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WOMEN'S HEALTH

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OBJECTIVES

After completing this chapter, the reader should be able to

- Describe how the hypothalamic-pituitary-ovarian axis influences the normal reproductive cycle
- Explain how follicle-stimulating hormone, luteinizing hormone, estradiol, and progesterone affect the menstrual cycle and how they differ in premenopausal women, postmenopausal women, and women after oophorectomy
- Describe clinical symptoms, physical findings, and accompanying laboratory abnormalities in women with secondary amenorrhea
- Describe proposed diagnostic criteria, physical and radiological findings, and accompanying laboratory abnormalities in women with polycystic ovary syndrome
- Describe signs of virilization, causes of hirsutism, and associated laboratory abnormalities
- Describe pertinent medical history, physical examination findings, and laboratory and gynecologic procedures to determine causes of infertility in women
- List and describe how drugs interfere with laboratory values of follicle-stimulating hormone, luteinizing hormone, progesterone, prolactin, and testosterone

ANATOMY AND PHYSIOLOGY

The reproductive cycle depends on the complex cyclic interactions between hypothalamic gonadotropin-releasing hormone (GnRH), the pituitary gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and the ovarian sex steroid hormones estradiol (E_2) and progesterone.[1] Through positive and negative feedback loops, these hormones stimulate ovulation, facilitate implantation of the fertilized ovum, or induce menstruation. Feedback loops between the hypothalamus, pituitary gland, and ovaries are depicted in **Figure 22-1.** If the levels or relationship of any one (or more) of the above hormones become altered, the reproductive cycle becomes disrupted, and ovulation and menstruation cease.

MENSTRUAL CYCLE

The reproductive cycle is divided into three phases: menstruation and the follicular phase, ovulation, and the luteal phase.[1,2] These three phases referring to the status of the ovary during the reproductive cycle are depicted in **Figure 22-2**. The endometrium has the proliferative and secretory phases.

Phase I. Menstruation and the follicular phase. The first day of menstrual bleeding is considered day 1 of the typical 28-day menstrual cycle. During menstruation, the endometrium is sloughed in response to progesterone withdrawal. Women usually menstruate for three to five days. This is accompanied by the development of a new follicle during the follicular phase, with renewal of the endometrial lining of the uterus in preparation for implantation of an embryo.

Menstruation marks the beginning of the follicular phase of the cycle. With the beginning of menstruation, plasma concentrations of E_2, progesterone, and LH reach their lowest point. An increase in FSH begins approximately two days before the onset of menstruation and continues in response to the reduction in negative feedback at the pituitary gland. Under the influence of FSH, the granulosa cells in the ovarian follicle begin to secrete E_2.

E_2 begins to rise in plasma by the fourth day of the cycle. E_2 stimulates LH receptors on the theca cells in the ovarian follicle, further increasing secretion of androgen precursors, which are converted by aromatase to E_2 in granulosa cells. The upregulation of LH receptors and hormone production prepares the granulosa and theca cells for progesterone synthesis after ovulation.

With rising E_2 levels, there is negative feedback to the pituitary gland to decrease the release of FSH and positive feedback to the pituitary gland to increase the release of LH. During the early follicular phase of the cycle, the FSH:LH ratio is <1; as the cycle progresses, the FSH:LH ratio becomes >1, demonstrating both positive and negative feedback effects of E_2 on the pituitary gland.

Phase II. Ovulation. As the dominant follicle secretes more and more E_2, there is marked positive feedback to the pituitary gland to secrete LH. By days 11 to 13 of the normal cycle, an LH surge occurs, which triggers ovulation. Ovulation occurs within 24–36 hours of the LH surge, causing the oocyte to be expelled from the follicle and the follicle to be converted into corpus luteum to facilitate progesterone production

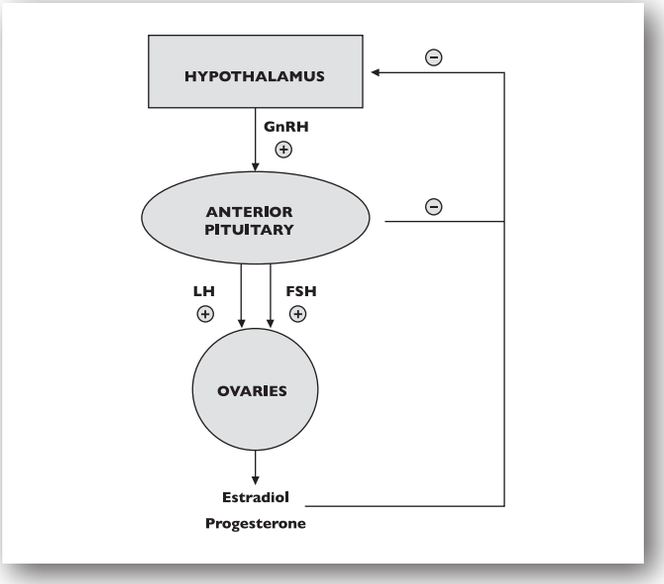

FIGURE 22-1. Hypothalamic-pituitary-ovarian axis (GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; FSH = follicle-stimulating hormone; (+) = stimulation of hormone secretion; (-) = inhibition of hormone secretion).

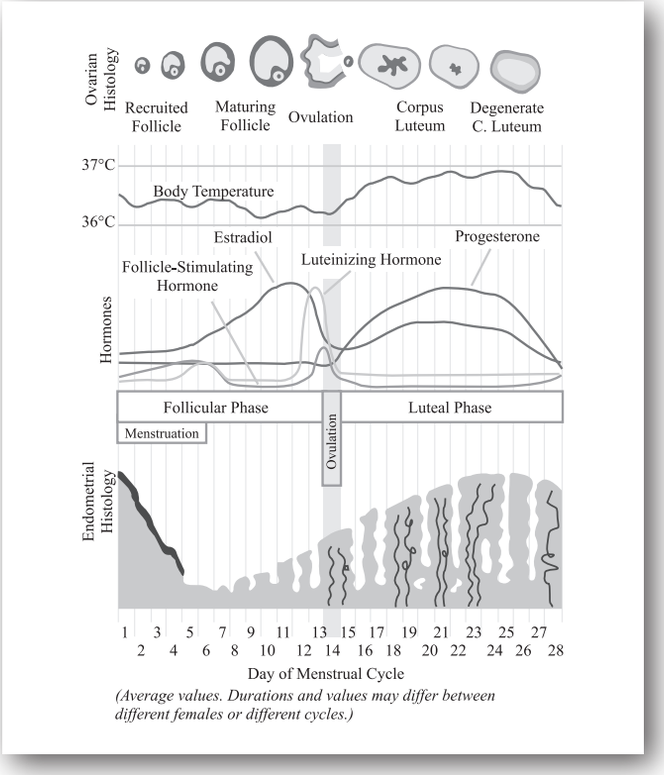

FIGURE 22-2. The menstrual cycle.

during the remainder of the cycle. In addition, there is a slight increase in the basal body temperature (BBT) after ovulation.

Phase III. Luteal phase. The luteal phase of the menstrual cycle is characterized by a change in secretion of sex steroid hormones from E_2 predominance to progesterone predominance. As FSH rises early in the cycle, stimulating production of E_2, additional LH receptors are created in the granulosa cells and then theca cells. With the LH surge at the time of ovulation, LH facilitates production of progesterone.

The production of progesterone begins approximately 24 hours before ovulation and rises rapidly thereafter. A maximum production of progesterone occurs 3–4 days after ovulation and is maintained for approximately 11 days following ovulation. If fertilization and implantation do not occur, progesterone production diminishes rapidly, initiating events leading to the beginning of a new cycle.

Adequate progesterone production is necessary to facilitate implantation of the fertilized oocyte into the endometrium and to sustain pregnancy into the early first trimester. If the initial rise in FSH is inadequate and the LH surge does not achieve maximal amplitude, an "inadequate luteal phase" can occur, resulting in progesterone production that is inadequate to facilitate implantation of a fertilized oocyte or to sustain pregnancy. The corpus luteum has a fixed life span of 13–14 days unless pregnancy occurs. If the oocyte becomes fertilized and implants within the endometrium, the early pregnancy begins secreting human chorionic gonadotropin, which sustains the corpus luteum for another six to seven weeks.

Physiologic plasma levels of progesterone exert negative feedback on pituitary secretion of both FSH and LH. During the luteal phase of the cycle, both FSH and LH are suppressed to low levels. As the corpus luteum fails and progesterone secretion diminishes, FSH begins to rise to prepare a woman for the next reproductive cycle.

AMENORRHEA

Amenorrhea is the absence or abnormal cessation of the menses.[3] Primary and secondary amenorrhea describe the occurrence of amenorrhea before and after menarche, respectively. Primary amenorrhea can be diagnosed if a patient has normal secondary sexual characteristics but no menarche by 16 years of age.[4] Secondary amenorrhea is the absence of menses for three months in women with previously normal menstruation and for nine months in women with previous oligomenorrhea (scant menses). Secondary amenorrhea is more common than primary amenorrhea.[5] The reader is referred to other texts for the evaluation of primary amenorrhea.

The prevalence of amenorrhea not due to pregnancy, lactation, or menopause is approximately 3–4%.[3,5] History, physical examination, and measurement of FSH, thyroid-stimulating hormone (TSH), and prolactin will identify the most common causes of amenorrhea. **Table 22-1** illustrates how symptoms elicited from a patient history assist in diagnosing the cause of amenorrhea.[4,6]

During the physical examination, the clinician should note the presence of galactorrhea, thyromegaly, or other evidence of hypothyroidism or hyperthyroidism, hirsutism, acne, or signs of virilization.[7] In addition, the patient's body mass index (BMI) should be calculated. A BMI <20 may indicate hypothalamic ovulatory dysfunction, such as occurs with anorexia