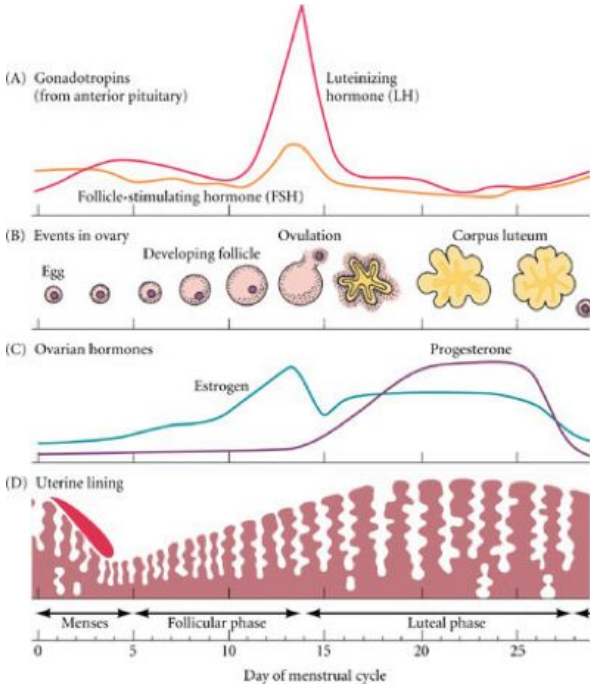
Ovary	Endometrium
follicular maturation, ovulation and corpus luteum formation	either to prepare it for conception or shedding of the menstrual endometrium

Pituitary Gland:

Location	Blood supply
Lies below the hypothalamus at the base of the brain within a bony cavity called (sella turcica) above it, dura matter (diaphragma sellae). divided into 2 portions: 1. Neurohypophysis: which consists of : - the posterior lobe (pars nervosa) - the neural stalk (infundibulum) - the median eminence which is in direct continuity with the hypothalamus and central nervous system. 2. Adenohypophysis: which consist of : - pars distails (anterior lobe). - pars intermedia (intermediate lobe), - pars tuberalis which surrounds the neural stalk  	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: you have to know it by your heart 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 consists of α and β subunits.
The α subunit of FSH, LH, and TSH are identical.
The same α subunits are also present in human chorionic glycoprotein(hcg) we never measure the alpha because it can be misleading
The β subunit are specific and variable for each hormone.

hCG is a dimer consisting of a 145 amino acid beta-subunit that is unique to hCG and a 92 amino acid alpha-subunit. The alpha-subunit is identical to that for luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH) and that's why we measure β not α

half-life: LH: 30 min, FSH: several hrs

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)

FSH: starts to increase by the beginning of the cycle and is responsible for the growth of 20-35 follicles.Only **one** reaches maturation and the rest is lost.The more follicles growing the more chance of successful ovulation but on the other hand if a high number of follicles are growing each month menopause will be reached earlier than those having having less follicles growing(this is the cause of the variety in the age of menopause) .When females are born they have around 2 million primordial follicles but many go into atresia and around 300,000 remain by the time of puberty.

LH: starts to increase at the same time as FSH but in a steady level and reaches a **surge in the middle** of the cycle and causes ovulation (ovulation means that the dominant follicle (the one that reached the maximum maturity compared to the other follicles) will rupture and the ovum will be released.

During the second half of the cycle both hormones have a steady decline.
Ovaries secrete Estrogen and Progesterone from the growing follicle estrogen increases more in the beginning of the cycle and progesterone is more steady.During ovulation (the LH surge) the maximum amount of estrogen is released (lasts 36-72 hours best chance of getting pregnant). Following that estrogen will drop and progesterone will increase, it is being released by the corpus luteum(yellow body) Progesterone is important in the second half of the cycle because it is responsible for turning the endometrium to secretory phase.
If no pregnancy occurs the corpus luteum will turn into corpus albicans (white body) and the estrogen and progesterone will drop so nothing is left to support the thick endometrium and it will start to shed and menstruation will occur.
Menstruation duration: Length of bleeding first till last day of bleeding.

Menstrual cycle:From the first day of bleeding in the current month till the first day of bleeding of the next month it is not fixed(17 - 35 days is within normal range).
Stress causes cycle irregularity because it increases prolactin(suppresses FSH and LH) and endorphins.Anatomical and pathological issues can also affect the cycle length.
The endometrium :
Follicular phase:In the first half of the cycle under the effect of estrogen it is thickened and there is increased blood vessels.It changes if the cycle gets shorter or longer .
Luteal Phase: During the second half and under the effect of progesterone the endometrium will be secretory and the blood vessels will be coiled. It is always fixed and it is 14 days prior to menstruation.

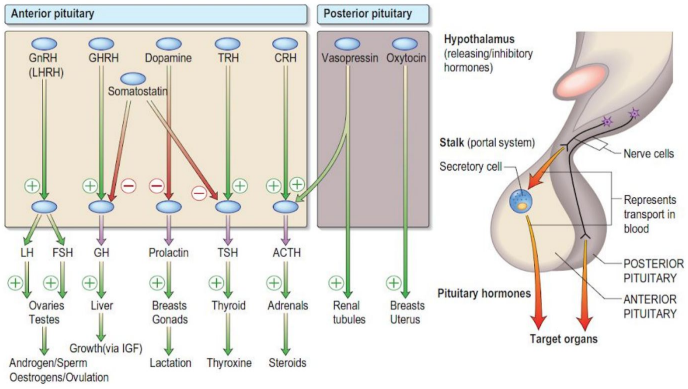
A major characteristic of follicular growth and estradiol secretion is explained by the the two-gonadotropin (LH and FSH), two-cell (theca cell and granulosa cell).

- LH stimulates the **theca cells** to produce androgens (androstenedione and testosterone).
- FSH 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 gonadotropins, resulting in the LH surge and ovulation.
- 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 functional regression is 14 days after the LH surge in the **absence** of pregnancy.

Hypothalamic-Pituitary Axis:

Hypothalamus:

Is controlling the pituitary gland through releasing hormones which are peptide hormones. so they are very important in the synthesis and release of the trophic hormones of the pituitary gland except prolactin hormone which is under inhibitory effect, dopamine effect.



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:

1. GnRH
2. thyrotropin-releasing hormone (TRH)
3. somatotropin release-inhibiting factor (SRIF) or somatostatin
4. Corticotropin releasing factor (CRF)
5. prolactin release-inhibiting factor (PIF)/dopamine.

Normal ovulatory cycle is divided into proliferative (or follicular) phase and secretory (or luteal phase). Follicular phase starts with the onset of the menses till preovulatory LH surge and ovulation, luteal phase then starts till next menses .

- 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.
- 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.
- Continuous (non pulsatile) infusion of GnRH results in reversible inhibition of gonadotropin secretion through a process of down regulation or desensitization of pituitary gonadotropin.(can be used to stop menstruation for medical purposes)
- GnRH receptors are present in other sites beside pituitary gland e.g., ovary

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 regulatory 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.
- 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.
- Three types of Estrogen in the body:
- Estradiol: Nonpregnant Reproductive years.
- Estrone:After Menopause (does not protect the heart like Estradiol).

Progestins:

- During follicular development, the ovary secretes only very small amounts of progesterone and 17 α 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 17 α -hydroxy-progesterone.
- The elevation of **basal body temperature** is temporarily related to the central effect of progesterone.During the second half of the cycle and under the effect of progesterone the body basal temperature will go up by (3-3.5) and this is one of the indicators of ovulation. It is one of the methods to detect ovulation يقيس kit بس الحين تغير الوضع صار فيه بالصيدليات ال estradiol in the urine
- Secretion of progestins by the corpus luteum reaches a maximum 5 to 7 days after ovulation and returns to baseline shortly before menstruation.
- Should pregnancy occur, progesterone levels and therefore basal body temperature remain elevated.

Androgens:

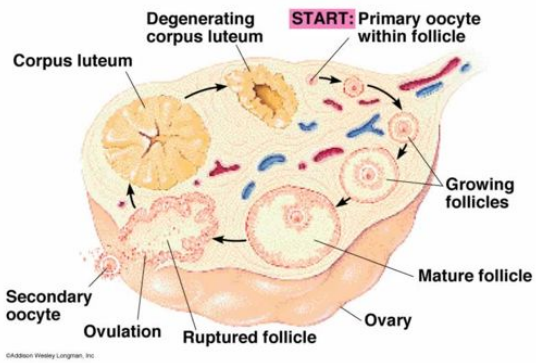
- Both the ovary and the adrenal glands secrete small amounts of testosterone.
- Most of the testosterone is derived from the metabolism of androstenedione, which is also secreted by both the ovary and the adrenal gland.
- Near midcycle, an increase occurs in plasma androstenedione, due to enhanced secretion 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.
- 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 the beginning FSH rises which stimulate many follicles but then it drops and that's because there is only one dominant follicles and increases of FSH receptors on it so you don't need a much of FSH to stimulate it.
- 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 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.
- 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 the follicle that is destined to ovulate.

Ovulation :

Ovulation: rupture of the stigma

- Most important event: **LH surge**
- 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.
- Gradual: several minutes → an hour
- **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

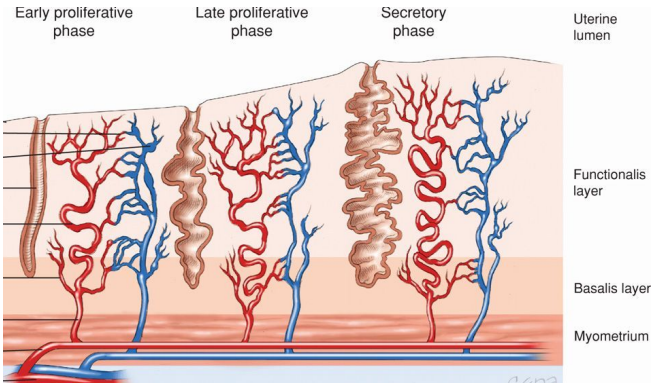
- After ovulation and under the influence of LH, the **granulosa cells** of the ruptured follicle undergo luteinization.
- Major source of ovarian **progesterone**
- These luteinized granulosa cells, plus the surrounding theca cells, capillaries, and connective tissue, form the **corpus luteum**, which **produces copious amounts of progesterone and some estradiol.** If pregnancy occur placenta will continue to secrete progesterone .
- **The normal functional lifespan of the corpus luteum is about 9 to 10 days** if no pregnancy occurs
- 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:



This is very important for endometrial sample
For example when a women come to me with 6 months without menses first i will roll out pregnancy (even if it long period) then when i make sure that she is not pregnant, i found that the endometrium is thick in the ultrasound, i will offer her endometrial sample to look at the histopathology if it's normal, hyperplasia(precancerous) or cancerous

(roll out pregnancy then ultrasound then endometrial sample)

and it is important to tell the pathologist at which phase of the cycle if i can .

1- Menstrual phase:	2- Proliferative phase:	3-Secretory phase:
disruption of endometrial tissues, WBC infiltration, RBCs extravasation 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.	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.	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(spiral artery spasm) takes place, causing ischemia of the endometrium followed by leukocyte infiltration and red blood cell extravasation (secondary to prostaglandins production by the endometrium) prostaglandin release will stimulate smooth muscle contraction of the uterus which characterized by **cramping** (when you have anovulation you won't have cramping) 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.

*Sperms can survive for 72 hours in the uterus. So even if the ovulation occur one day after the intercorse, there is a chance for fertilization وعشان كذا ننصح اللي يخططون للحمل ان يكون الجماع يوم ورا يوم

So in summary and to make it easier let's put it all together

Initially we have rise in FSH which will stimulate follicles to produce estradiol which will rise (LH is stable in the first half of the cycle) then FSH will start to drop but estradiol will continue to rise, WHY ? because of the dominant follicles with many FSH receptors which produce estradiol, estrogen levels rising (48-72 hours before LH surge) is imp for LH surge to occur(if it's elevated & tonic not rising LH surge won't occur like PCOS) which result is ovulation . so LH surge⟶ ovulation , ovulation⟶corpus luteum , corpus luteum will produce progesterone in secretory phase until the middle of the last half of the cycle , if there is no pregnancy(no HCG) corpus luteum regress to corpus albicans and progesterone decreases & when it is below a certain level ⟶ spiral arteriole constriction , necrosis , release of prostaglandin and menses

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.

The commonest cause of secondary amenorrhea is anovulation and that's why the patient doesn't have menses
So just give her progesterone

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.

answers : 1) a 2) b