A 19-year-old woman presents to her gynecologist with complaints of not having had a period for 6 months. She reports having normal periods since menarche at age 12. She denies sexual activity, thyroid symptoms, or a milky breast discharge. She has no medical problems and is not taking any medications. On examination, she is thin but otherwise normally developed. The patient makes several comments about the fact that she thinks she is fat and is not satisfied with her body image. In comparison to other patients of her age, she is extremely underweight. She reports exercising excessively to “lose weight.” The remainder of the examination is normal except for a slow heart rate and dry skin with lanugo. A pregnancy test is negative, and thyroid function tests are normal. The patient is diagnosed with anorexia nervosa and referred for treatment and counseling.

- What is the pathophysiological cause of her amenorrhea?

- Which cells in the ovary secrete estrogen?

- What is the major hormone produced by the corpus luteum?
ANSWERS TO CASE 41: REPRODUCTION IN THE FEMALE

Summary: A 19-year-old woman presents with secondary amenorrhea and anorexia nervosa.

◆ Pathophysiology of amenorrhea: Hypothalamic state caused by the patient’s anorexia nervosa, resulting in decreased gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus and, as a result, decreased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) production and secretion.

◆ Estrogen secretion in ovary: Granulosa cells (convert testosterone to estrogen with the enzyme aromatase).

◆ Major hormone produced by the corpus luteum: Progesterone.

CLINICAL CORRELATION

Many conditions may result in secondary amenorrhea. It is often helpful to remember the various levels where normal function may be lost. If there is a history of cervical surgery, cervical stenosis may be present, resulting in an anatomic obstruction of menses. Ovarian problems also result in amenorrhea and menstrual irregularities. Possible causes of ovarian dysfunction include premature ovarian failure, a history of chemotherapy and/or radiation causing destruction of ovarian tissue, and polycystic ovarian syndrome. Finally, if there is a problem with the hypothalamic axis, FSH and LH may not be secreted, and therefore the ovary will not be stimulated to produce estrogen/progesterone. Patients with hypothyroidism, hyperprolactinemia, anorexia, excessive stress, and excessive exercise all may have hypothalamic dysfunction that affects stimulation of their ovaries. A primary ovarian problem can be differentiated from a primary hypothalamic problem by checking the FSH level. If the FSH level is high, the ovary is where the problem is, and if the FSH is low, the hypothalamus is likely to be the source of the problem. If an FSH level were drawn on this patient with anorexia, it probably would be low. Her amenorrhea can be corrected by hormonal medications or by treating her anorexia.

APPROACH TO FEMALE REPRODUCTIVE PHYSIOLOGY

Objectives
1. Know the ovarian anatomy and hormones.
2. Understand the control of ovarian function.
3. Know the regulation of menstrual cycle.
4. Be able to chart the normal hormone levels throughout the menstrual cycle.

Definitions

Amenorrhea: Cessation of menses for 6 months or three times the normal menstrual interval.

Primary amenorrhea: Condition where a female has never had menses and has not had menses by the age of 16 years, regardless of secondary sexual development.

Secondary amenorrhea: Condition where a female has had menses previously and now has absence of menses as defined in amenorrhea.

Hypothalamic Dysfunction: Alterations of gonadotropin releasing hormone pulsatile secretion that may be due to a variety of disorders such as hyperprolactinemia, hypothyroidism, anorexia nervosa, or excessive exercise.

DISCUSSION

Ovarian Anatomy and Hormones

Human ovaries are paired ellipsoid pelvic structures that are attached to the uterus by the utero-ovarian ligament and the pelvic side wall by the infundibulopelvic ligament. They produce the oocytes and the hormones responsible for the events that lead to fertilization and the establishment of pregnancy. Ovaries are composed of two areas: a central zone, or medulla, and a peripheral zone, or cortex. The medulla contains the ovarian support structures, including the blood, lymph vessels, and nerve fibers. The cortex contains the two functional ovarian structures, follicles and corpora lutea, in varying states of development or regression. Most follicles exist in a nondeveloping pool and are called primordial follicles. A number of primordial follicles begin development, but usually only one develops into the ovulatory (graafian) follicle. Follicles that fail to continue to develop undergo self-destruction and are referred to as atretic. Developing follicles may be classified as primary, secondary, tertiary, and graafian as they mature. Tertiary (those which contain a fluid-filled cavity) and larger follicles have two primary cell types separated by a basement membrane. Granulosa cells surround the maturing oocyte and the fluid-filled cavity of the follicle. The basement membrane surrounds the granulosa cells and separates them from several outer layers of cells called thecal cells. Both granulosa and thecal cells contribute to the synthesis of estradiol. Androgens are synthesized by the thecal cells, cross the membrane and are converted to estradiol by the granulosa cells. After ovulation, the granulosa cells are transformed in a process called luteinization into the luteal cells of the corpus luteum, which is responsible for the synthesis of...
progesterone. If fertilization fails to occur, the corpus luteum undergoes self-destruction in a process called luteolysis. Corpora luteal structures in their early stages of development and late stages of regression are referred to as corpus hemorrhagicum and corpus albicans, respectively.

**Control of Ovarian Function**

Ovarian function is regulated primarily by FSH and LH secreted by the anterior pituitary. Their secretion is regulated by the GnRH produced by the hypothalamic area of the brain. The hypothalamus integrates numerous positive and negative signals that affect reproductive function. The integrated message is a pulsatile secretion of GnRH at a pulse frequency to facilitate the secretion of FSH and/or LH. GnRH pulses occur at hourly to less frequent intervals. Peripheral levels of estrogen and progesterone act (feedback) at the level of the hypothalamus and/or pituitary to influence FSH and LH (pulse frequency) secretion positively and/or negatively.

Follicular development is regulated by the peripheral levels of FSH and LH and/or LH pulse frequencies, depending on the state of follicle development. Transformation of primordial follicles into a cohort of developing primary follicles is independent of FSH and LH support. Several of the primary follicles continue to develop into tertiary follicles and then are recruited for further development by elevated levels of FSH during the first week of the menstrual cycle. A follicle at this stage then is selected as the dominant follicle for further development and ovulation. The exact nature of dominant follicle selection is unknown, but hourly pulses of LH are important for further development of the dominant follicle. Elevated peripheral levels of estradiol from the developing dominant follicle suppress peripheral FSH (negative feedback) levels and ultimately stimulate (positive feedback) the preovulatory surge of LH to ovulate the mature graafian follicle.

Luteinization of the granulosa cells of the ovulated follicle to form the corpus luteum is dependent on the preovulatory surge of LH. LH also is required for maintenance of the corpus luteum with the resulting progesterone and a low-level estrogen secretion during the luteal phase of the cycle. The resulting elevated peripheral progesterone levels reduce the frequency of LH pulses from hourly to once every 3 to 4 hours (negative feedback). In the absence of implantation of a fertilized oocyte, the corpus luteum has an inherent life span of 14 days. Mechanisms involved in luteolysis of the human corpus luteum are not fully understood, but may involve intraovarian prostaglandin F$_{2\alpha}$.

**Menstrual Cycle Regulation**

Most of the ovarian activities described above occur over a period of 28 days (Figure 41-1). This period in humans is called the menstrual cycle because it involves vaginal shedding of the uterine mucosa: menstruation. The first day
The 14 days preceding ovulation are characterized by increasing peripheral levels of estrogen from follicular development and are called the follicular phase. The 14 days after ovulation are characterized by a transitory increase in peripheral progesterone and to a lesser extent estrogen levels from CLINICAL CASES

**Figure 41-1.** Relative peripheral pituitary and ovarian hormones levels during the menstrual cycle. The preovulatory surge of luteinizing hormone (LH) occurs on day 15. LH pulses are not shown. LH pulses occur hourly during the late follicular phase of the cycle and every 3 to 4 hours during the luteal phase.

of menstruation is designated as day 1 of the menstrual cycle. **Ovulation** of the graafian follicle occurs around **midcycle after the preovulatory LH peak.** The 14 days preceding ovulation are characterized by increasing peripheral levels of estradiol from follicular development and are called the follicular phase. The 14 days after ovulation are characterized by a transitory increase in peripheral progesterone and to a lesser extent estrogen levels from...
the corpus luteum and are called the luteal phase. There is greater variability in the duration of the follicular phase than the luteal phase, accounting for the considerable variation in the length of the menstrual cycle in humans. Undoubtedly, factors affecting follicular development contribute to the variation in length of the follicular phase. At the uterine level, the **follicular phase** is referred to as the **proliferative phase**. During this period of estradiol influence, the uterine endometrium increases in thickness and the uterine glands lengthen. During the **luteal phase**, when **progesterone levels are elevated**, the **uterine glands are coiled and secretory**. The phase with respect to the endometrium is called **secretory**. When the corpus luteum regresses and progesterone levels decline, the endometrial mucosa thins and is shed. This thinning is accompanied by necrosis of endometrial blood vessels, leading to spotty hemorrhages and contributing to the menstrual flow.

**COMPREHENSION QUESTIONS**

[41.1] A patient with a 29-day menstrual cycle probably ovulated on which of the following days?

A. Day 13  
B. Day 14  
C. Day 15  
D. Day 16

[41.2] How does a basal body temperature chart reflect ovulation?

A. Increased basal body temperature with LH surge  
B. Decreased basal body temperature with LH surge  
C. Increased basal body temperature with decreased progesterone level  
D. Increased basal body temperature with elevated progesterone level  
E. Increased basal body temperature with increased peripheral estradiol levels

[41.3] How does progesterone affect the pulsatile release of GnRH from the hypothalamus?

A. No change  
B. Increases  
C. Decreases  
D. Stops release altogether

[41.4] Withdrawal of which of the following hormones results in menstruation?

A. Estradiol  
B. FSH  
C. Progesterone  
D. LH
Answers

[41.1] C. The corpus luteum has an inherit life span of 14 days, resulting in a 14-day luteal phase. Ovulation occurs just before the luteal phase. Subtracting 14 days from the patient’s menstrual duration (29 days) gives an approximate day of ovulation (day 15).

[41.2] D. The elevated progesterone level during the luteal phase causes an increase in the patient’s basal body temperature by increasing the body’s thermoregulatory set point in the hypothalamus. A basal body temperature chart can be helpful to infertility patients by documenting the presence or absence of ovulation during a menstrual cycle.

[41.3] C. Progesterone causes a decrease in pulsatile release of GnRH.

[41.4] C. Withdrawal of the hormone progesterone results in sloughing of the endometrium (menstruation). If pregnancy occurs, the corpus luteum is “rescued” and production of progesterone continues (no menstruation).

PHYSIOLOGY PEARLS

❖ The central zone of the ovary (medulla) contains support structures for the ovary, and the peripheral zone (cortex) contains the follicles and corpora lutea in various stages of development.
❖ The follicular phase of the menstrual cycle varies in length among different individuals, whereas the luteal phase is relatively constant (14 days).
❖ The predominant hormones in the follicular and luteal phases are estradiol and progesterone, respectively.
❖ Elevated peripheral levels of estradiol result in the LH surge by positive feedback on the anterior pituitary.
❖ Ovulation is dependent on the preovulatory LH surge.

REFERENCES

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