Reviewed By
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Physiology of Menstrual Cycle & Ovulation

Objectives:

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

- → Slides
- → Important
- → Golden notes
- → Extra
- → Doctor's notes
- → Previous Doctor's notes
- → Reference

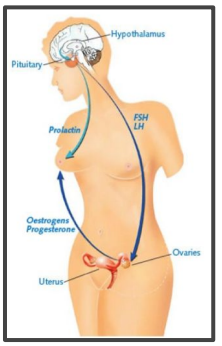
Kaplan Video

Editing File

Reproductive Cycle

Dr. Nadine Ninja Nerd

Reproductive Cycle:



→ **Reproductive cycle (*menstrual cycle*):** a normal physiological phenomena, a complex interactions among **hypothalamus**, **pituitary gland** (*higher center*), **ovaries** and **endometrium** (*genetal tract*[1]), that occur in females between:
  → **Menarche:** first menstruation, signifies potential reproductivity.
    → **Mean age:** 12 - 13.
  → **Menopause:** end of reproductive phase, signifies diminished ovarian function (*non-responding follicles*).
    → **Mean age:** 51.
→ The reproductive cycle can be viewed from the perspective of each of four physiologic components.
  → These endocrine events occur in concert in a uniquely integrated fashion.

Menstrual Cycle

→ **Gonadotropins:** luteinizing hormone (LH) + follicle-stimulating hormone (FSH).
→ **Sex steroid hormones:** estradiol + progesterone.
→ Cyclic changes in gonadotropins and sex steroid hormones (mainly E2 & P4) have effect on:

Ovaries

Gonadotropins + sex steroids → functional (*hormonal*) & morphologic changes in ovary → follicular maturation → ovulation → corpus luteum formation.

Endometrium

Gonadotropins + sex steroids → functional (*hormonal*) & morphologic changes (*enlargement*) → successful implantation of fertilized ovum **or** physiologic shedding of menstrual endometrium (*if early pregnancy doesn't occur*).

→ **Normal cycle start:** first day of menstrual bleeding.
→ **Normal cycle ends:** just before the first day of the next menses.
→ **Average length of each cycle:** 28 (±7) days.

→ **Levels of physiological changes during menstrual cycle:**
1. Neuroendocrine / Hormonal Level
2. Ovaries level
3. Uterus level

→ Hypothalamus produces GnRH → pituitary gland produces FSH (*act on the 1st half of the cycle*) + LH (*act on the 2nd half of the cycle*) → ovary produces estrogen (*main hormone in 1st half of the cycle*) & progesterone (*main hormone in 2nd half of the cycle*).

1. There are other elements that take effect in between, like the thyroid and the hymen.

1. Neuroendocrine / Hormonal Level

Hypothalamus GnRH:

→ **GnRH:** Gonadotropin releasing hormone.
  → A decapeptide that is synthesized primarily in the arcuate nucleus.
  → **Half-life:** 2 - 4 minutes (very short).
  → Reaches the anterior pituitary via **hypophyseal portal vessels**.
  → **Secreted by:** hypothalamus.
  → **Responsible for:** LH and FSH synthesis & release from gonadotrophs in pituitary gland.
→ GnRH receptors are present in other sites beside pituitary e.g. **ovaries** → suggests that GnRH may have a direct effect on ovarian function.

→ Secreted in a **pulsatile** fashion throughout the menstrual cycle:
  → **Early follicular phase:** more frequent pulses - lower amplitude (*Q 90 mins*).
  → **Preovulatory:** Q 60 - 70 mins.
  → **Luteal phase:** less frequent pulses - higher amplitude (*variable*).
→ Continuous release → **downregulation** of receptors + **desensitization** of uterus[1].

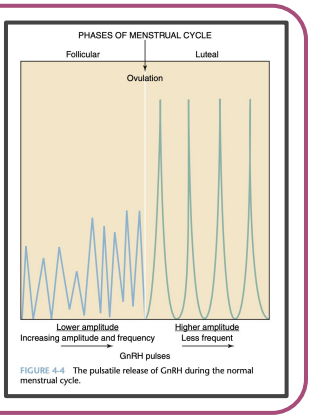


FIGURE 4-4 The pulsatile release of GnRH during the normal menstrual cycle.

→ **Mechanisms controlling GnRH secretion:**

↑ GnRH Secretion	🚫 GnRH Secretion
→ **Estradiol:** enhance hypothalamic release of GnRH (+ve feedback). → **Norepinephrine:** stimulates GnRH release (+ve feedback).	→ **Gonadotropins:** inhibitory effect on GnRH release. → **Dopamine:** direct inhibitory effect on GnRH secretion (*patients with amenorrhea due to dopamine agonists use which inhibits GnRH secretion*). → **Serotonin:** inhibit GnRH pulsatile release.

GnRH Analogues:

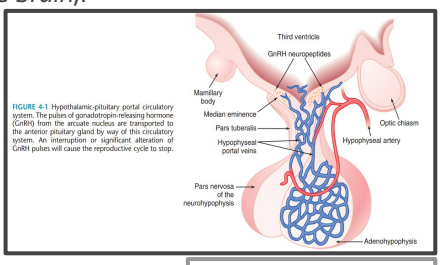
→ Nonapeptides and contain only 9 amino acids, can be either:
  → **Pulsatile:**
    → IV and SC administration of exogenous pulsatile GnRH.
    → Induces **ovulation**.
    → **Used in:** selected women not ovulating as a result of **hypothalamic dysfunction** (***e.g:*** *IVF for ovulation induction*).
  → **Continues:**
    → Continuous (non-pulsatile) infusion of GnRH → downregulation or desensitization of pituitary gonadotrophs → reversible inhibition of gonadotropin secretion.
    → **Used in:** therapy of **ovarian hormone-dependent disorders** (*hyperandrogenic or hyperestrogenic state*): **endometriosis** - **leiomyomas** (fibroids) - **hirsutism** - **precocious puberty** (*estrogen → early closure of bony epiphysis → short stature of child | Given GnRH continuously for 6 months → prevent estrogen secretion → amenorrhea*) and **abnormal uterine bleed**.

1. Young girls don't go through puberty because of the lack of the pulistile release so we can give it to non-ovulatory girls in a pulsatile manner to induce ovulation via increasing estrogen levels and producing an LH surge.

1. Neuroendocrine / Hormonal Level

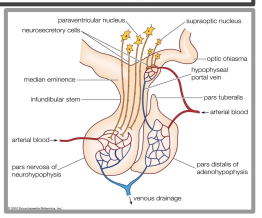
Pituitary Gland:

→ Lies below hypothalamus at **sella turcica** (*a bony cavity at base of the brain*).
→ Separated from the cranial cavity by **diaphragma sellae** (*condensation of dura mater overlying the sella turcica*).



Hypothalamic-Pituitary Axis:

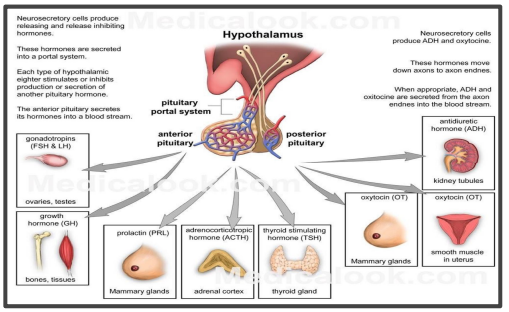
→ **Pituitary portal system:** the arterial blood supply to median eminence + neural stalk, a major avenue of transport for hypothalamic secretions to anterior pituitary.



Major Parts/Divisions/Portions of the Pituitary Gland:

→ **Anterior Pituitary Gland (*Adenohypophysis*):**
  → **Consists of:** pars distalis (*anterior lobe*) + pars intermedia (*intermediate lobe*) + pars tuberalis (*surrounds neural stalk).*
  → **Derived from:** ectoderm.
  → Contains 3 different cell types that produce/**secrete** 6 protein hormones into hypophyseal portal circulation:
    → **Acidophiles:** growth hormone (GH) + prolactin.
    → **Basophils:** follicle stimulating hormone (FSH) + luteal Hormone (LH) + adrenocorticotropic hormone (ACTH) + thyroid-stimulating hormone (TSH).
    → **Chromophobes:** reserve cells, some says it secretes prolactin.

→ **Posterior Pituitary Gland (*Neurohypophysis*):**
  → **Consists of:** posterior lobe (*pars nervosa*) + neural stalk (*infundibulum*) + median eminence.
  → **Derived from:** neural tissue (has neural axons).
  → In direct continuity with hypothalamus & CNS.
  → **Function: stores** & secretes hormones synthesized in hypothalamus (vasopressin "*antidiuretic hormone*" + oxytocin) and transport them along neuronal projections from supraoptic and paraventricular nuclei of hypothalamus to circulation.
    → Oxytocin effects both the breast & uterus.



FSH, LH, and TSH:

→ FSH and LH are synthesized and stored in **gonadotrophs**.
→ **Glycoproteins:** compounds consist of α and β subunits:
  → **Examples:** FSH - LH - TSH.
  → **α subunits of FSH, LH, and TSH:** identical.
    → Same α subunit is present in human chorionic gonadotropin (hCG).
      → hCH is released from the placenta.
  → **β subunits of FSH, LH, and TSH:** variable & individual for each hormone (hormone specific).
→ **Half life for circulating FSH:** several hours.
→ **Half life for circulating LH:** about 30 mins.

Clinical Point:

→ **β** hCG in blood > 5 → pregnancy.
→ **β** hCG should be ordered to check for pregnancy (**not α hCG!**), why?
  → Similar α subunits → misleading (e.g. surge of LH in mid cycle maybe mistaken for pregnancy).
→ Both hypo and hyperthyroidism can affect the menstrual cycle.

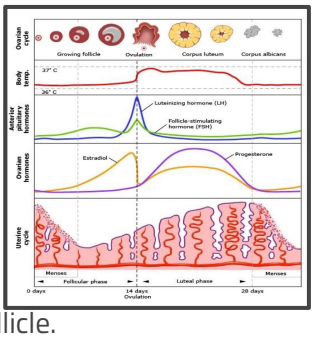
→ All hormones which are produced are releasing hormones except dopamine as it inhibits prolactin.
→ Important hormones in ovulation are: FSH, LH, TSH and prolactin.
→ High level of prolactin inhibit the ovulation ,that's why in lactation the high level of prolactin causes Lactational amenorrhea.
→ In infertility cases we measure FSH, LH, TSH and prolactin in the 2nd day of menses.Then GH and ACTH.

2. Ovaries Level (Ovarian Cycle)

Ovarian Cycle:

→ **Normal ovarian cycle:** follicular phase + luteal phase.
  → **Follicular phase:** onset of menses → preovulatory LH surge (variable duration).
  → **Luteal phase:** onset of preovulatory LH surge → first day of menses (fixed duration =14 days).
→ Regressing corpus luteum of the preceding cycle → ↓ estradiol and progesterone → ↑ FSH by a negative feedback mechanism → stimulates follicular growth + estradiol secretion.

Estrogens:



→ Gradually ↑ in follicular phase.
→ **Early follicular development:** relatively ↓ circulating estradiol levels.
→ **1 week before ovulation:** slowly then rapidly ↑ circulating estradiol levels.
→ **Used in:** ovulation induction.
→ **Aromatization:** conversion of testosterone to estradiol in granulosa cell of follicle.
  → Aromatase (enzyme) coverts androstenedione (*precursor of testosterone*) to estrone (*weak estrogen*).
→ **- ve feedback:** ↓ estrogen levels → FSH gives a negative inhibitory feedback for LH release at hypothalamic–pituitary level.
→ **+ ve feedback:** ↑ GnRH receptor concentrations + ↑ estradiol sustained for 50 hours → positive stimulatory feedback → LH surge.

Progestins:

→ The main hormone in pregnancy.
→ **Follicular development:** very small amounts of progesterone & 17α-hydroxyprogesterone by ovary.
→ **Bulk of progesterone:** from peripheral conversion of adrenal pregnenolone and pregnenolone sulfate.
→ **Just before ovulation:** unruptured but luteinizing graafian follicle ↑ amounts of progesterone.
→ **Maximum:** 5 to 7 days after ovulation (mid luteal - day 21), secretion by corpus luteum.
→ **Baseline return:** shortly before menstruation.
→ **Corresponds with:** ↑ basal body temperature.
→ How to differentiate if the female is ovulating or has polycystic ovaries (anovulation)?
  → Measure her mid luteal serum progesterone levels 7 days before next expected menses.
→ **Clinical point:** to know if ovulation happened at the second phase of the cycle (between day 20 and 22), do post ovulation test (measures progesterone level).

Androgens

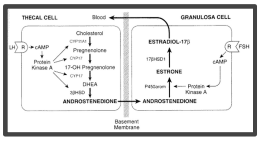
→ **PCOS:** ↑ androgen levels.
→ **Near mid-cycle:** ↑ secretion from follicle → ↑ plasma androstenedione.
→ **Luteal phase:** ↑ secretion by corpus luteum → ↑ plasma androstenedione (second).
→ **Derived from:** metabolism of androstenedione + ovary (*small amounts*) + adrenal gland (*small amounts*).
  → **Ovary:** small amounts of DHT + small amounts of DHEA.
  → **Adrenal glands:** majority of DHEA + all DHEA-S.
→ **Weak androgens:** dehydroepiandrosterone (DHEA) & DHEA sulfate (DHEA-S).
→ **Very potent androgens:** dihydrotestosterone (DHT).
  → **Bulk of DHT:** from conversion of androstenedione and testosterone.
→ Androstenedione and testosterone are precursors of estrogen and are produced in the theca cells.
  → In lower concentrations → stimulate aromatase.
  → In high concentrations → inhibit aromatase.
→ Androgens inhibit FSH induction of LH receptors.

2. Ovaries Level (Ovarian Cycle)

Steroidogenesis:

1 Theca and Granulosa Cell Theory (Two-Cell Theory):

→ Each cell is theorized to perform separate functions.
→ LH stimulates theca cells to produce androgens (androstenedione and testosterone)
→ FSH then stimulates the granulosa cells to convert androgens into estrogens (androstenedione → estrone & testosterone → estradiol).



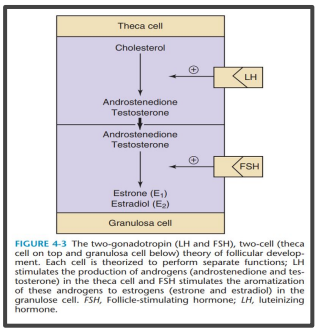
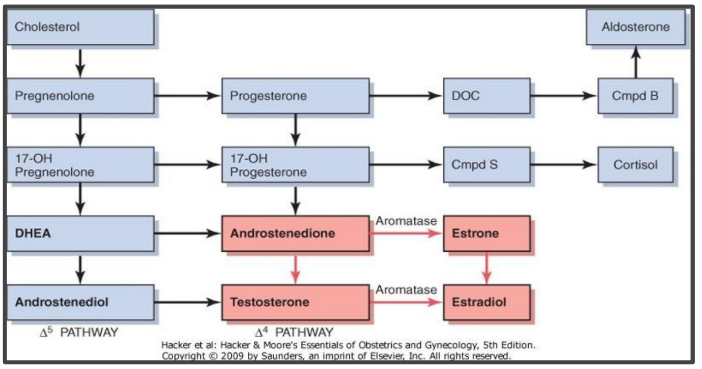


FIGURE 4-3 The two-gonadotropin (LH and FSH), two-cell (theca cell on top and granulosa cell below) theory of follicular development. Each cell is theorized to perform separate functions; LH stimulates the production of androgens (androstenedione and testosterone) in the theca cell and FSH stimulates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

→ LH → cholesterol converted to androstenedione (testosterone) → testosterone converted to estradiol by aromatase (affected by FSH) → estradiol released in blood.
→ Granulosa cell is affected by FSH.
→ Theca cell is affected by LH.

2 Steroidogenic Pathways in Ovary



→ Pathway is found in both ovaries & adrenal cortex.
→ Adrenal most common to produce female androgens & progesterones.

Serum-Binding Proteins:

→ Circulating estrogens & androgens are mostly bound to:
  → Specific sex hormone binding globulins (SHBG).
  → serum albumin.
→ Remaining fraction of sex hormones is unbound (free) → biologically active.
→ **Synthesis of SHBG:**
  → **Location:** liver.
  → ↑ **by:** estrogens - thyroid hormones.
  → ↓ **by:** testosterone.

Types of Estrogen ★:

Types of Estrogen		
Estradiol (E2)	**Estriol (E3)**	**Estrone (E1)**
Released with menstruation	Released with pregnancy	Released with menopause

2. Ovaries Level (Ovarian Cycle)

Ovarian Cycle: *Repeated for better understanding*

→ **Normal ovarian cycle:** follicular phase + luteal phase.
  → **Follicular phase:** onset of menses → preovulatory LH surge (variable duration).
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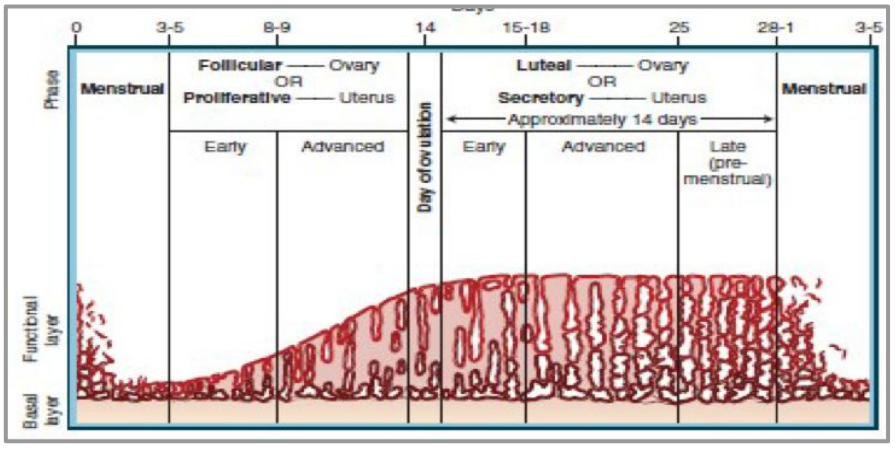
→ Regressing corpus luteum of the preceding cycle → ↓ estradiol and progesterone → ↑ FSH by a negative feedback mechanism → stimulates follicular growth + estradiol secretion.

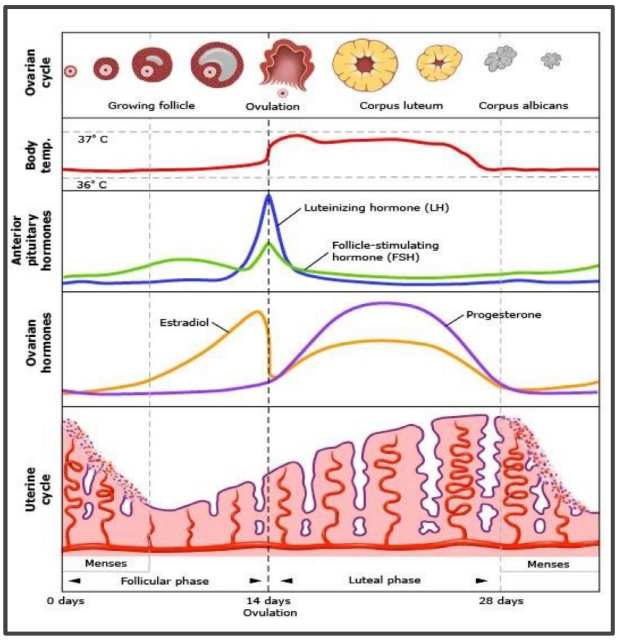
Phase	Menstrual Phase	Proliferative / Follicular / Estrogen Phase	Ovulation Phase[2]	Secretory / Luteal / Progesterone Phase
Average start & end day (*assuming 28 days cycle*[1])	1 - 4 days	5 - 13 days	13-16 days	16-28 days
			Fixed duration: 14 days	

→ **Duration of a regular cycle:** 3 - 5 weeks, average of 4 weeks.
→ **Duration of the first half of a regular cycle:** 1 - 3 weeks based on a female's cycle.
→ A cycle more than 5 weeks is an irregular cycle.

→ **To calculate ovulation date, you need:** duration of menses + duration of cycle "comes every how many days?".
→ **To calculate the exact date of ovulation:** date of next menses - 14 days.

→ **1st half of cycle:** secreted estrogen & progesterone, but **estrogen** is the main hormone.
→ **2nd half of cycle:** secreted estrogen & progesterone, but **progesterone** is the main hormone.





1. 17-35 days is the normal variation of the female cycle. How can we find the ovulation time? the variation happens at the beginning of the cycle (follicular phase) while the luteal phase is fixed (14 days). To find the time of ovulation subtract 14 from the menstrual cycle.
2. There are 24-36 hrs where ovum is available for fertilization after ovulation (high chance of pregnancy) it can also survive for 72 hrs.

2. Ovaries Level (Ovarian Cycle)

Ovarian Cycle:

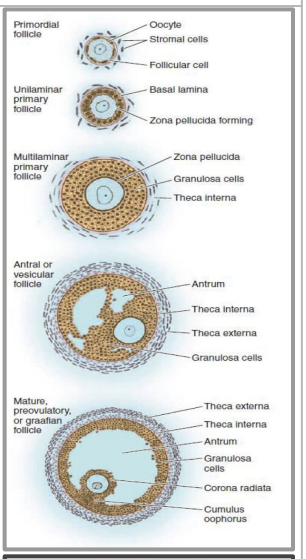
Menstrual Phase

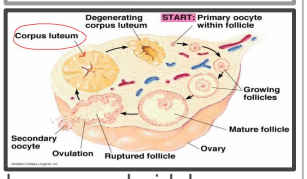
→ Menstrual bleeding, menses, period.
→ Lasts 3 - 5 days on average, can extend to 2-8 days (shouldn't exceed 7 days).
→ Discharge of bloody fluid containing endometrial cells, glandular secretions, and blood cells.
→ Strong constriction + proteolytic activity → functional striatum of endometrial tissue dies → discharged during menstrual bleeding.

Follicular Phase

FSH induce follicular growth

Follicular Development:





→ **Number of oocytes in a fetus (20 weeks' gestation):** 6 - 7 million.
→ **Number of oocytes at birth:** 1 - 2 million in both ovaries.
  → **Why?** Because of significant atresia (physiologic loss) of oogonia.
→ **Number of oocytes at** puberty: 300,000 and 400,000 oocytes are available for ovulation.
  → **Why?** Because of ongoing atresia.
  → Only **400 to 500 actually ovulating** (menopause = 0).

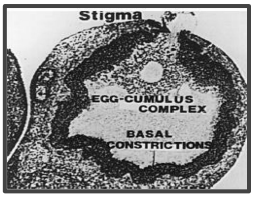
1. **Primordial follicle:** oocyte-granulosa cell complex.
   → **8 - 10 weeks gestation:** oocytes become progressively surrounded by precursor granulosa cells.
     → Precursor granulosa cells with the oocyte separate themselves from the underlying stroma by a basal lamina → primordial follicle.
2. **Primary follicle:**
   → **20 - 24 weeks' gestation:** follicular cells of primordial follicle become cuboidal + stromal cells around the follicle become prominent → primary follicle.
3. **Secondary follicle:**
   → A primary follicle with zona pellucida formed.
   → Granulosa cells proliferate.
   → Clear gelatinous material surrounds the ovum → zona pellucida is formed.
4. **Graafian follicle:** forms as the innermost 3 or 4 layers of rapidly multiplying granulosa cells become cuboidal and adherent to ovum (cumulus oophorus).
   → **Antrum forms:** fluid-filled area among the granulosa cells.
   → Primary oocyte migrates eccentrically to the wall of the follicle.
   → **Corona radiata:** elongated innermost layer of granulosa cells of cumulus (in contact with zona pellucida) → released with oocyte at ovulation.
   → **Basement membrane:** thin covering of granulosa cells.
   → **Theca interna & theca externa:** two coats of connective tissue cells outside the basement membrane.

→ **During each cycle:** ↑ FSH (*first days of cycle*) → cohort of follicles (several ovarian follicles) is stimulated & recruited each cycle to compete for dominance.
  → One follicle or two in case of twins (dominant follicle / graafian follicle) → differentiation and maturation.
    → **Maturation depends on:** FSH & LH receptors, ↑ by estrogen.
    → The follicle with highest number of FSH receptors → undergo ovulation.
  → Others follicle → atresia.
→ FSH stimulates granulosa cells → recruits a group of maturing follicles in ovary → ↑ estradiol + inhibin B in growing follicles → negative feedback to pituitary gland → 🚫 FSH release.

2. Ovaries Level (Ovarian Cycle)

Ovarian Cycle:

Ovulation



→ High level of estradiol for 30 hrs → LH surge → ovulation.
→ **Most important event in ovulation: LH surge** (*sudden increase*).
  → Sequence of structural & biochemical changes culminate in ovulation → preovulatory ↑ LH.

→ **Before ovulation:** general dissolution of the entire follicular wall, particularly the portion that is on the surface of the ovary.
  → **Cause:** proteolytic enzymes.

→ Degeneration of surface cells → stigma forms + follicular basement membrane bulges through the stigma.

→ Rupture of the stigma → oocyte, with corona radiata, and some cells of the cumulus oophorus are expelled into peritoneal cavity → ovulation.
  → **Ovulation:** a gradual phenomenon, several minutes → as long as an hour or more.

→ **During follicular phase:** estrogen suppress LH secretion from pituitary gland.
→ When the ovum has nearly matured levels of estrogen reach a threshold above which they stimulate LH production (positive feedback loop).
→ The release of LH matures the ovum and weakens the wall of the follicle in the ovary forming a stigma. Rapture of the stigma causes the fully developed follicle to release its secondary oocyte which is also accompanied by some cells (corona radiata & cumulus cells).
→ After being released from the ovary, the ovum is swept into the fallopian tube where the sperm penetrates the zona pellucida and corona radiata resulting in fertilization.
→ Basal body temperature ↑ with ovulation under progesterone effect (*thermogenic effect*).

Luteal Phase

Luteinization and Corpus Luteum Function:

→ After ovulation + under LH influence → granulosa cells of ruptured follicle undergo luteinization.

→ **Corpus luteum:** a solid body that is formed in the ovary after the ovum is released to the fallopian tube.
  → **Composed of:** luteinized granulosa cells + surrounding theca cells + capillaries + connective tissue.
  → **Normal functional lifespan:** 9 - 10 days if no pregnancy, 7 - 9 weeks in pregnancy.
    → **If pregnancy occurs:** corpus luteum is gradually replaced by corpus albicans (*avascular scar*).
  → **Produces:** progesterone (*copious amounts*) + estradiol (*some*).
  → Major source of progesterone → vital role in making endometrium receptive to blastocyst implantation.

→ LH maintains corpus luteum.
→ ↑ levels of estrogen & progesterone → ↓ LH & FSH production → corpus luteum maintains itself.

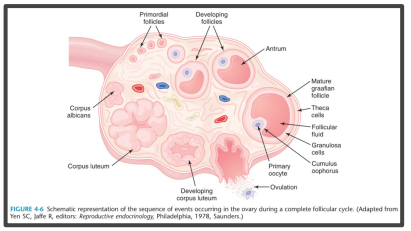


Figure 1

Figure 1: *events occurring in ovary during a complete cycle*
1. Approach ovaries' surface.
2. Fuse with ovary surface.
3. Release proteolytic enzymes.

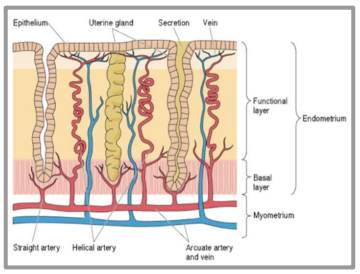
3. Uterus Level

Endometrial Physiology:

- → Responsive to estrogen, progesterone, and androgens (androgens e.g.: some treatment drugs).
- → **Results in:** menstruation or implantation and pregnancy.
- → Zones of endometrium:
  - → **Stratum Basalis (inner/basel portion):**
    - → Deeper layer.
    - → Relatively unchanged during each menstrual cycle and after menstruation.
    - → Contains stem cells that function to renew the functionalis.
    - → **Basal arteries:** regular blood vessels found in basalis.
  - → **Stratum Functionalis (outer portion):** made up of stratum compactum + stratum spongiosum.
    - → Superficial layer.
    - → Undergoes cyclic changes in morphology and function during menstrual cycle.
    - → Sloughed off at menstruation.
    - → Spiral arterioles: specially coiled blood vessels seen in functionalis, ↓ progesterone → undergoes spasm → PG released → ischemia + layer slougher.
- → **Estrogen:** enlarging glands and blood vessels → in tumors we focus on estrogen.
- → **Progesterone:** ↑ glands secretions.

Stages of Endometrial Cyclic Histophysiology:

01 Menstrual Phase



- → **Menstrual Phase:** the first four days of the menstrual cycle (day 1 = first day of menses), characterized by:
  - → Disruption & disintegration of endometrial glands & stroma.
  - → Leukocyte infiltration (*WBCs infiltration*).
  - → RBCs extravasation.
  - → Rupture of blood vessels + sloughing of functionalis + compression of the basalis.

02 Proliferative Phase

- → **Characterised by:** endometrial proliferation or growth.
- → Large secretion of estrogen → marked proliferation of:
  - → Epithelial lining cells.
  - → Endometrial glands.
  - → Connective tissue of stroma
- → Division of stem cells that migrate through stroma to form new epithelial lining of the endometrium → pseudostratified.
- → ↑ spiral arteries length in stroma.
- → Estrogen-dominant endometrium → unstable.
  - → If prolonged anovulation → hyperplasia + irregular shedding over time.

03 Secretory Phase

- → Ovulation → corpus luteum secrete progesterone → stimulates glandular cells to secrete glycogen, mucus, & other substances → tortuous glands + dilated filled (with these substances) lumens.
- → Edematous endometrial stroma + convoluted spiral arteries one day before menses → endometrial ischemia + release of prostaglandins → necrosis → painful cramps + menstruation.
- → Progesterone-dominant endometrium → stable.
  - → No irregular shedding over time.

3. Uterus Level

Endometrial Physiology:

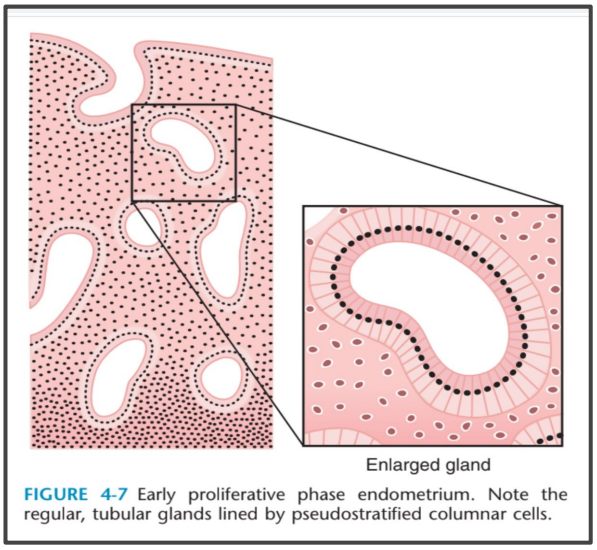


FIGURE 4-7 Early proliferative phase endometrium. Note the regular, tubular glands lined by pseudostratified columnar cells.

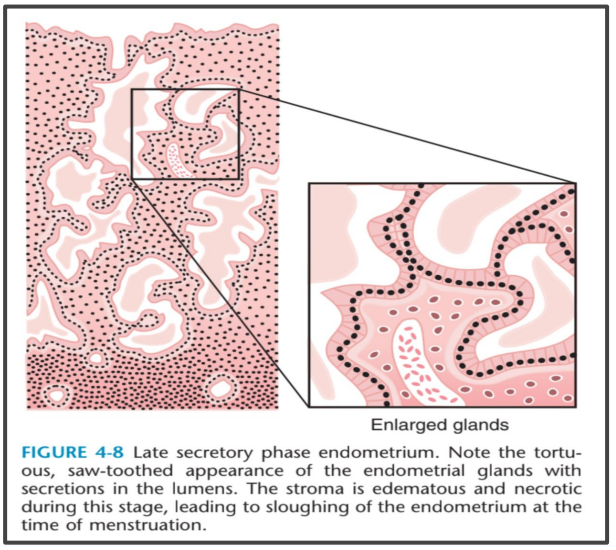


FIGURE 4-8 Late secretory phase endometrium. Note the tortuous, saw-toothed appearance of the endometrial glands with secretions in the lumens. The stroma is edematous and necrotic during this stage, leading to sloughing of the endometrium at the time of menstruation.

Estrogen → endometrial hyperplasia with atypia (*dysplasia*)

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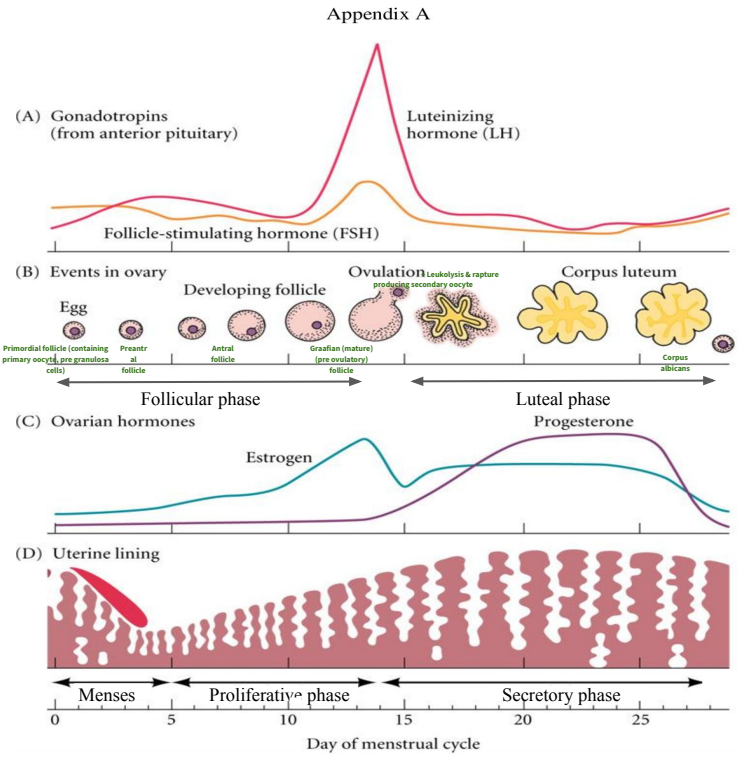
Ovarian	Theca cells produce androgens in response to LH. Granulosa cells aromatize androgens to estrogens in response to FSH (see Figure 4-3). Ovarian inhibins (A and B) inhibit and activin stimulates gonadotropins.	Follicular, ovulatory, and luteal phases. Average overall cycle length is 28 (±7) days. Luteal phase is generally constant at 12 to 14 days. Follicular phase may vary.	LH triggers ovulation at midcycle. LH then stimulates the corpus luteum to produce P4 and some E2. With pregnancy, placental hCG rescues the corpus luteum by mimicking LH.
Endometrial	Estradiol (E2) from the ovary stimulates growth (proliferation) and progesterone (P4) from the corpus luteum converts endometrium to secretory and withdrawal of E2 and P4 leads to menstruation (see Figures 4-7 and 4-8).	Menstrual, proliferative, and secretory phases. The endometrial component changes the most on a daily basis. Histology may be used to "date" the endometrium and determine day of cycle.	Menstruation is the only visible component. Because it is visible, it is where the cycle is said to start but menstruation actually represents the end of the previous cycle.

FSH, Follicle-stimulating hormone; *GnRH*, gonadotropin-releasing hormone; *hCG*, human chorionic gonadotropin; *LH*, luteinizing hormone; *LH-RH*, luteinizing hormone–releasing hormone.

Summary



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A

→ Hormones coming from the anterior pituitary gland **FSH & LH** under the stimulation of GnRH from the hypothalamus.
  → **FSH** (Follicular Stimulating Hormone): responsible for the initial stimulation & maturation of the follicles in the beginning of the cycle (first day of menstruation).
  → **LH**: surge in the middle of the cycle, responsible for ovulation.
→ The follicle which reaches maximum growth will ovulate. Both LH & FSH will be very low at the end of the cycle through the negative feedback effect of elevated circulating estradiol and progesterone.

B

→ The granulosa cells of the growing follicles releases estrogen creating a +ve feedback on LH. After 50 hours of high estrogen levels (200pg) positive feedback on the release of gonadotropins is created, resulting in LH surge.
→ LH surge takes 36 hours, 24 hours to reach the peak and 10-12 hours to ovulates. At the peak of LH the follicle will rupture and the ovum will be released the ovum will be converted to corpus luteum which will release large amounts of **progesterone**: which inhibits the estrogen proliferation, causes secretion, enlarges the increased number of endometrial glands, increases the secretions of the vacuoles & spiral vessels will be more coiled to prepare the endometrium for pregnancy.
→ Progesterone will be responsible for protecting the pregnancy, corpus luteum will survive for 3 months (till the placenta forms) with the help of HCG. HCG supports corpus luteum which will provide progesterone for ovum and endometrium supporting the pregnancy and creating a cycle. 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.
→ If there was no pregnancy, progesterone will luteinize the endometrium and corpus luteum will be converted to corpus albicans by day 23 causing sharp decrease in the level of the progesterone causing menses.

C

→ Follicles will release a great amount of **estrogen** at the beginning of the cycle, which will decrease at the time of ovulation. progesterone, on the other hand, will increase with ovulation.

D

→ The **functional layer** of the endometrium is the layer that changes with the ministerial cycle while no changes occur at the basal layer.
→ Estrogen is responsible for the growth in the functional layer at the beginning of the cycle (increase in the depth from 0.5 mm to 8 mm, stroma & number of cells converting the single layer of low columnar epithelium into pseudostratified). In the later half of the cycle estrogen will decrease and progesterone will increase changing the grown endometrium into luteinized endometrium progesterone can't act on the endometrium without the preparation of estrogen. if there was no pregnancy estrogen and progesterone levels will fall which can't support the endometrium leading it to shed out.
→ Progesterone in **early pregnancy** it induces endometrial secretory changes favorable for blastocyst implantation.
→ Progesterone in **later pregnancy** its function is to induce immune tolerance for the pregnancy and prevent myometrial contractions.

Quiz

Question 1:

→ **What is the name of the mature follicle?**

A. Stigma
B. Graafian follicle
C. Corpus luteum
D. Primordial follicle

Question 2:

→ **Continuous release of GnRH lead to upregulation of the gonadotropin?**

A. True
B. False

Question 3:

→ **In the follicular phase, which of the following is correct?**

A. High progesterone
B. High estrogen
C. Decrease thickness of the endometrium
D. Corpus luteum formation

Question 4:

→ **How long is the second half of the menstrual cycle?**

A. 7 days
B. 14 days
C. 50 hours
D. Variable

Question 5:

→ **All of the following hormones are produced in the basophils except?**

A. FSH
B. TSH
C. Growth hormone
D. ACTH

1	2	3	4	5
B	B	B	B	C

Quiz

Question 1:

→ **Which of the following hormones causes ovulation?**

A. LH
B. Estrogen
C. Progesterone
D. FSH

Question 2:

→ **In the luteal phase, which of the following is correct?**

A. High progesterone
B. High estrogen
C. Decrease thickness of the endometrium
D. Follicular growth

Question 3:

→ **Which type of estrogen is released with menstruation?**

A. Estrone
B. Estriol
C. Estradiol
D. Estrien

Question 4:

→ **To test pregnancy we measure which hormone level?**

A. Progesterone
B. Beta HCG
C. Alpha HCG
D. Alpha LH

Question 5:

→ **Which hormone is produced by corpus luteum that makes the endometrium receptive to the implantation of the blastocyst?**

A. LH
B. Estrogen
C. Progesterone
D. FSH

1	2	3	4	5
A	A	C	B	C

Reference

CHAPTER 4

Female Reproductive Physiology

JOSEPH C. GAMBONE

CLINICAL KEYS FOR THIS CHAPTER

- The female reproductive cycle (menstrual cycle) may be viewed as four separate physiologic cycles (hypothalamic, pituitary, ovarian, and endometrial) but is actually a highly complex and integrated event. This 28 (±7) day cycle allows for the maturation and release of an oocyte (usually only one) that if fertilized may implant in a receptive endometrium. If fertilization and implantation do not occur, the end result is menstruation.
- Communication between the hypothalamus, which releases gonadotropin-releasing hormone (GnRH) in pulses, and the pituitary gland is essential to permit the pituitary to respond to changes in ovarian hormones (estradiol and progesterone) and other factors. This essential communication results in both negative and positive feedback for the release of the pituitary gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These gonadotropins, also released in pulses, stimulate follicular growth in the ovary (FSH) such that one dominant follicle releases an oocyte in response to a midcycle surge in LH. Other growth factors and peptides such as inhibin-A, inhibin-B, and activin act systemically and locally to control follicular growth.
- After oocyte release, the dominant (graafian) follicle becomes the corpus luteum and secretes both estradiol (E2) and progesterone (P4). The endometrium responds to E2 with growth or proliferation before ovulation and to P4 and E2 after ovulation with maturation that allows for implantation if fertilization occurs. The corpus luteum continues to maintain the uterine lining, stimulated by human chorionic gonadotropin (hCG) from the placental tissue if a pregnancy occurs.
- Fertilization and implantation begin with normal sperm function and penetration of the oocyte in the fallopian tube. Fertilization restores the diploid number of chromosomes and determines the sex of the zygote. The fertilized ovum reaches the endometrium about 3 days after ovulation and after another several days the blastocyst implants.
- As the blastocyst burrows into the endometrium, the trophoblastic strands branch to form the primitive villi. The villi are first distinguished about the 12th day after fertilization and are the essential structures of the placenta. The placenta is the life-support system for the developing fetus for the rest of pregnancy.

Reproductive Cycle

Each female reproductive cycle (menstrual cycle) represents a complex interaction between the hypothalamus, pituitary gland, ovaries, and endometrium. Cyclic changes in the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) and sex steroid hormones, mainly estradiol (E2) and progesterone (P4), induce functional as well as morphologic changes in the ovary, resulting in follicular maturation, ovulation, and corpus luteum formation. Similar changes at the level of the endometrium allow for successful implantation of the fertilized ovum or a physiologic shedding of the menstrual endometrium when an early pregnancy does not occur. By convention, the normal cycle begins on the first day of menstrual bleeding and ends just before the first day of the next menses. The average length of each cycle is 28 (±7) days.

The reproductive cycle can be viewed from the perspective of each of four physiologic components (Table 4-1). The cyclic changes within the hypothalamic-pituitary axis, ovary, and endometrium are sequentially approached in this chapter, as if they were four separate cycles, but these endocrine events occur in concert in a uniquely integrated fashion. The chapter also includes a discussion of spermatogenesis, fertilization, implantation, and placentation.

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Hypothalamic-Pituitary Axis

PITUITARY GLAND

The pituitary gland lies below the hypothalamus at the base of the brain within a bony cavity (sella turcica) and is separated from the cranial cavity by a condensation of dura mater overlying the sella turcica (diaphragma sellae). The pituitary gland is divided into two major portions, the neurohypophysis and the adenohypophysis (Figure 4-1). **The neurohypophysis, which consists of the posterior lobe (pars nervosa), the neural stalk (infundibulum), and the median eminence, is derived from neural tissue and is in direct continuity with the hypothalamus and central nervous system. The adenohypophysis, which consists of the pars distalis (anterior lobe), pars intermedia (intermediate lobe), and pars tuberalis, which surrounds the neural stalk, is derived from ectoderm.**

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 neurohypophysis serves primarily to transport oxytocin and vasopressin (antidiuretic hormone) along neuronal projections from the supraoptic and paraventricular nuclei of the hypothalamus to their release into the circulation.

The anterior pituitary contains different cell types that produce six protein hormones: follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), prolactin, growth hormone (GH), and adrenocorticotropic hormone (ACTH).

The gonadotropins, FSH and LH, are synthesized and stored in cells called **gonadotrophs,** whereas TSH is produced by **thyrotrophs.** FSH, LH, and TSH are glycoproteins, consisting of α and β subunits. The α subunits of FSH, LH, and TSH are identical. The same α subunit is also present in human chorionic gonadotropin (hCG). The β subunits are individual for each hormone. The half-life for circulating LH is about 30 minutes, whereas that of FSH is several hours. The difference in half-lives may account, at least in part, for the differential secretion patterns of these two gonadotropins.

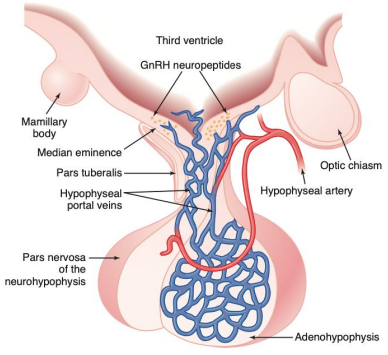

FIGURE 4-1 Hypothalamic-pituitary portal circulatory system. The pulses of gonadotropin-releasing hormone (GnRH) from the arcuate nucleus are transported to the anterior pituitary gland by way of this circulatory system. An interruption or significant alteration of GnRH pulses will cause the reproductive cycle to stop.

Prolactin is secreted by **lactotrophs.** Unlike the case with other peptide hormones produced by the adenohypophysis, **pituitary release of prolactin is under tonic inhibition by the hypothalamus.** The half-life for circulating prolactin is about 20 to 30 minutes. In addition to its lactogenic effect, prolactin may directly or indirectly influence hypothalamic, pituitary, and ovarian functions in relation to the ovulatory cycle, particularly in the pathologic state of chronic hyperprolactinemia (see Chapter 33).

GONADOTROPIN SECRETORY PATTERNS

A normal ovarian cycle can be divided into a follicular and a luteal phase (Figure 4-2). The follicular phase begins with the onset of menses and culminates in the preovulatory surge of LH. The luteal phase begins with the onset of the preovulatory LH surge and ends with the first day of menses.

Decreasing levels of estradiol and progesterone from the regressing corpus luteum of the preceding cycle initiate a rise of FSH by a negative feedback mechanism, which stimulates follicular growth and estradiol secretion. A major characteristic of follicular growth and estradiol secretion is explained by the two-gonadotropin (LH and FSH) two-cell (theca and granulosa cell) theory of ovarian follicular development. According to this theory, there are separate cellular functions in the ovarian follicle wherein LH stimulates theca cells to produce androgens (androstenedione and testosterone) and FSH then stimulates the granulosa cells to convert these androgens into estrogens (androstenedione to estrone and testosterone to estradiol) as depicted in Figure 4-3. Initially, at lower levels of estradiol, there is a negative feedback effect on the release of LH from the pool of gonadotropins in the pituitary gonadotrophs. When estradiol levels rise later in the follicular phase (>200 picograms for >50 hours), there is a positive feedback on the release of gonadotropins, resulting in the LH surge and ovulation. The latter occurs 36 to 44 hours after the onset of this midcycle LH surge. With pharmacologic doses of progestins contained in contraceptive pills, there is a profound negative feedback effect on gonadotropin-releasing hormone (GnRH) so that none of the gonadotropin pool is released. Hence, ovulation is blocked (see Chapter 27).

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, should pregnancy fail to occur. The net effect is a slight rise in serum FSH, which initiates new follicular growth for the next cycle. The duration of the corpus luteum's functional regression is such that menstruation generally occurs 14 days after the LH surge in the absence of pregnancy. When pregnancy occurs, the corpus luteum is "rescued" by hCG which acts like LH and progesterone production continues.

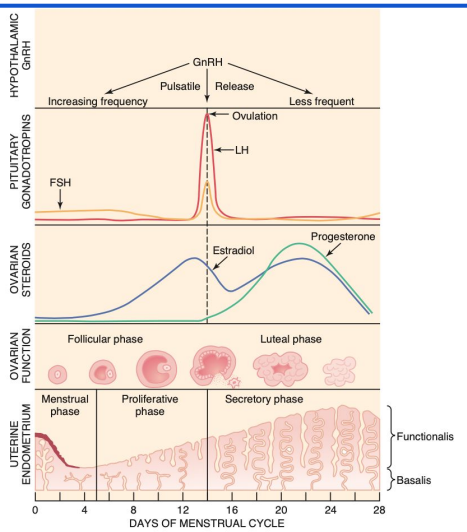

FIGURE 4-2 Hormone activity and levels during a normal menstrual cycle. All four components of the cycle (hypothalamic, pituitary, ovarian, and endometrial) are represented in the figure. These components work in a highly integrated way in a cycle that represents one of the most complex endocrine/end organ systems in physiology. *FSH*, Follicle-stimulating hormone; *GnRH*, gonadotropin-releasing hormone; *LH*, luteinizing hormone.

HYPOTHALAMUS

Five different small peptides or biogenic amines that affect the reproductive cycle have been isolated from the 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).** Only GnRH and PIF are discussed in this chapter.

GnRH is a decapeptide that is synthesized primarily in the arcuate nucleus. It has a very short half-life of 2 to 4 minutes. It is responsible for the synthesis and release of both LH and FSH. Because it usually causes the release of more LH than FSH, it is less commonly called LH-releasing hormone (LH-RH) or LH-releasing factor (LRF). **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 reaches the anterior pituitary via the hypophyseal portal vessels and stimulates the synthesis of both FSH and LH, which are stored within gonadotrophs. Subsequently, GnRH activates and transforms these molecules into releasable forms. GnRH can also induce immediate release of both LH and FSH into the circulation. Receptors for GnRH have been found in other tissues including the ovary, suggesting that GnRH may have a direct effect on ovarian function as well.

GnRH is secreted in a pulsatile fashion throughout the menstrual cycle as depicted in Figure 4-4. The frequency of GnRH release, as assessed indirectly by

Reference

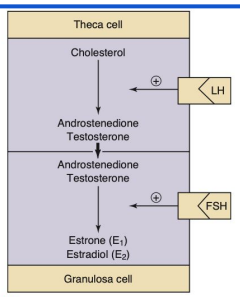

FIGURE 4-3 The two-gonadotropin (LH and FSH), two-cell (theca cell on top and granulosa cell below) theory of follicular development. Each cell is theorized to perform separate functions; LH stimulates the production of androgens (androstenedione and testosterone) in the theca cell and FSH stimulates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

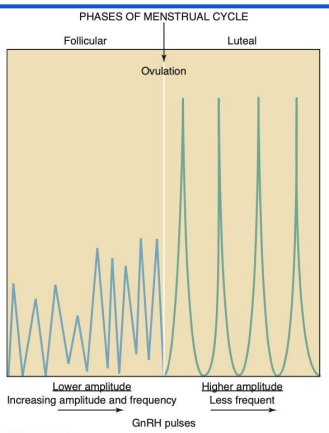

FIGURE 4-4 The pulsatile release of gonadotropin-releasing hormone (GnRH) during the normal menstrual cycle.

measurement of LH pulses, varies considerably among individuals. GnRH pulses in the follicular phase are more frequent and of lower amplitude, whereas in the luteal phase the pulses occur less frequently but are of higher amplitude.

Intravenous and subcutaneous administration of exogenous pulsatile GnRH has been used to induce ovulation in selected women who are not ovulating as a result of hypothalamic dysfunction. **A continuous (nonpulsatile) infusion of GnRH results in a reversible inhibition of gonadotropin secretion through a process of "downregulation" or desensitization of pituitary gonadotrophs.** This represents the basic mechanism of action for the GnRH analogues (nonapeptides, containing only nine amino acids) that have been successfully used in the therapy of such ovarian hormone-dependent disorders as endometriosis, leiomyomas (fibroids), hirsutism, and precocious puberty. There are both agonistic and antagonistic analogues of GnRH.

Several mechanisms control the secretion of GnRH. **Estradiol appears to enhance 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 an inhibitory effect on GnRH release.** Catecholamines may play a major regulatory role as well. Dopamine is synthesized in the arcuate and periventricular nuclei and may have a direct inhibitory effect on GnRH secretion via the tuberoinfundibular tract that projects onto the median eminence. Serotonin also appears to inhibit GnRH pulsatile release, whereas norepinephrine stimulates it. Endogenous opioids suppress release of GnRH from the hypothalamus in a manner that may be partially regulated by ovarian steroids.

The hypothalamus produces PIF, which exerts chronic inhibition of prolactin release from the lactotrophs. A number of pharmacologic agents (e.g., chlorpromazine) that affect dopaminergic mechanisms also influence prolactin release. Dopamine itself is secreted by hypothalamic neurons into the hypophyseal portal vessels and inhibits prolactin release directly within the adenohypophysis. Based on these observations, it has been proposed that hypothalamic dopamine may be the major PIF. In addition to the regulation of prolactin release by PIF, the hypothalamus may also produce prolactin-releasing factors (PRF) that can elicit large and rapid increases in prolactin release under certain conditions, such as breast stimulation during nursing. Neither PIF nor PRF has been clearly characterized biochemically as of 2014. TRH serves to stimulate prolactin release as well. This phenomenon may explain the association between primary hypothyroidism (with secondary TRH elevation) and hyperprolactinemia. **The precursor protein for GnRH, called GnRH-associated peptide (GAP), has been identified to be both a potent inhibitor of prolactin secretion and an enhancer of gonadotropin release. These findings suggest that this GnRH-associated peptide may also be a physiologic PIF** and could explain the inverse relationship between gonadotropin and prolactin secretions seen in many reproductive states.

Ovarian Cycle

ESTROGENS

During early follicular development, circulating estradiol levels are relatively low. About 1 week before ovulation, levels begin 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 and is depicted in Figure 4-3. The levels generally reach a maximum 1 day before the midcycle LH peak. After this peak and before ovulation, there is a marked and precipitous fall. During the luteal phase, estradiol rises to a maximum 5 to 7 days after ovulation and returns to baseline shortly before menstruation. Estrone (E1, a weaker estrogen) 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 (Figure 4-5).

PROGESTINS

During follicular development, the ovary secretes only very small amounts of progesterone and 17α-hydroxyprogesterone. 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-hydroxyprogesterone. The elevation of basal body temperature is temporally related to the central effect of progesterone. As with estradiol, 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, but 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, which reflects 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 dehydroepiandrosterone (DHEA) and virtually all DHEA sulfate (DHEA-S), which are weak androgens, are secreted by the adrenal glands, although small amounts of DHEA are secreted by the ovary.

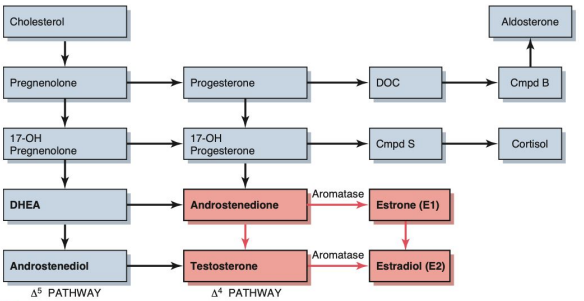

FIGURE 4-5 Steroidogenic pathways showing aromatization in red. *Cmpd B*, Corticosterone; *Cmpd S*, II-deoxycortisol; *DHEA*, dehydroepiandrosterone; *DOC*, desoxycorticosterone; *OH*, hydroxylase.

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. It is unclear whether steroids bound to serum proteins (e.g., albumin) are accessible for tissue uptake and utilization. The synthesis of SHBG in the liver is increased by estrogens and thyroid hormones but decreased by testosterone.

PROLACTIN

Serum prolactin levels do not change strikingly during the normal menstrual cycle. Both the serum level of prolactin and prolactin release in response to TRH are somewhat more elevated during the luteal phase than during the mid-follicular phase of the cycle. This suggests that high amounts of circulating estradiol and progesterone may enhance prolactin release. **Prolactin release varies throughout the day with the highest levels occurring during sleep.**

Prolactin may participate in the control of ovarian steroidogenesis. Prolactin concentrations in follicular fluid change markedly during follicular growth. The highest prolactin concentrations are seen in small follicles during the early follicular phase. Prolactin concentrations in the follicular fluid may be inversely related to the production of progesterone. In addition, hyperprolactinemia may alter gonadotropin secretion. Despite these observations, the physiologic role of prolactin during the normal menstrual cycle has not been clearly established.

FOLLICULAR DEVELOPMENT

The number of oocytes is maximal in the fetus at 6 to 7 million at 20 weeks' gestation. Significant atresia (physiologic loss) of oogonia occurs so that at birth, only 1 to 2 million remain in both ovaries. At puberty (with ongoing atresia) between 300,000 and 400,000 oocytes are available for ovulation with only 400 to 500 actually ovulating. **After puberty, 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 approximately 8 to 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.** The follicular cells become cuboidal and the stromal cells around the follicle become prominent. This process, which takes place in the fetal ovary at between 20 and 24 weeks' gestation, results in a **primary follicle.** As granulosa cells proliferate, a clear gelatinous material surrounds the ovum, forming the **zona pellucida.** This larger unit is called a **secondary follicle.**

In the adult ovary, **a graafian follicle** forms as the innermost three or four layers of rapidly multiplying granulosa cells become cuboidal and adherent to the ovum **(cumulus oophorus).** In addition, a fluid-filled antrum forms among the granulosa cells. As the liquor continues to accumulate, the antrum enlarges and the centrally located primary oocyte migrates eccentrically to the wall of the follicle. The innermost layer of granulosa cells of the cumulus, which are in close contact with the zona pellucida, become elongated and form the **corona radiata.** The corona radiata is released with the oocyte at ovulation. Covering the granulosa cells is a thin basement membrane, outside of which connective tissue cells organize themselves into two coats: the **theca interna** and **theca externa.**

During each cycle, a cohort of follicles is recruited for development. Among the many developing follicles, only one (the dominant follicle) usually continues differentiation and maturation into a follicle that ovulates. The remaining follicles undergo atresia. On the basis of in vitro measurement of local steroid levels, growing follicles can be classified as either estrogen-predominant or androgen-predominant. **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 approximately 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 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 thecal cells. In nondominant follicles, high local androgen levels may enhance follicular atresia. However, in the follicle destined to reach ovulation, FSH induces the formation of aromatase enzyme and its receptor 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.** These are essential for the appropriate response to the LH surge, leading to the final stages of maturation, ovulation, and the luteal phase production of progesterone. Thus, **the presence of greater numbers of FSH receptors and granulosa cells and increased induction of aromatase enzyme and its receptors may differentiate between the follicle of the initial cohort that will eventually ovulate and those that will undergo atresia.**

Growth factors such as insulin, insulin-like growth factor (IGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF) may also play significant mitogenic roles in folliculogenesis, including enhanced responsiveness to FSH. Ovarian peptide hormones, inhibin-A, inhibin-B, and activin, have roles in gonadotropin regulation. Both forms of inhibin act to inhibit FSH, whereas activin stimulates FSH release and potentiates its action in the ovary. Ovarian granulosa cells also produce müllerian inhibiting hormone (MIH), levels of which now provide a more accurate assessment of ovarian reserve and potential female fertility (see Chapter 34).

OVULATION

The preovulatory LH surge initiates a sequence of structural and biochemical changes that culminate in ovulation. **Before ovulation, a general dissolution of the entire follicular wall occurs, particularly the portion that is on the surface of the ovary.** Presumably 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 cells of the cumulus oophorus are expelled into the peritoneal cavity, and ovulation takes place.

Ovulation is now known from ultrasonic studies to be a gradual phenomenon, with the collapse of the follicle taking from several minutes to as long as an hour or more. The oocyte adheres to the surface of the ovary, allowing an extended period during which the muscular contractions of the fallopian tube may bring it in contact with the tubal epithelium. Probably both muscular contractions and tubal ciliary movement contribute to the entry of the oocyte into, and the transportation along, the fallopian tube. Ciliary activity may not be essential, because some women with immotile cilia also become pregnant.

At birth, primary oocytes are in the prophase (diplotene) stage of the first meiotic division. They continue in this phase until the next maturation division occurs (years later) in conjunction with the midcycle LH surge. **A few hours preceding ovulation, the chromatin is 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.** The second maturation spindle forms immediately and the oocyte remains at the surface of the ovary. No further development takes place until after ovulation and fertilization have occurred. At that time, and before the union of the male and female pronuclei, another division occurs to reduce the chromosomal component of the egg pronucleus to 23 single chromosomes (22 plus X or Y), each composed of the one monad. The ovum and a second polar body are thus formed. The first polar body may also divide.

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 connective 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*. The events occurring in the ovary during a complete cycle are shown in Figure 4-6.

Histophysiology of the Endometrium

The endometrium is uniquely responsive to the circulating progestins, androgens, and estrogens. It is this responsiveness that gives rise to menstruation and makes implantation and pregnancy possible.

Functionally, the endometrium is divided into two zones: (1) the **outer portion,** or **functionalis,** which undergoes cyclic changes in morphology and function during the menstrual cycle and is sloughed off at menstruation; and (2) the **inner portion,** or **basalis,** which remains relatively unchanged during each menstrual cycle and, after menstruation, provides stem cells for the renewal of the functionalis. **Basal arteries** are regular blood vessels found in the basalis, whereas **spiral arteries** are specially coiled blood vessels seen in the functionalis.

The cyclic changes in histophysiology of the endometrium can be divided into three stages: the menstrual phase, the proliferative or estrogenic phase, and the secretory or progestational phase.

Reference

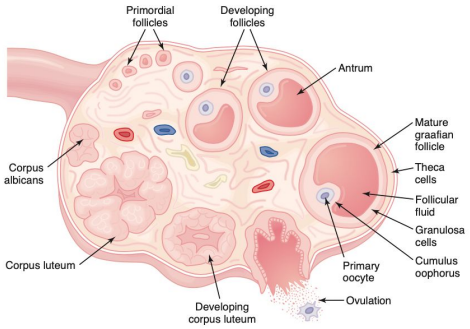

FIGURE 4-6 Schematic representation of the sequence of events occurring in the ovary during a complete follicular cycle. (Adapted from Yen SC, Jaffe R, editors: *Reproductive endocrinology,* Philadelphia, 1978, Saunders.)

MENSTRUAL PHASE

Because it is the only portion of the cycle that is visible externally, 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. Despite these degenerative changes, early evidence of renewed tissue growth is usually present at this time within the basalis of the endometrium.

PROLIFERATIVE PHASE

The proliferative phase is characterized by endometrial proliferation or growth secondary to estrogenic stimulation. Because the bases of the endometrial glands lie deep within the basalis, these epithelial cells are not destroyed during menstruation.

During this phase of the cycle, the large increase in estrogen secretion causes marked cellular proliferation of the epithelial lining, the endometrial glands, and the connective tissue of the stroma (Figure 4-7). 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.

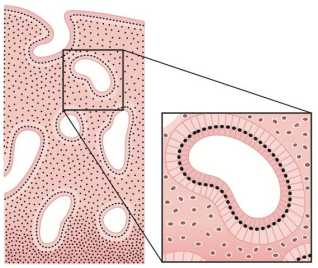

FIGURE 4-7 Early proliferative phase endometrium. Note the regular, tubular glands lined by pseudostratified columnar cells.

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 (Figure 4-8).

The marked changes that occur in endometrial histology during the secretory phase permit relatively precise timing (dating) of secretory endometrium.

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. It is thought that these events occur secondary to prostaglandin production by the endometrium. The resulting necrosis causes menstruation or sloughing of the endometrium. Ironically, 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. The four components of the "integrated" female reproductive cycle are summarized in Table 4-1.

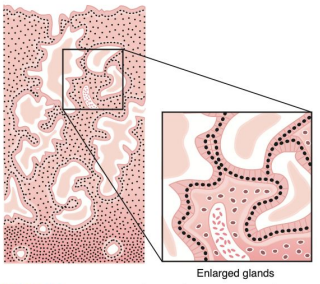

FIGURE 4-8 Late secretory phase endometrium. Note the tortuous, saw-toothed appearance of the endometrial glands with secretions in the lumens. The stroma is edematous and necrotic during this stage, leading to sloughing of the endometrium at the time of menstruation.

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