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Physiology of the normal menstrual cycle

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INTRODUCTION — The normal menstrual cycle is a tightly coordinated cycle of stimulatory and inhibitory effects that results in the release of a **single mature oocyte** from a pool of hundreds of thousands of primordial oocytes. A variety of factors contribute to the regulation of this process including hormones and paracrine and autocrine factors that are still being identified. The cyclic changes in the major pituitary and gonadal hormones are illustrated in the figure (figure 1 and figure 2).

The physiology of the normal menstrual cycle will be discussed here. Detection of ovulation and ultrasound evaluation of the menstrual cycle are reviewed separately. (See "Ultrasound evaluation of the normal menstrual cycle" and "Evaluation of the menstrual cycle and timing of ovulation".)

PHASES AND DURATION OF THE MENSTRUAL CYCLE — By convention, the first day of menses represents the first day of the cycle (day 1). The cycle is then divided into two phases: follicular and luteal.

- The follicular phase begins with the onset of menses and ends on the day of the luteinizing hormone (LH) surge.
- The luteal phase begins on the day of the LH surge and ends at the onset of the next menses.

The average adult menstrual cycle lasts 28 to 35 days, with approximately 14 to 21 days in the follicular phase and 14 days in the luteal phase [1,2]. There is relatively little cycle variability among women between the ages of 20 and 40 years. In comparison, there is significantly more cycle variability for the first five to seven years after menarche and for the last 10 years before cessation of menses (figure 3) [1].

In general, menstrual-cycle length peaks at about age 25 to 30 years and then gradually declines so that women in their forties have slightly shorter cycles. Changes in intermenstrual interval are primarily due to changes in the follicular phase; in comparison, the luteal phase remains relatively constant [3].

The remainder of this topic will review the hormonal, ovarian, and endometrial changes that occur during the different phases of the menstrual cycle.

EARLY FOLLICULAR PHASE — The early follicular phase in humans is the time when the ovary is the least hormonally active, resulting in low serum estradiol and progesterone concentrations (figure 1). Release from the negative feedback effects of estradiol, progesterone, and probably luteal phase

inhibin A results in a late luteal/early follicular phase increase in gonadotropin-releasing hormone (GnRH) pulse frequency and a subsequent increase in serum follicle-stimulating hormone (FSH) concentrations of approximately 30 percent [4]. This small increase in FSH secretion appears to be required for the recruitment of the next cohort of developing follicles, one of which will become the dominant and ultimately ovulatory follicle during that cycle [5-7].

Serum inhibin B concentrations, secreted by the recruitable pool of small follicles, are maximal at this time and may play a role in suppressing the FSH rise at this time in the cycle (figure 4) [8]. There is also a rapid increase in LH pulse frequency at this time, from one pulse every four hours in the late luteal phase to one pulse every 90 minutes in the early follicular phase [9].

The early follicular phase is also associated with a unique neuroendocrine phenomenon: slowing or cessation of LH pulses during sleep that does not occur at other times of the menstrual cycle (figure 5). How this occurs in not known.

Ovaries and endometrium — Ovarian ultrasonography has demonstrated that the ovary is quiescent in the early follicular phase except for the occasionally visible resolving corpus luteum from the previous cycle. The endometrium is relatively indistinct during menses and then becomes a thin line once menses is complete. It is normal to see small follicles of 3 to 8 mm in diameter at this time. (See "Ultrasound evaluation of the normal menstrual cycle".)

MID-FOLLICULAR PHASE — The modest increase in FSH secretion in the early follicular phase gradually stimulates folliculogenesis and estradiol production, leading to progressive growth of the cohort of follicles selected that cycle. As several follicles initially grow to the antral stage, their granulosa cells hypertrophy and divide, producing increasing serum concentrations of first estradiol via FSH stimulation of aromatase and then inhibin A from the granulosa cells in the ovaries.

The increase in estradiol production feeds back negatively on the hypothalamus and pituitary, resulting in suppression of mean serum FSH and LH concentrations as well as the LH pulse amplitude. In comparison, the GnRH pulse generator speeds up slightly to a mean LH pulse frequency of about one per hour (versus one per 90 minutes in the early follicular phase). GnRH stimulation is presumably due to release of negative feedback effects of progesterone from the previous luteal phase. (See "Physiology of gonadotropin-releasing hormone".)

Ovarian and endometrial changes — Within about seven days from the onset of menses, several 9 to 10 mm antral follicles are visible on ovarian ultrasonography. The rising serum estradiol concentrations result in proliferation of the uterine endometrium, which becomes thicker, with an increase in the number of glands and the development of a "triple stripe" pattern on ultrasound [10] (figure 2). (See "Ultrasound evaluation of the normal menstrual cycle".)

LATE FOLLICULAR PHASE — The serum concentrations of estradiol and inhibin A increase daily during the week before ovulation due to release from the growing follicle. Serum FSH and LH concentrations are falling at this time due to negative feedback effects of estradiol and perhaps other hormones released from the ovary (figure 1). As the dominant follicle is selected, FSH induces LH receptors in the ovary and increases ovarian secretion of intrauterine growth factors such as insulin-like growth factor-I (IGF-I).

Ovarian, endometrial, and cervical mucus changes — By the late follicular phase, a single dominant follicle has been selected, while the rest of the growing cohort of follicles gradually stop developing and undergo atresia. The dominant follicle increases in size by about 2 mm per day until a mature size of 20 to 26 mm is reached. (See "Ultrasound evaluation of the normal menstrual cycle".)

Rising serum estradiol concentrations result in gradual thickening of the uterine endometrium and an increase in the amount and "stringiness" (Spinnbarkeit) of the cervical mucus. Many women are able to detect this change in mucus character. Studies of cervical mucus samples during the menstrual cycle demonstrate a late follicular-phase peak in the mucin protein MUC5B that may be important for sperm transit to the uterus [11].

LUTEAL PHASE: MID-CYCLE SURGE AND OVULATION — Serum estradiol concentrations continue to rise until they reach a peak approximately one day before ovulation. Then, a unique neuroendocrine phenomenon occurs: the mid-cycle surge [12]. The surge represents a switch from negative feedback control of LH secretion by ovarian hormones (such as estradiol and progesterone) to a sudden positive feedback effect, resulting in a 10-fold increase in serum LH concentrations and a smaller rise in serum FSH concentrations (figure 1). In addition to estrogen and progesterone, other ovarian factors contribute to the LH surge, because it cannot be recreated simply by administering estrogen and a progestin to women in the early to mid-follicular phase to achieve serum concentrations similar to those at the mid-cycle [13].

At this time the frequency of LH pulses continues to be approximately one per hour, but the amplitude of the LH pulses increases dramatically. The switch from negative to positive feedback of LH release is poorly understood. An increase in the number of pituitary GnRH receptors may contribute but there is probably no change in GnRH input to the pituitary [14].

Ovarian changes — The LH surge initiates substantial changes in the ovary. The oocyte in the dominant follicle completes its first meiotic division. In addition, the local secretion of plasminogen activator and other cytokines required for the process of ovulation is increased [15,16]. The oocyte is released from the follicle at the surface of the ovary approximately 36 hours after the LH surge. It then travels down the fallopian tube to the uterine cavity. There is a close relation of follicular rupture and oocyte release to the LH surge; as a result, measurements of serum or urine LH can be used to estimate the time of ovulation in infertile women. (See "Evaluation of the menstrual cycle and timing of ovulation".)

Even before the oocyte is released, the granulosa cells surrounding it begin to luteinize and produce progesterone. Progesterone acts rapidly to slow the pulse generator so that LH pulses become less frequent by the termination of the surge.

Endometrium — The gradually increasing serum progesterone concentrations have a profound impact on the endometrial lining, leading to cessation of mitoses and "organization" of the glands [17]. This change can be detected on ultrasonography relatively soon after ovulation: the "triple stripe" image is lost and the endometrium becomes more uniformly bright [10] (figure 2). (See "Ultrasound evaluation of the normal menstrual cycle".)

MIDDLE TO LATE LUTEAL PHASE — Progesterone secretion from the corpus luteum [18] results in gradually rising progesterone concentrations in the middle to late luteal phase. This leads to progressive slowing of LH pulses down to one pulse every four hours. Pulses of progesterone occur soon after these slow LH pulses. As a result, there can be significant excursions in serum progesterone concentrations during the luteal phase (figure 6) [19]. Inhibin A is also produced by the corpus luteum, and serum concentrations of inhibin A peak in the mid-luteal phase. Inhibin B secretion is virtually absent during the luteal phase (figure 4). Serum leptin concentrations are highest in the luteal phase [20]. (See "Physiology of leptin".)

In the late luteal phase, a gradual decrease in LH secretion results in a gradual fall in progesterone

and estradiol production by the corpus luteum in the absence of a fertilized oocyte. If, however, the oocyte becomes fertilized, it implants in the endometrium several days after ovulation. The early embryo begins to make chorionic gonadotropin, which maintains the corpus luteum and progesterone production.

Endometrial changes — The decline in estradiol and progesterone release from the resolving corpus luteum results sequentially in the loss of endometrial blood supply, endometrial sloughing, and the onset of menses approximately 14 days after the LH surge. Menses is a relatively imprecise marker of hormonal events in the menstrual cycle, since there is considerable inter-individual variability in the relationship between the onset of endometrial sloughing and the fall in serum hormone concentrations during the luteal phase [4] (figure 2).

In response to falling corpus luteum steroid production, the hypothalamic-pituitary axis is released from negative feedback and FSH levels rise, thereby beginning the next cycle.

SUMMARY — By convention, the first day of menses represents the first day of the cycle (day 1). The cycle is then divided into two phases: follicular and luteal.

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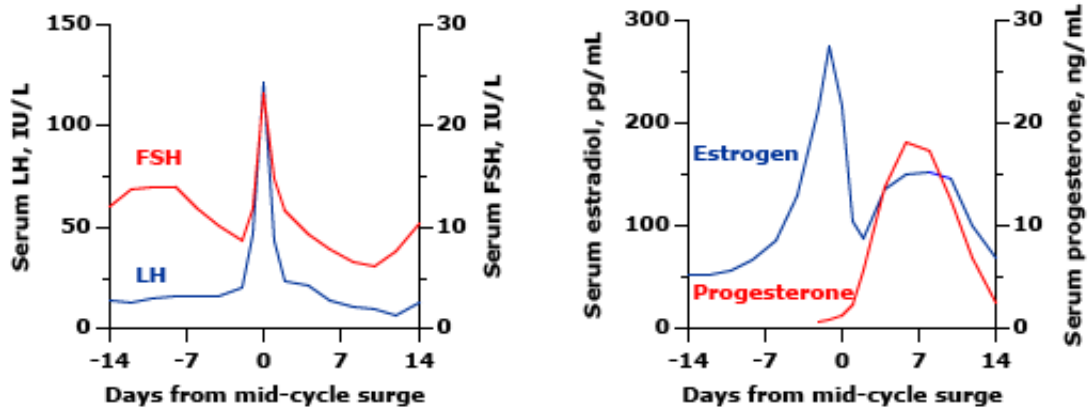
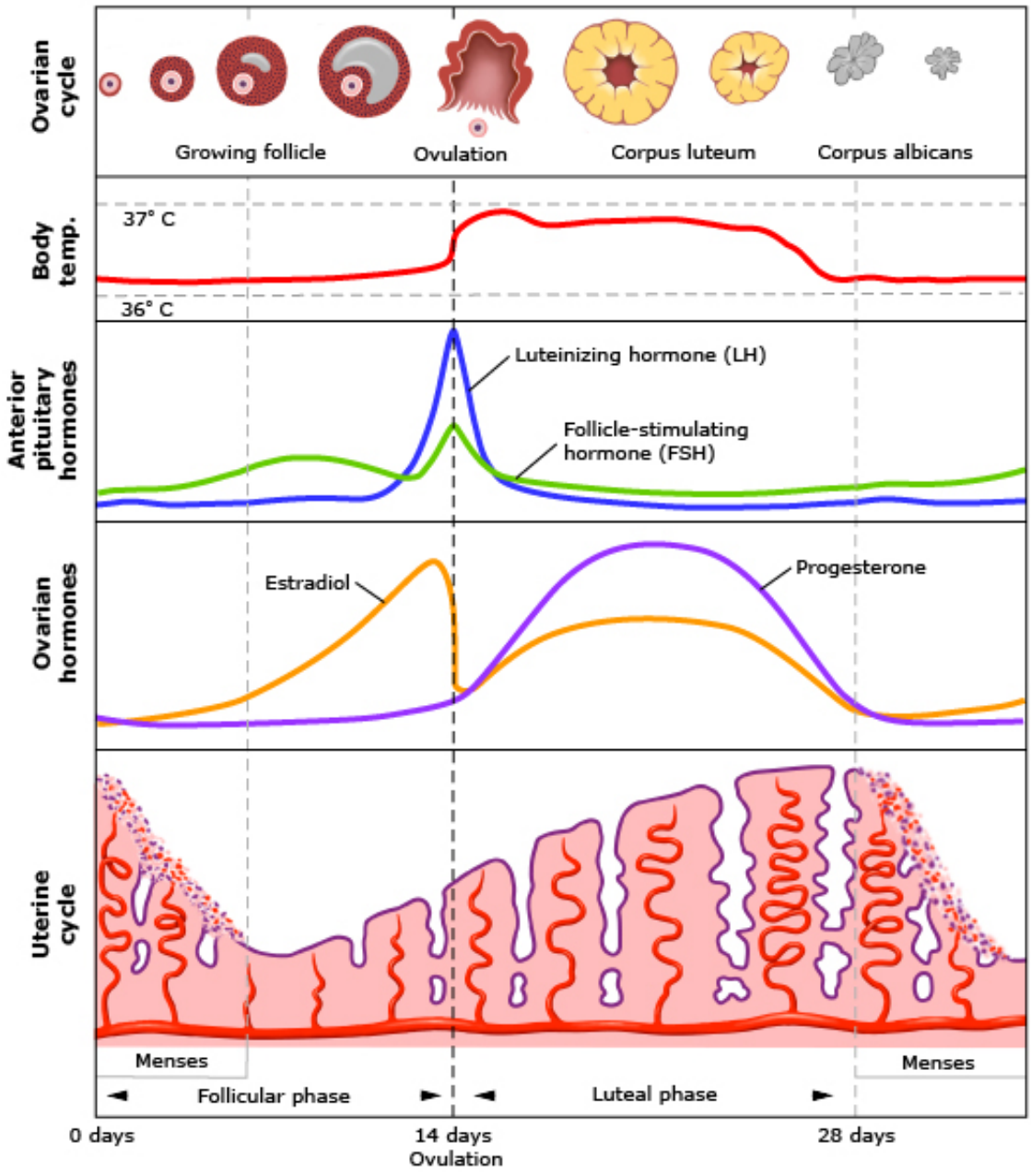
GRAPHICS

Hormonal changes during normal menstrual cycle

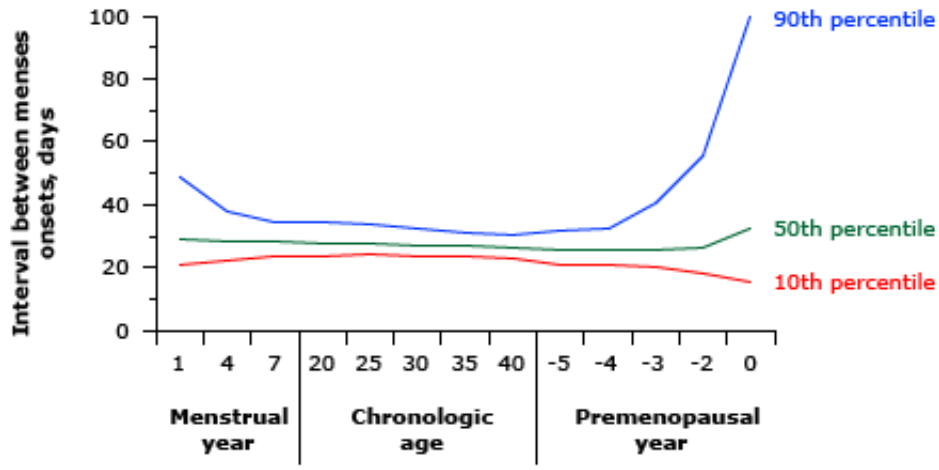


Sequential changes in the serum concentrations of the hormones released from the pituitary (FSH and LH; left panel) and from the ovaries (estrogen and progesterone; right panel) during the normal menstrual cycle. By convention, the first day of menses is day 1 of the cycle (shown here as day -14). The cycle is then divided into two phases: the follicular phase is from the onset of menses until the LH surge (day 0); and the luteal phase is from the peak of the LH surge until the next menses. To convert serum estradiol values to pmol/L, multiply by 3.67, and to convert serum progesterone values to nmol/L, multiply by 3.18.

Menstrual cycle

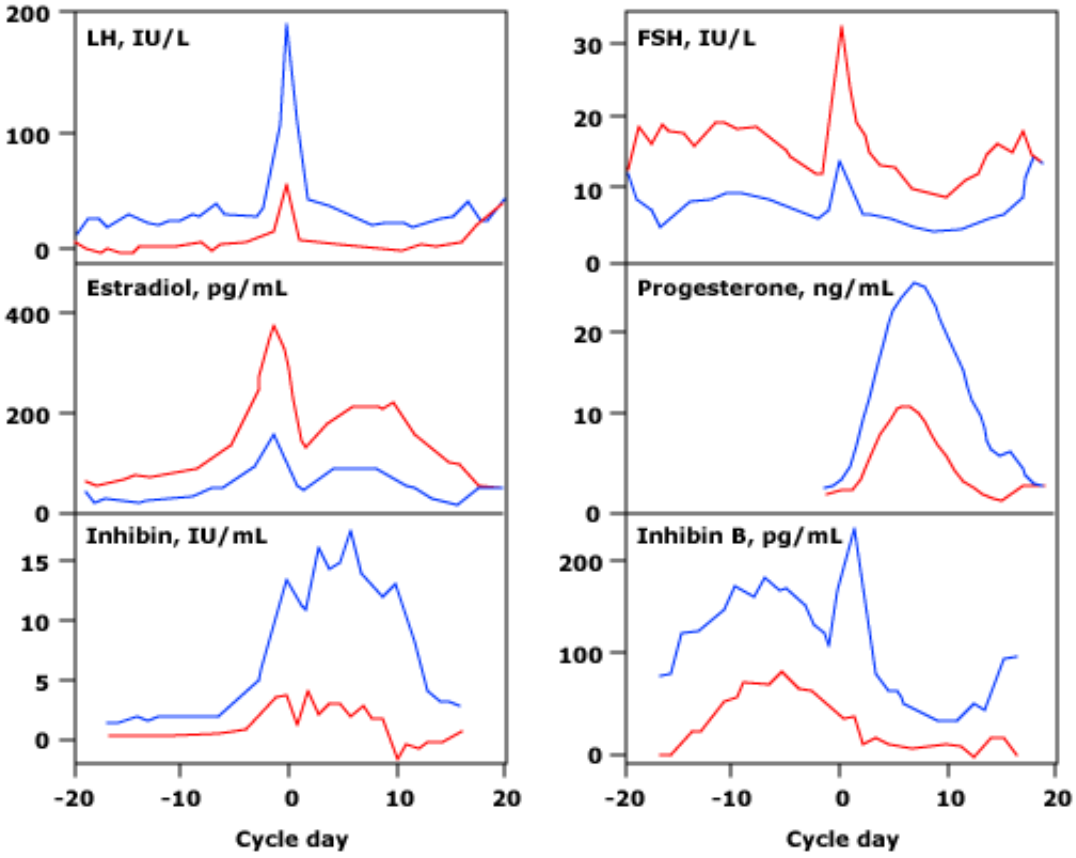


Age-related duration of menses



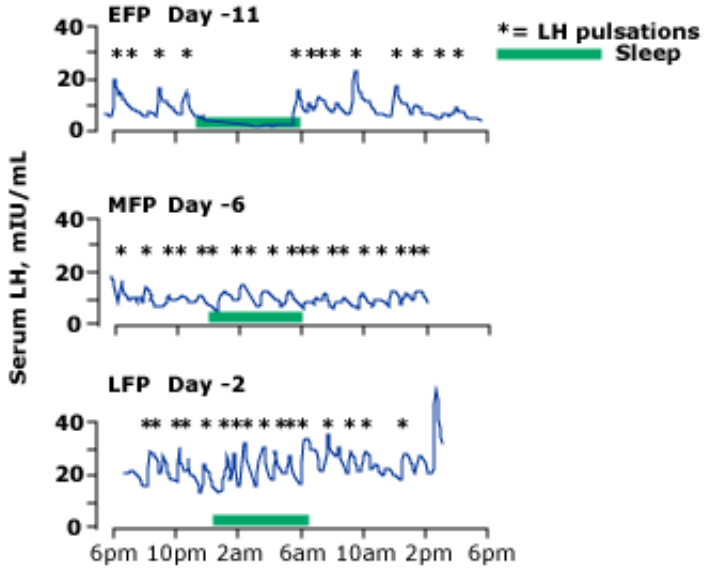
Selected percentiles for the distribution of menstrual interval by age based on data from over 200,000 cycles. Longer intermenstrual intervals occur in women just after menarche and in the years preceding menopause. *Data from: Treloar, AE, Boynton, RE, Behn, BG, Brown, BW, Int J Fertil 1967; 12:77.*

Hormone levels



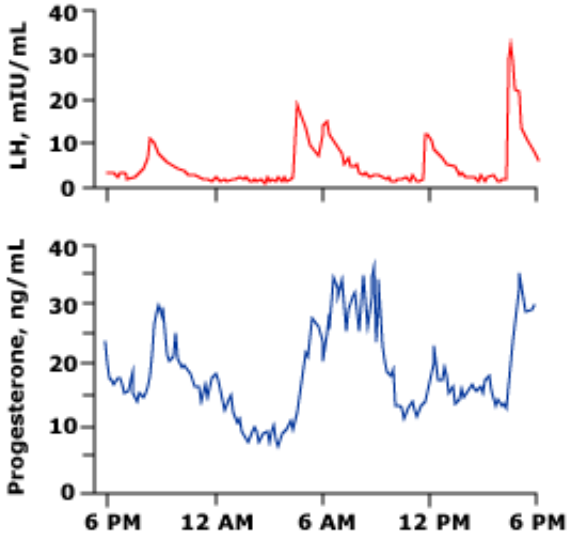
Mean daily levels of gonadotropins, sex steroids, and inhibins in older (ages 35-46 years; n=21), shown in red, and younger women (ages 20-34 years; n=23), shown in blue. *Data from Welt, CK, McNicholl, DJ, Taylor, AE, Hall, JE. J Clin Endocrinol Metab 1999; 84:105.*

Episodic LH secretion during the follicular phase



Patterns of episodic LH secretion during early (EFP), middle (MFP), and late (LFP) phases of the menstrual cycle. Day 0 is the day of the midcycle LH surge. There is a unique suppression of LH secretion during sleep in the EFP. *Data from Filicori, M, Santoro, N, Merriam, GR, Crowley, WF Jr, J Clin Endocrinol Metab 1986; 62:1136.*

LH pulses stimulate progesterone release in mid-luteal phase



Serum concentrations of luteinizing hormone and progesterone during 24 hours of blood sampling at 10 minute intervals in a normal woman studied during the mid-luteal phase. There is a significant correlation between LH pulses and increased serum progesterone concentrations. To convert serum progesterone values to nmol/L, multiply by 3.18. *Data from Filicori, M, Butler, JP, Crowley, WF Jr, J Clin Invest 1984; 73:1638.*

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