HORMONAL REGULATION OF OVARIAN ACTIVITY

In the testes spermatogenesis and testosterone secretion occur continuously at a steady rate. The *ovary*, however, shows a cyclical pattern of activity. Thus, follicle formation (including ovum growth) and ovulation, as well as the formation and regression of the corpus luteum, all occur in sequence within a single cycle that is then repeated. Similarly, the secretion of ovarian hormones *estrogen* and *progesterone* follow a cyclical pattern, estrogen appearing in the follicular phase followed by progesterone in the luteal phase (plate 154). Average duration of the ovarian cycle in the mature human female is 28 days. Cycles begin at puberty and are interrupted only during pregnancy and lactation and by illness, and they cease after the age of fifty. Here, we study how the ovarian hormones, the anterior pituitary gonadotropins, and the hypothalamus interact to ensure the orderly operation of the ovarian cycle.

HYPOTHALAMUS & PITUITARY REGULATE THE OVARIES

Gonadotropins LH & FSH directly regulate follicular and luteal functions—The anterior pituitary secretes two gonadotropin hormones that regulate the activity of the ovary—the *follicle-stimulating hormone* (FSH) and the *luteinizing hormone* (LH). Gonadotropins are glycoprotein hormones secreted from the basophilic gonadotrope. Both LH and FSH are necessary for ovarian activity, although each may act in different phases of the cycle. FSH is essential in proliferation and growth of granulosa cells early in the follicular phase and later for increase of the theca interna cells.

LH, however, stimulates estrogen production and release by follicle cells as well as inducing ovulation and growth of the corpus luteum and its secretion of progesterone and estrogen. Gonadotropins exert their actions on granulosa and theca interna cells by binding to their own receptors on plasma membranes, acting via the G-protein → adenylate cyclase → cyclic AMP pathway (plate 12,114). The young granulosa cells have mainly FSH receptors but mature ones also carry LH receptors. The later-forming theca interna cells have both LH and FSH receptors.

Pulsatile release of GnRH from the hypothalamus controls pituitary LH & FSH—Secretion of LH and FSH are controlled by the *gonadotropin-releasing hormone* (GnRH), a peptide neurohormone released from the hypothalamus. GnRH is synthesized by GnRH-containing hypothalamic neurons, which release GnRH by their axon terminals into the *portal hypophyseal capillaries*, for rapid and direct delivery to the anterior pituitary gonadotrope cells. Receptors for GnRH are found on the plasma membrane of the gonadotropes. GnRH action is cAMP mediated.

GnRH release is not continuous but occurs in approximately hourly pulses. To increase gonadotropin secretion, GnRH amount per pulse (pulse amplitude) or the number of pulses (pulse frequency) increases, and vice versa. LH release is also known to take place in pulses that occur shortly after each GnRH pulse, but FSH release is less pulsatile and occurs more slowly. The frequency and amplitude of the GnRH pulses are under the control of two mechanisms—a hypothalamic "clock" that sets the overall duration of the cycle and the timing of major events within the ovarian cycle and the negative feedback control of estrogen on the hypothalamus.

ESTROGEN CONTROLS GnRH RELEASE THROUGH FEEDBACK

Negative feedback at onset—Low levels of estrogen at the end of the ovarian cycle, acting via *negative feedback*, stimulates the hypothalamus to increase its pulsatile output of GnRH. This leads to increased output of FSH and LH from the pituitary. FSH rises sharply in the first days and remains high for most of the follicular phase; LH shows a steady increase. FSH and LH stimulate follicular growth and secretion of estrogen. By day 13 of the cycle, estrogen level peaks while FSH and LH diminish, due to the negative feedback inhibition by estrogen.

Positive feedback at midcycle—At this point a new *positive feedback* mechanism comes into play: high estrogen levels cause a marked rise in LH (an LH burst) and a moderate one in FSH levels. Exactly how negative feedback switches to positive feedback in midcycle is not known. Increased estrogen increases the frequency of GnRH pulses and possibly augments the GnRH receptors on the gonadotrope cells, enhancing their sensitivity to GnRH pulses. These events produce the preovulatory burst of LH secretion that triggers the process of ovulation within several hours.

Return of negative feedback in the luteal phase—The postovulatory high levels of LH (and also of FSH) promote corpus luteum growth and progesterone (with some estrogen) release. By midluteal days the negative feedback effect returns; high estrogen and progesterone act to lower LH and FSH for most of the luteal phase. If the estrogen level is kept high from the beginning of the cycle, ovulation will not occur. This observation is the basis for the use of estrogen-like compounds in contraceptive pills (plate 161).

Inhibin from ovarian granulosa cells inhibits FSH secretion—The protein hormone *inhibin* also plays a role in ovarian regulation. Inhibin is secreted by the granulosa cells and exerts a negative feedback effect on the pituitary to inhibit FSH secretion. Inhibin levels are low in the follicular phase and high in the luteal phase.

Regression of the corpus luteum marks the end of an ovarian cycle—The corpus luteum begins to regress around day 25 of the cycle. Absence of hormonal signals from the implanted embryo (hCG) and the reduced LH and FSH levels signal the regression. A number of local hormones, such as prostaglandins and proteolytic enzymes, promote lysis of the corpus luteum. Regression of the corpus luteum reduces progesterone and estrogen output. This event marks the end of the ovarian cycle and promotes the shedding of the endometrium and menstruation.

FACTORS INFLUENCING OVARIAN FUNCTION

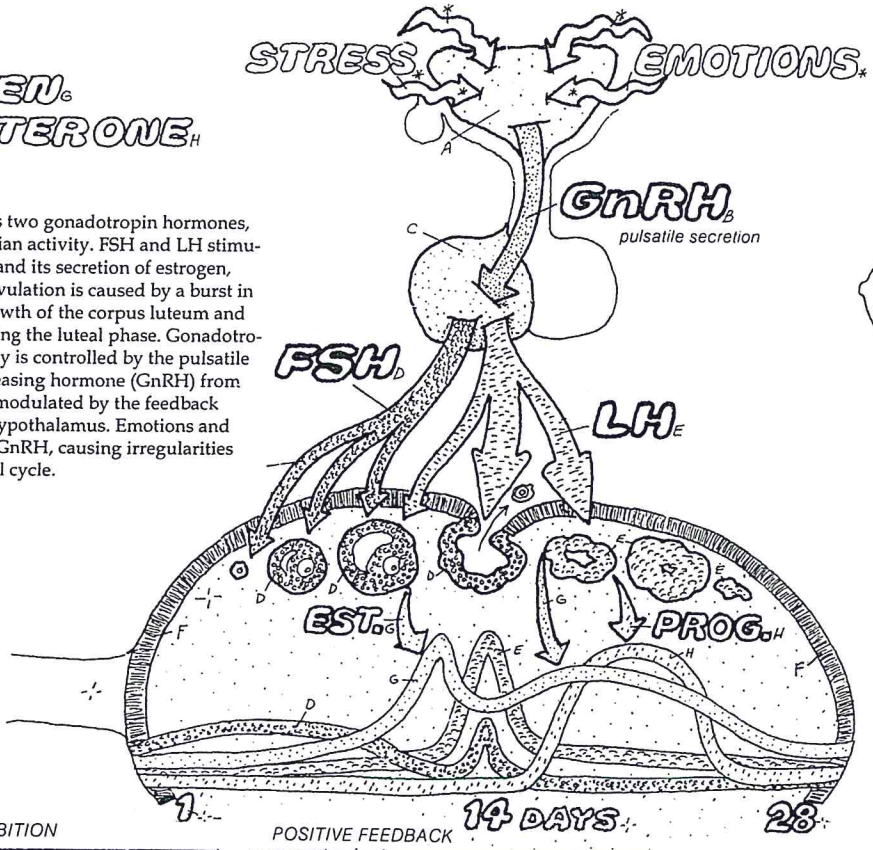
Illness, malnutrition, severe stress, and emotional crises interfere with the operation of the ovarian cycle. Stress and emotional crises act on the higher brain centers and, from there, on the hypothalamus, interfering with the pattern of GnRH release. Often the release is inhibited, leading to reduction in FSH and LH levels and consequently diminished secretion of sex hormones. Depending on the timing of the stress, diminished estrogen may cause undue menstruation (spotting) or delayed menstruation (secondary amenorrhea) that occurs in the absence of endometrial proliferation.

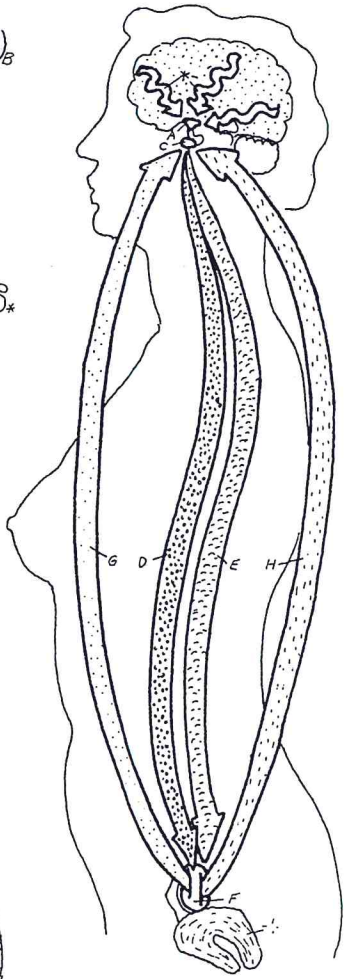
CN: Use the same colors as on the preceding page for FSH (D), LH (E), estrogen (G), and progesterone (H). Use light colors for A and C.
1. Color the large control illustration in the center.
2. Color the three bottom panels. Color only the bold portions of the hormone levels. Color gray that portion of the endometrium involved during the period described. The dotted ascending line in the left panel represents reduced levels of estrogen. Note that bold dotted lines in the right panel represent a cessation of FSH and LH secretion.
3. Color the diagram in the upper right.

HYPOTHALAMUS$_A$
GONADOTROPIN-RELEASING HORMONE (GnRH)$_B$
ANTERIOR PITUITARY GLAND$_C$
FOLLICLE-STIMULATING HORMONE (FSH)$_D$
LUTEINIZING HORMONE (LH)$_E$

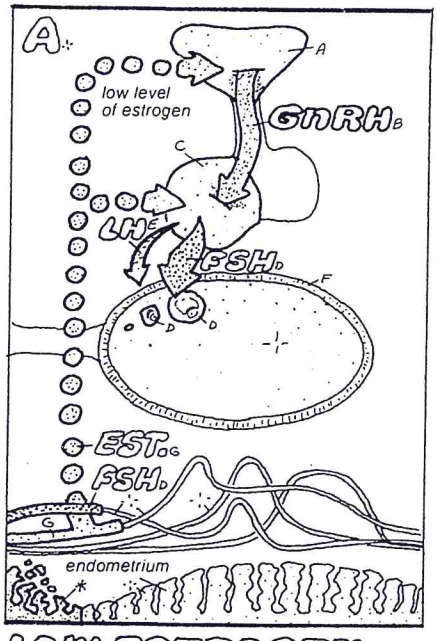
OVARY$_F$
ESTROGEN$_G$
PROGESTERONE$_H$
INHIBIN$_I$

The anterior pituitary releases two gonadotropin hormones, FSH and LH, to regulate ovarian activity. FSH and LH stimulate the growth of the follicle and its secretion of estrogen, during the follicular phase. Ovulation is caused by a burst in LH, which also stimulates growth of the corpus luteum and secretion of progesterone during the luteal phase. Gonadotropin secretion from the pituitary is controlled by the pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus but is also modulated by the feedback effects of sex steroids on the hypothalamus. Emotions and stress disturb the secretion of GnRH, causing irregularities in ovulation and the menstrual cycle.





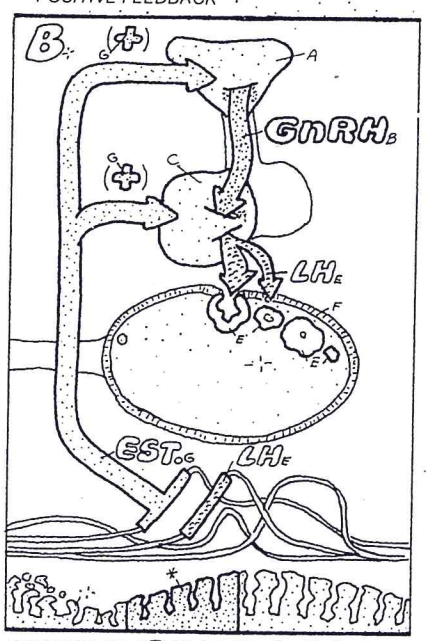
RELEASE FROM FEEDBACK INHIBITION



LOW ESTROGEN$_G$

Low estrogen levels in the menstrual phase, acting via a negative feedback mechanism, increase release of GnRH, which in turn increases FSH and LH release (see also panel C). These stimulate follicular growth and elevate estrogen levels to their peak by day 13 of the ovarian cycle.

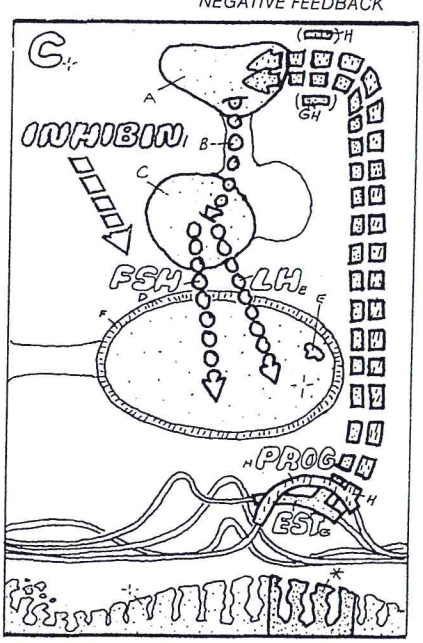
POSITIVE FEEDBACK



HIGH ESTROGEN$_G$

High preovulatory levels of estrogen act via positive feedback to increase GnRH pulse frequency which triggers a burst of LH release by day 14. High LH leads to ovulation, growth of the corpus luteum, and its secretion of progesterone, which peaks at day 22; estrogen secretion continues at lower levels. Inhibin from granulosa cells inhibits FSH secretion in the luteal phase.

NEGATIVE FEEDBACK



HIGH ESTROGEN$_G$ & HIGH PROGESTERONE$_H$

In the absence of fertilization and an implanted embryo, high estrogen and progesterone levels reduce secretion of LH and FSH by negative feedback. Reduced gonadotropin levels lead to regression of the corpus luteum and decreased output of sex steroids, then menstruation. The cycle continues with panel A.

FUNCTIONS OF THE OVARY: SECRETION & ACTIONS OF FEMALE SEX HORMONES

Estrogen and *progesterone* are the hormones of the ovary. They are steroid compounds derived ultimately from cholesterol. *Estradiol*, the most potent and the main estrogen secreted, has two hydroxyl groups; progesterone has two ketone groups. As female sex hormones, they regulate many aspects of female reproduction, sexuality, and secondary sex characteristics.

Granulosa and theca cells participate in estrogen secretion—In primates, estrogen can be formed by both *granulosa* and *theca interna* cells of ovarian follicles. The theca cell layer is vascularized, allowing access to plasma cholesterol used for synthesis of estradiol, which is released into the plasma. The granulosa cell layer is avascular; these cells lack access to plasma cholesterol and synthesize estradiol by converting androgen precursors, which diffuse from theca cells. Estrogen from granulosa cells is released into the follicle antrum to stimulate ovum growth. Estrogen secretion by theca and granulosa cells is stimulated by pituitary LH and FSH.

Cyclical changes in estrogen and progesterone secretion—During the *follicular phase*, estrogen secretion increases as follicle cells grow and proliferate; peak levels are reached by days 12–13 of the ovarian cycle. After ovulation, estrogen output diminishes due to the transformation of the follicle into a corpus luteum, but secretion continues into the third and fourth weeks. Progesterone secretion increases after ovulation when LH stimulates formation of the corpus luteum. *Luteal cells* of the corpus luteum are the source of progesterone and have receptors for the gonadotropins LH and FSH, both of which are necessary for optimal secretion of female sex steroids. Progesterone secretion peaks by the middle of the luteal phase (days 20–22) and declines thereafter. The lowest levels of both estrogen and progesterone occur in the absence of fertilization. Pregnancy promotes survival of the corpus luteum and marked increases in estrogen and progesterone secretion.

Uterine Endometrium Shows a Monthly Cycle

The principal actions of estrogen and progesterone in the female reproductive system are on the *uterine endometrium*. This uterine mucosal lining is the site of *implantation* of the young embryo. To prepare for implantation, the endometrium undergoes cyclical changes, building up its wall to receive the embryo and destroying it in the absence of fertilization. The endometrial cyclical changes occur as a result of changes in the plasma levels of ovarian estrogen and progesterone and therefore follows the pattern of the ovarian cycle.

Estrogen promotes endometrial proliferation & thickening—Estrogen stimulates the epithelial cells of the *basal layer* of the endometrium to proliferate, forming a thick mucosa and numerous *endometrial (uterine) glands* with extensive blood vessels (*spiral arteries* and *veins*). These events constitute the *proliferative* phase of the endometrial cycle (days 6–14). At ovulation, the endometrium is fully grown (about 5 mm thick). The *myometrium*, the smooth muscle layer under the endometrium, is less affected.

Progesterone promotes secretion of endometrial glands—After ovulation, increasing levels of progesterone from the corpus luteum stimulate the endometrial gland to secrete a juice rich in proteins and glycogen that is important for survival and maintenance of the preimplantation and implanting embryo and for adherence of the implanted embryo. This part of the endometrial cycle, promoted by the action of progesterone, is termed the *secretory phase* and lasts through days 14–28 of the cycle. Progesterone is needed to sustain pregnancies.

Menstruation is caused by shedding and bleeding of endometrial tissue—In the absence of fertilization, the hormonal signals from the embryo for survival of the corpus luteum—i.e., human chorionic gonadotropin (hCG)—will not occur. The corpus luteum regresses, decreasing estrogen and progesterone secretion in the later part of the secretory phase. This weakens the endometrium, reducing blood flow and causing local oxygen deficiency *(ischemic phase)*. By day 28, the endometrium begins to collapse and shed. Endometrial debris, along with some blood, constitutes the *menstrual flow* (menstruation, menses). This *menstrual phase* lasts about five days. The growth of follicles and increasing estrogen output during the next follicular phase terminate the menstrual phase and begin the next proliferative phase. Although the menstrual phase is the last phase of the endometrial cycle, in keeping with the events of the ovarian cycle it is customarily represented as the first phase (days 1–5).

Menarche and menopause—Menstrual cycles commence at puberty (*menarche*), usually at 12 to 13 years of age. Early cycles usually lack ovulation. In the early fifties, menstrual cycles cease (*menopause*). This event is a result of exhaustion of ovarian follicles and signals the end of reproductive functions, but not sexual activity. Menstrual cycles do not occur during pregnancy and in many lactating women.

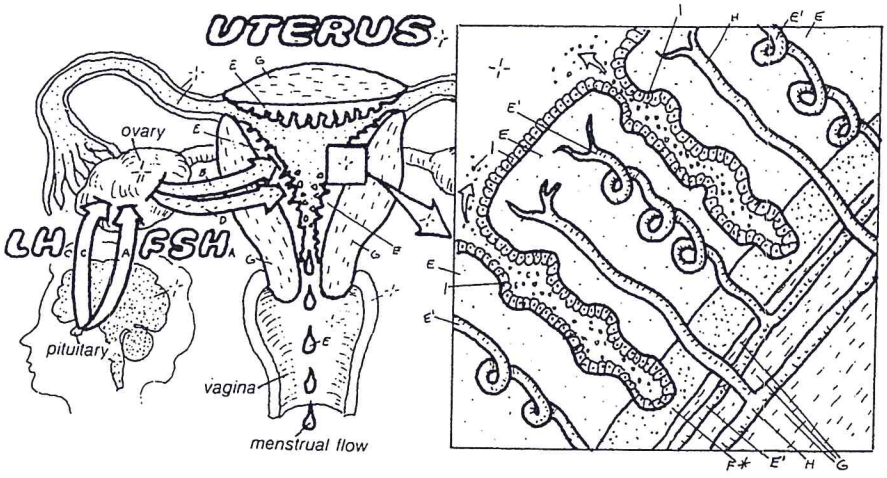
Other Effects of Estrogen & Progesterone

Effects on oviduct, myometrium, lactation, and feedback regulation—In the oviduct, estrogen stimulates the development of extensive mucosal folds and cilia, which function in transport of the ovum and young embryo. During pregnancy, estrogen stimulates the growth of uterine smooth muscle mass (myometrium), which functions in parturition and birth contractions (plate 158). Estrogen and progesterone stimulate mammary gland growth and support lactation (plate 159). Estrogen is mainly responsible for negative and positive feedback effects on the hypothalamus involved in regulation of its secretion (plate 155). In the brain and certain other tissues that are targets of male androgen hormones, estrogen is the true intracellular hormone mediating the androgenic effects, since androgens are converted to estrogens by aromatase.

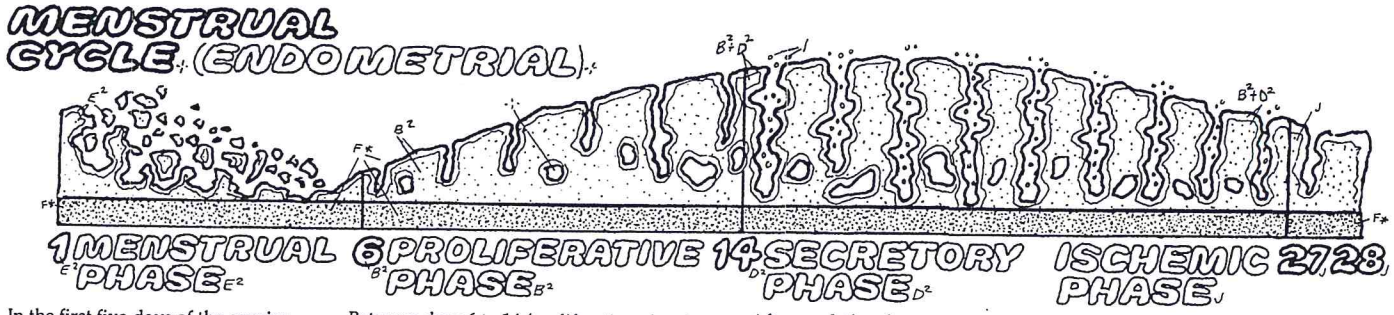
Estrogen promotes puberty and secondary sex characteristics in females—During puberty, estrogen (along with adrenal androgens) enhances bone calcium deposition and growth. It also promotes growth of the uterus, vagina, and oviducts, as well as the mammary glands. Estrogen is responsible for development of secondary sex characteristics in adolescent females and their maintenance during maturity. These include soft skin and increased subcutaneous fat, particularly in breasts and buttocks, leading to the mature female shape. Estrogen promotes the growth of a wide pelvis and closure of epiphyseal plates in long bones. Some female secondary sex characteristics, such as a high-pitched voice, narrow shoulders, smaller bone and body mass, and lack of facial and body hair, are due to the absence of male androgens.

Estrogen may protect against aging diseases—Heart attacks due to coronary occlusion and abnormal cholesterol metabolism are rare in premenopausal women but increase sharply after menopause when plasma estrogen is deficient. Estrogen in the brain may diminish the effects of Alzheimers disease. Estrogen deficiency underlies the marked increase in osteoporosis and bone fractures in elderly women. Estrogen replacement therapy can ameliorate these aging disorders.

CN: Use the same colors for FSH (A) and LH (C) as on the preceding page. Use red for E, blue for H.
1. Begin with the bottom panel, and follow the FSH contribution to the ovarian cycle and the growth of the follicular cells into the sex hormone cycle panel. Then do the LH and luteal phase portion of the ovarian cycle.
2. Go to the upper left corner and color the diagram of the uterus. Color the enlargement of the uterine wall section.



The pear-shaped uterus is connected to the uterine tubes dorsally and to the vagina ventrally, through the uterine cervix. The uterine wall consists of two layers, the muscular myometrium and mucosal endometrium. The endometrium is an epithelium consisting of a permanent basal layer and a functional layer that is continually rebuilt and destroyed. Within the endometrium are the uterine glands, spiral arteries, veins, and the surface epithelium.

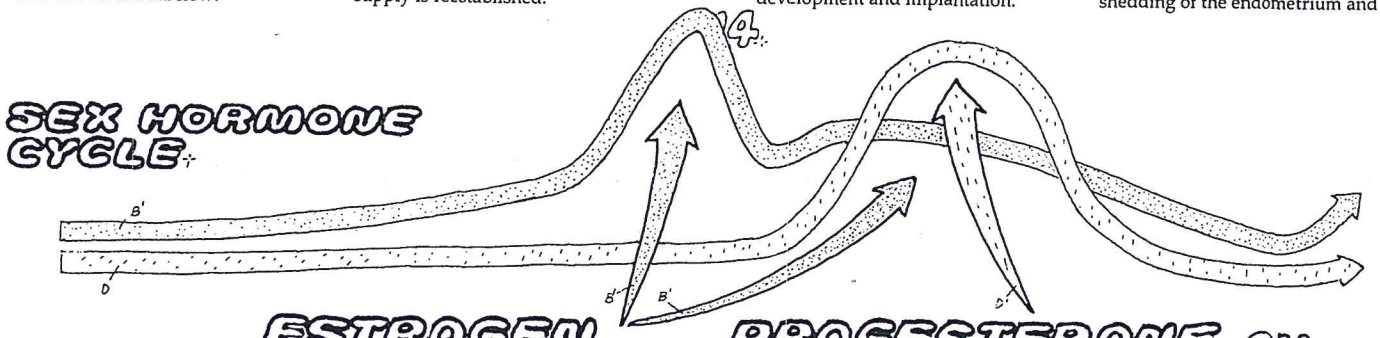


In the first five days of the ovarian cycle, the endometrium is shed, and the debris mixed with blood constitutes the menstrual flow.

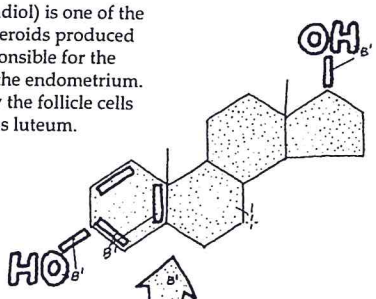
Between days 6 to 14 (proliferative phase), stimulated by estrogen, the endometrium is rebuilt, glands are formed, and the vascular supply is reestablished.

After ovulation, in response to progesterone, endometrial glands secrete uterine fluid necessary for embryonic development and implantation.

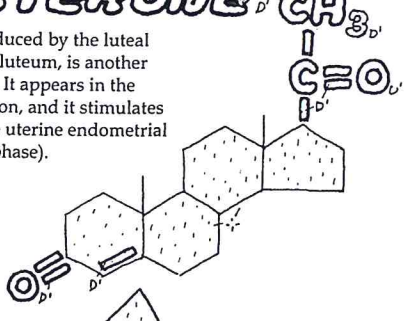
Without fertilization, estrogen and progesterone decline and endometrial blood flow diminishes (ischemic phase), causing the shedding of the endometrium and its blood.

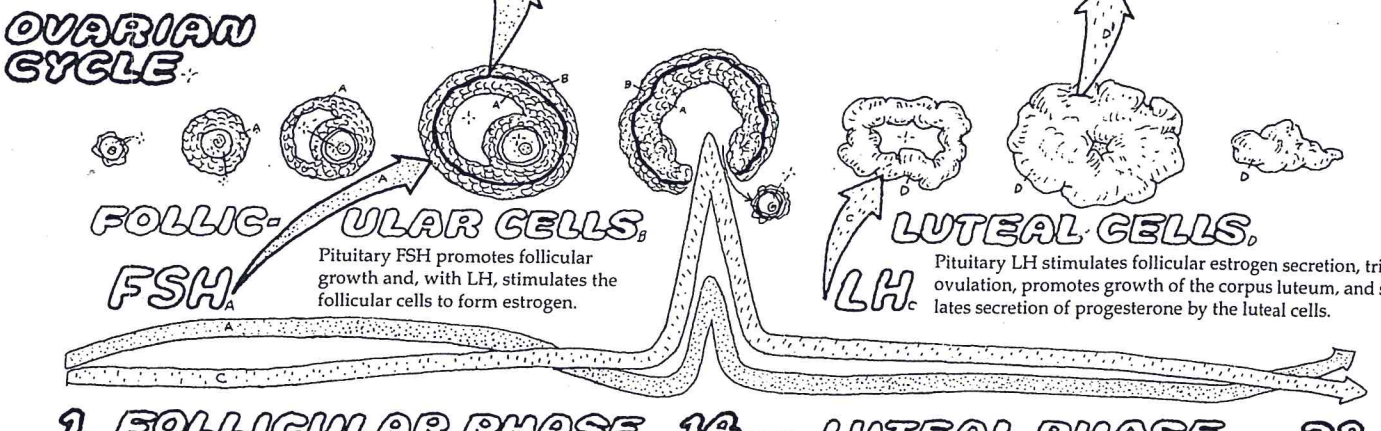


Estrogen (mainly estradiol) is one of the principal female sex steroids produced by the ovary. It is responsible for the proliferative phase of the endometrium. Estrogen is secreted by the follicle cells as well as by the corpus luteum.



Progesterone, produced by the luteal cells of the corpus luteum, is another female sex steroid. It appears in the blood after ovulation, and it stimulates the secretion of the uterine endometrial glands (secretory phase).





Pituitary FSH promotes follicular growth and, with LH, stimulates the follicular cells to form estrogen.

Pituitary LH stimulates follicular estrogen secretion, triggers ovulation, promotes growth of the corpus luteum, and stimulates secretion of progesterone by the luteal cells.