

PREGNANCY

Pregnancy is the state of having products of conception implanted normally or abnormally in the uterus or occasionally elsewhere. Pregnancy is terminated by spontaneous or elective abortion or delivery. Myriad physiologic changes occur in a pregnant woman and they affect every organ system.

Diagnosis

In a patient who has regular menstrual cycles and is sexually active, a period delayed by more than a few days to a week would be suggestive of pregnancy. Even at this early stage, patients may exhibit signs and symptoms of pregnancy. The classic finding of "morning sickness" can begin this early and often continues through 12–16 weeks of gestation. On physical examination, a variety of findings indicate pregnancy (Table 1-1).

Many home pregnancy tests have a high sensitivity and will be positive around the time of the missed menstrual cycle. These urinary tests and the hospital laboratory serum assays test for the beta subunit of human chorionic gonadotropin (β -hCG). This hormone produced by the placenta will rise to a peak of 100,000 mIU/mL by 10 weeks of gestation, decrease throughout the second trimester, and then level off at approximately 20,000 to 30,000 mIU/mL in the third trimester.

A viable pregnancy can be confirmed by ultrasound, which may show the gestational sac as early as 5 weeks, or at a β -hCG of 1,500 to 2,000 mIU/mL, and the fetal

heart as soon as 6 weeks, or a β -hCG of 5,000 to 6,000 mIU/mL.

Terms and Definitions

From the time of fertilization until the pregnancy is 8 weeks along (10 weeks gestational age [GA]), the conceptus is called an embryo. After 8 weeks until the time

TABLE 1-1

Signs and Symptoms of Pregnancy

Signs

Chadwick's sign: Bluish discoloration of vagina and cervix

Goodell's sign: Softening and cyanosis of the cervix at or after 4 weeks

Ladin's sign: Softening of the uterus after 6 weeks

Breast swelling and tenderness

Development of the linea nigra from umbilicus to pubis

? Telangiectasias

Palmar erythema

Symptoms

Amenorrhea

Nausea and vomiting

Breast pain

Quickening—fetal movement

of birth, it is designated a **fetus**. The term **infant** is used for the period between delivery and 1 year of age. Pregnancy is divided into trimesters. The **first trimester** lasts until **14 weeks GA**, the **second trimester** from 14 until **28 weeks GA**, and the **third trimester** from 28 weeks until delivery. An infant delivered prior to **24 weeks** is considered to be **preivable**, from 24 to 37 weeks is considered **preterm**, and from 37 to 42 weeks is considered **term**. A pregnancy carried beyond **42 weeks** is considered **postdate or postterm**.

Gravidity refers to the number of times a woman has been pregnant, and **parity** refers to the number of pregnancies that led to a birth beyond **20 weeks GA** or of an infant weighing more than **500 g**. A more specific designation of pregnancy outcomes divides them into term and preterm deliveries, number of abortuses, and number of living children. A woman having given birth to one set of preterm twins, one term infant, and with two miscarriages would be a G4 P1-1-2-3. A multiple gestation is just one delivery but obviously may change the number of living children by more than one. In this designation abortuses includes both therapeutic and spontaneous abortions.

Dating of Pregnancy

The GA of a fetus is the age in weeks and days measured from the last menstrual period (LMP). **Developmental age (DA) is the number of weeks and days since fertilization**. Because fertilization usually occurs about 14 days after the first day of the prior menstrual period, **the GA is 2 weeks more than the DA**.

Classically, Nagele's rule for calculating the estimated date of confinement (EDC) is to **subtract 3 months from the LMP and add 7 days**. Thus, a pregnancy with an LMP of 4/13/00 would have an EDC of 1/20/01. Exact dating uses an EDC calculated as **280 days after a certain LMP**. If the date of ovulation is known, as in assisted reproductive technology (ART), the EDC can be calculated by **adding 266 days**. This dating can be confirmed and should be consistent with the examination of the uterine size at the first prenatal appointment.

With an uncertain LMP, ultrasound is often used to determine the EDC. **Ultrasound has a level of uncertainty that increases during the pregnancy but it is rarely off by more than 7-8% at any GA**. A safe rule of thumb is that **the ultrasound should not differ from LMP dating by more than 1 week in the first trimester, 2 weeks in the second trimester, and 3 weeks in the third trimester**. The dating done with crown-rump length in the first half of

the first trimester is probably even more accurate, to within 3-5 days.

Other measures used to estimate gestational age include pregnancy landmarks such as **auscultation of the fetal heart (FH) at 20 weeks by nonelectronic fetoscopy or at 10 weeks by Doppler ultrasound**, as well as **maternal awareness of fetal movement or "quickening," which occurs between 16 and 20 weeks**.

Physiology of Pregnancy

Cardiovascular

During pregnancy, **cardiac output increases by 30-50%**. Most increases occur during the first trimester, with the **maximum being reached between 20 and 24 weeks gestation and maintained until delivery**. **Systemic vascular resistance decreases during pregnancy**, resulting in a fall in arterial blood pressure. This decrease is most likely due to the elevated **progesterone** leading to smooth muscle relaxation. There is a decrease in systolic blood pressure of **5-10 mm Hg** and in diastolic blood pressure of **10-15 mm Hg** that nadirs at **24 weeks**. Between 24 weeks gestation and term, blood pressure slowly returns to prepregnancy levels but should never exceed them.

Pulmonary

There is an increase of **30-40% in tidal volume (V_T)** during pregnancy (Fig. 1-1) despite the fact that the total lung capacity is decreased by **5% due to the elevation of the diaphragm**. This increase in V_T decreases the expiratory reserve volume by about 20%. The increase in V_T with a constant respiratory rate leads to an increase in minute ventilation of 30-40%. This leads to an increase in alveolar PAO_2 and arterial (PaO_2) PO_2 levels and a decrease in $PACO_2$ and $Paco_2$ levels.

$Paco_2$ decreases to approximately 30 mm Hg by 20 weeks gestation from 40 mm Hg prepregnancy. This change leads to an increased CO_2 gradient between mother and fetus and is likely caused by elevated progesterone levels that either increase the respiratory system's responsiveness to CO_2 or act as a primary stimulant. Dyspnea of pregnancy occurs in 60-70% of patients. This is possibly secondary to decreased $Paco_2$ levels, increased V_T , or decreased total lung capacity (TLC).

Gastrointestinal

Nausea and vomiting occur in more than 70% of pregnancies. While this has been termed "morning sickness," it can happen anytime throughout the day. These symptoms have been attributed to the elevation in estrogen,

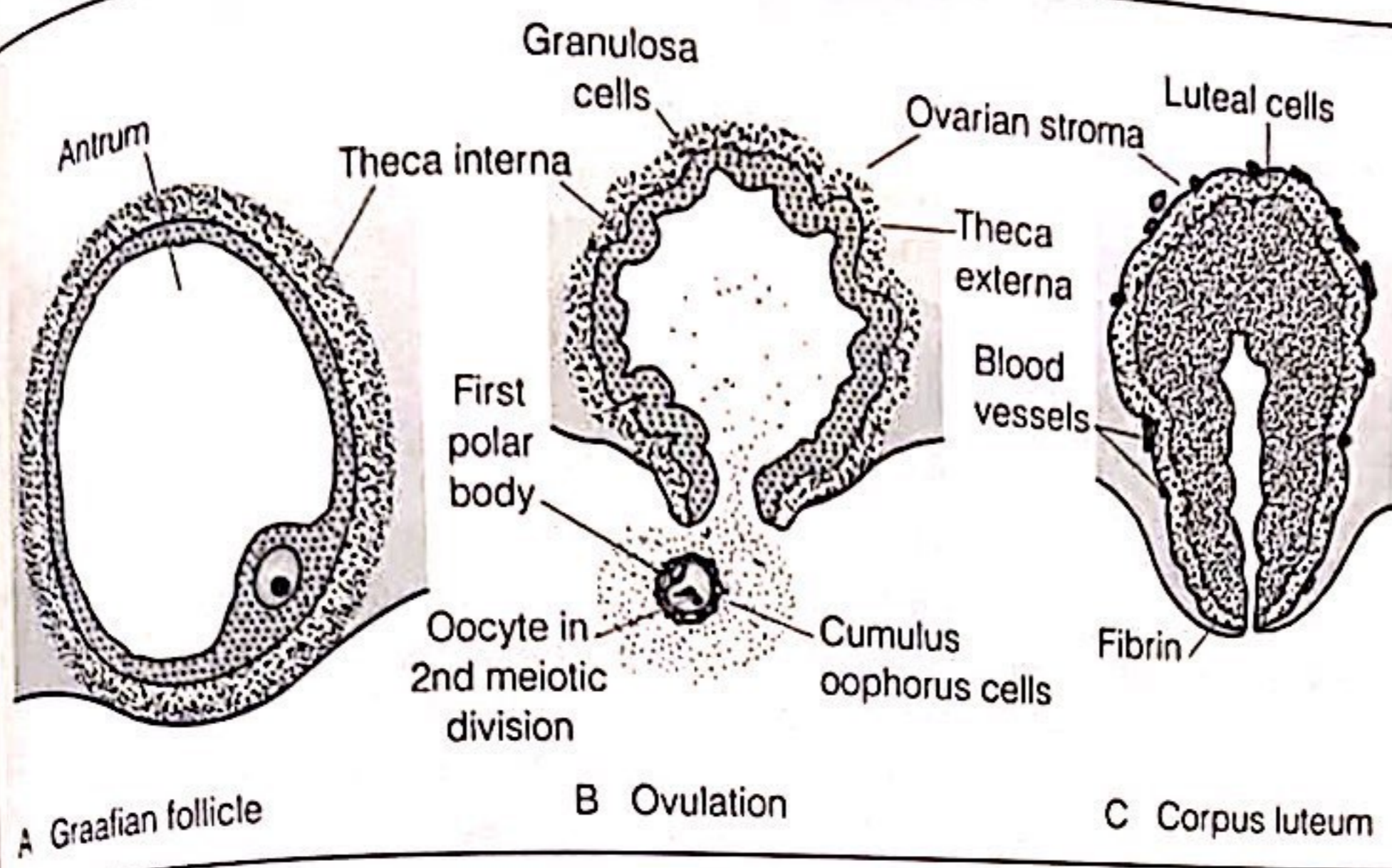


Figure 18-6 A. The graafian follicle just before rupture. B. Ovulation. The oocyte, beginning its second meiotic division, is discharged from the ovary, together with a large number of cumulus oophorus cells. The follicular cells remaining inside the collapsed follicle differentiate into luteal cells. C. Corpus luteum. Note the large size of the corpus luteum caused by hypertrophy and accumulation of lipid in the granulosa and theca interna cells. The remaining cavity of the follicle is filled with fibrin.

causes the endometrium to slough, initiating the menstrual phase. At the same time, FSH levels begin to slowly rise in the absence of negative feedback and the follicular phase starts again.

MENOPAUSE AND POSTMENOPAUSE

The "climacteric" marks the termination of the reproductive phase in a woman's life. At this point, nearly all the oocytes have undergone atresia, although a few remain and can be found on histologic examination. The term "menopause" denotes the final menstruation and marks the cornerstone event during the climacteric. The average age of menopause in the United States is 50-51 years. Various physiologic and hormonal changes occur during this period, including a decrease in estrogen, increase in FSH, and classic symptoms such as "hot flashes." If menopause occurs before the age of 40, it is considered premature.

Etiology

Menopause is generally heralded by menstrual irregularity as the number of oocytes capable of responding to

FSH and LH decrease and anovulation becomes more frequent. During this period, LH and FSH levels gradually rise because of decreased negative feedback from diminished estrogen production. The fall in estradiol levels leads to the symptoms of vasomotor flushing, sweats, mood changes, and depression. Early menopause is associated with cigarette smoking. Premature menopause is often a result of premature ovarian failure that is usually idiopathic. If it occurs before age 35, chromosomal studies can be sent to rule out a genetic basis (e.g., mosaicism).

Diagnosis

The diagnosis of menopause can usually be made by history and physical examination and confirmed by testing FSH levels. Patients will classically present between the ages of 48 and 52 with complaints of oligomenorrhea and vasomotor instability, sweats, mood changes, depression, dyspareunia, and dysuria. These symptoms generally disappear within 12 months, although a substantial proportion of women can remain symptomatic for years.

On physical examination there may be a decrease in breast size and change in texture. Vaginal, urethral, and

two-cell process with the theca interna cells producing androstenedione in response to LH stimulation and the granulosa cells converting this androstenedione to estradiol when stimulated by FSH. LH also rises and stimulates the synthesis of androgens, which are converted to estrogen. As rising estrogen levels negatively feed back on pituitary FSH secretion, the dominant follicle is protected from the decrease in FSH by its increased number of FSH receptors (Fig. 18-5).

Ovulation

Toward the end of the follicular phase, estrogen levels eventually surge to reach a critical level that triggers the anterior pituitary to release an LH spike. Ovulation occurs as the increase in LH levels causes the follicle to rupture and release the mature ovum (Fig. 18-6). The ovum usually passes into the adjoining fallopian tube and is swept down to the uterus by the cilia lining the tube. This process takes 3-4 days. Fertilization of the ovum must occur within 24 hours of ovulation or it degenerates.

Luteal Phase

After ovulation, the luteal phase ensues. The granulosa and theca interna cells lining the wall of the follicle form

the corpus luteum under stimulation by LH. The corpus luteum synthesizes estrogen and significant quantities of progesterone, which causes the endometrium to become more glandular and secretory in preparation for the implantation of a fertilized ovum. If fertilization occurs, the developing trophoblast synthesizes human chorionic gonadotropin (hCG), a glycoprotein very similar to LH, which maintains the corpus luteum so that it can continue production of estrogen and progesterone to support the endometrium until the placenta develops its synthetic function. If fertilization, with its consequent rise in hCG, does not occur, the corpus luteum degenerates, progesterone levels fall, the endometrium is not maintained, and menstruation occurs.

Menstruation

The endometrium of the uterus undergoes cyclical changes during the menstrual cycle. During the follicular phase, the endometrium is in the proliferative phase, growing in response to estrogen. During the luteal phase, the endometrium enters the secretory phase as progesterone levels rise and is prepared to support implantation. If the ovum is not fertilized, the corpus luteum degenerates and progesterone levels fall approximately 14 days, leading to a fall in estrogen and progesterone levels. The withdrawal of progesterone

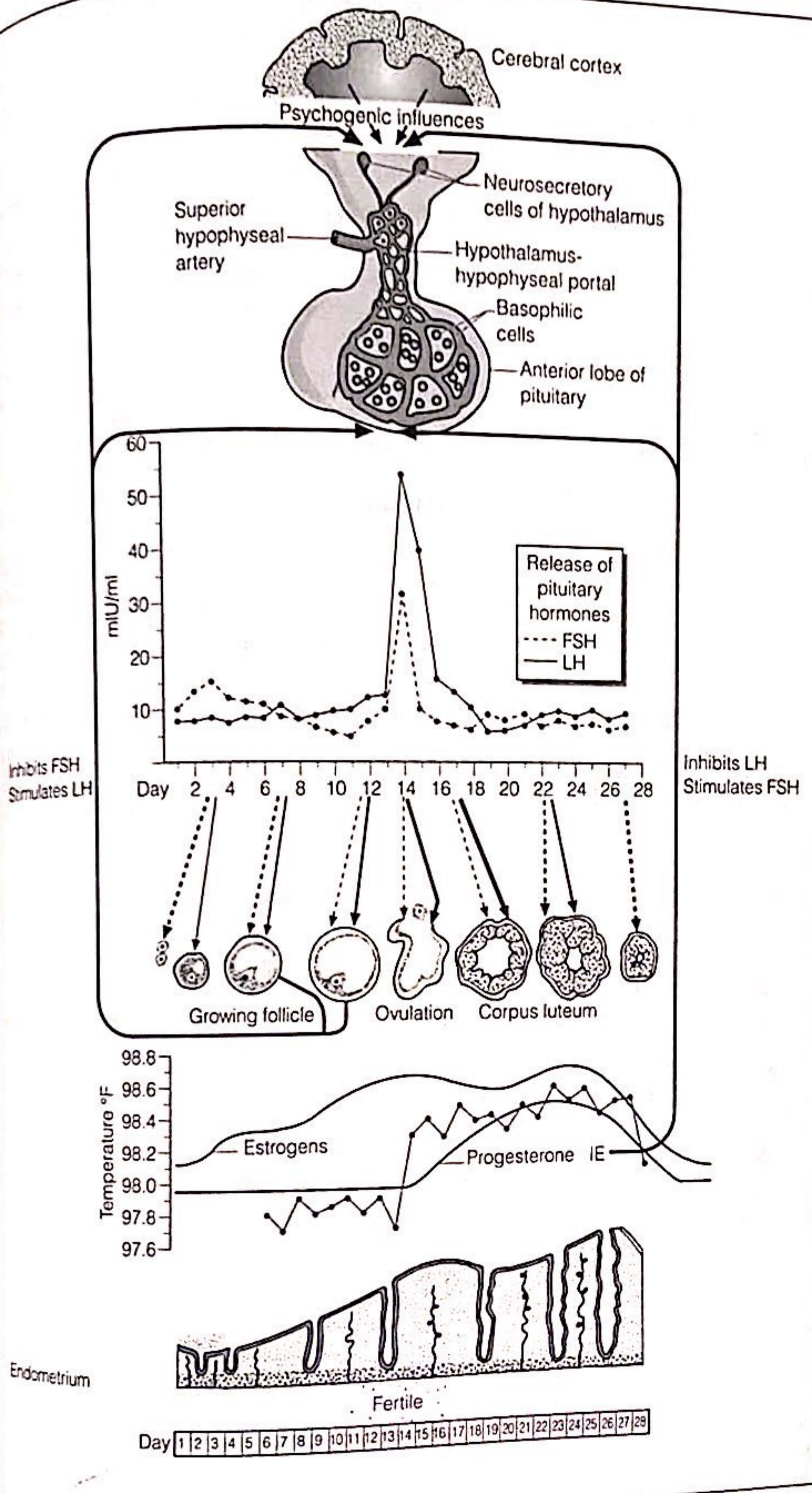


Figure 18-4 Normal menstrual cycle. Note the suprahypothalamic (cerebral, pineal), hypothalamic, pituitary, ovarian, and endometrial interrelations.

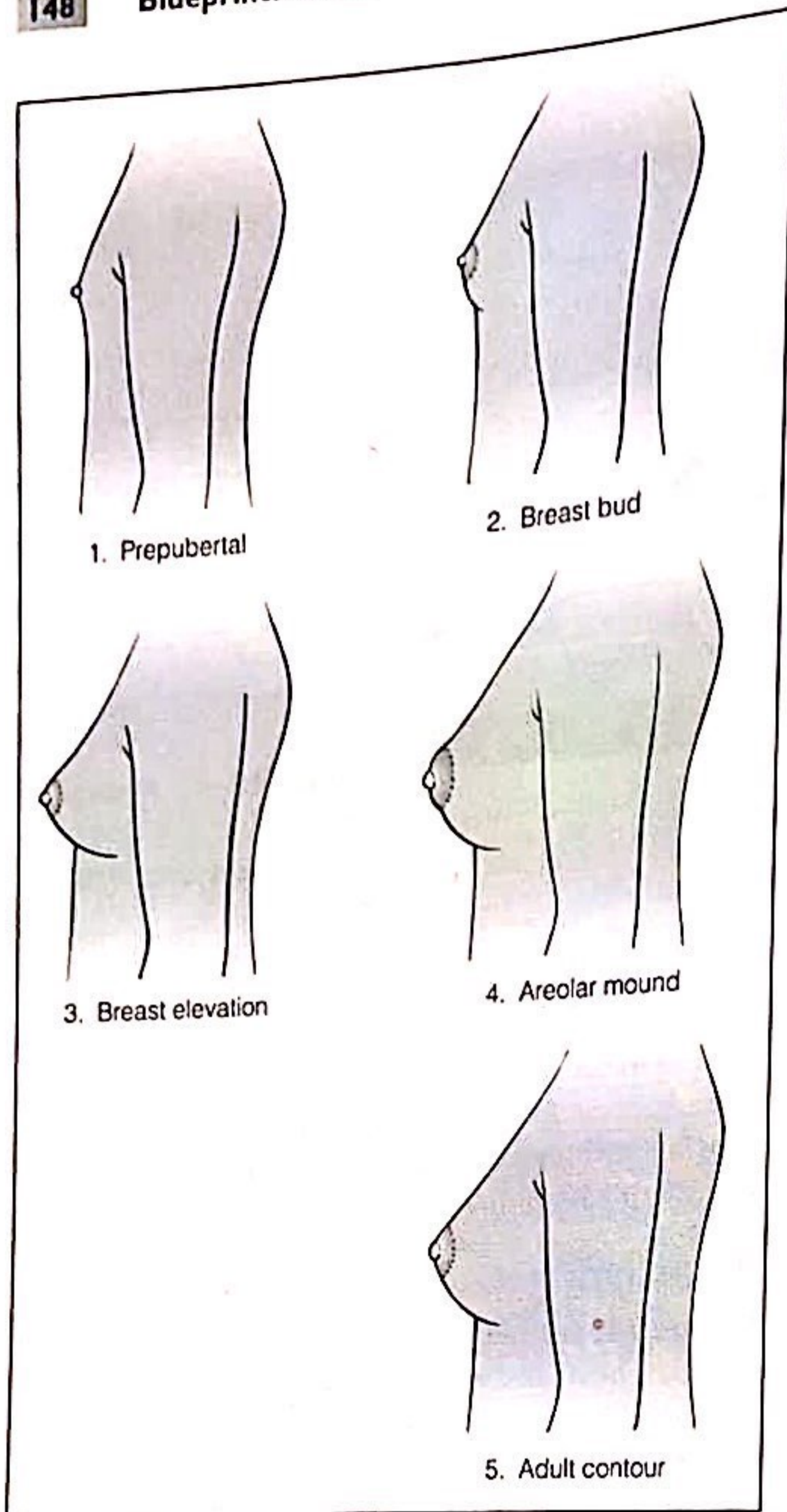


Figure 18-2 Tanner stages of thelarche.

approximately day 14, there is an LH spike in response to a preceding estrogen surge, which stimulates ovulation, the release of the ovum from the follicle. After ovulation the luteal phase begins. The remnants of the follicle left behind in the ovary develop into the corpus luteum. It is responsible for the secretion of progesterone, which maintains the endometrial lining in preparation to receive a fertilized ovum. If fertilization does not occur, the corpus luteum degenerates and progesterone levels fall. Without progesterone, the endometrial lining is sloughed off, which is known as menstruation.

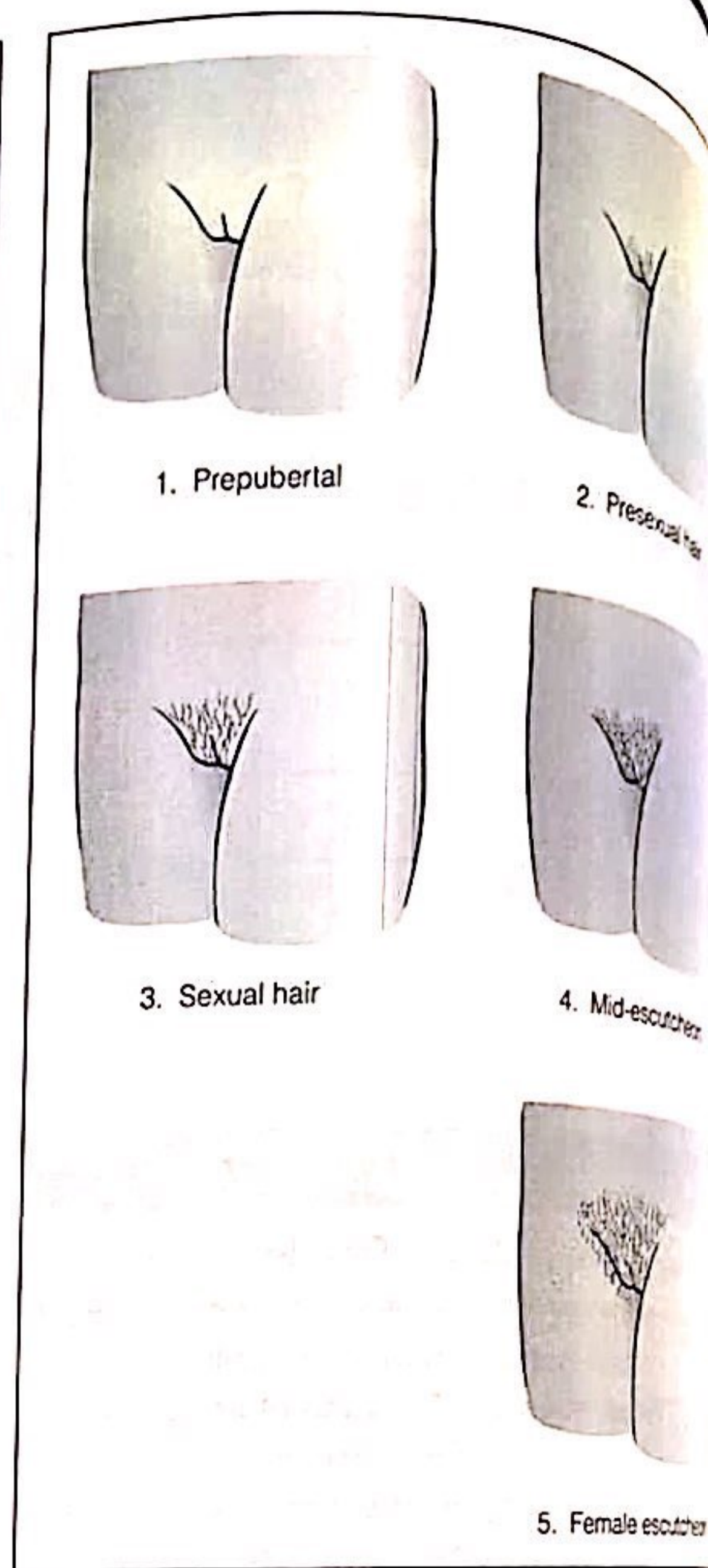


Figure 18-3 Tanner stages of pubarche.

Follicular Phase

The withdrawal of estrogen and progesterone during the luteal phase of the prior cycle causes a gradual increase in FSH. In turn, FSH stimulates growth of approximately 5 to 15 primordial ovarian follicles, initiating the follicular phase. Of these primordial follicles, one becomes the dominant follicle and develops and matures through ovulation. The developing follicle destined to ovulate produces estrogens, which enhances its own maturation and increases the production of FSH and LH receptors in an autocrine fashion. The estrogen is produced

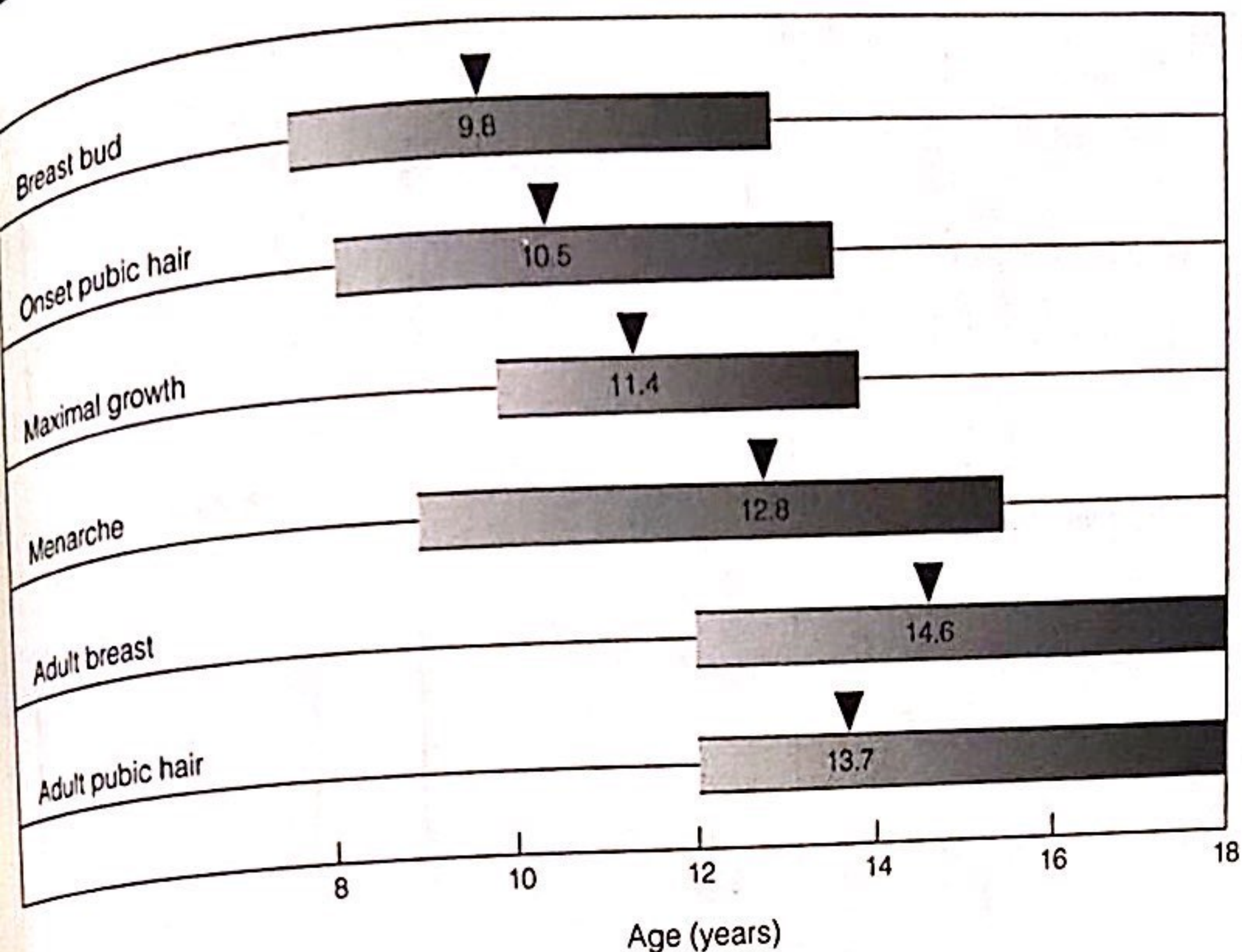


Figure 18-1 Average age of onset and range given for the events of puberty.

TABLE 18-1

The Tanner Stages of Breast Development

Stage 1	Preadolescent: Elevation of papilla only
Stage 2	Breast bud stage: Elevation of breast and papilla, areolar enlargement
Stage 3	Further enlargement of breast and areola without separation of contours
Stage 4	Projection of areola and papilla to form a secondary mound
Stage 5	Mature stage: projection of papilla only as areola recesses to breast contour

Adapted from Speroff L, Glass RH, and Kase NG, *Clinical gynecologic endocrinology and infertility*, 5th ed. Baltimore: Williams & Wilkins, 1994:377.

Peak Height Velocity

The growth spurt is characterized by an acceleration in growth rate around age 9-10, leading to a peak height velocity around age 12-13. The increased rate of growth is likely secondary to the increased level of growth hormone (GH) and somatomedin-C, which increases in response to increasing levels of estrogen. However, this relationship is dose related and excess levels of estrogen

will lead to decreased GH and somatomedin-C. Furthermore, because estrogen causes fusion of the epiphyseal plate in long bones, a rapid growth spurt may be followed by growth cessation.

Menarche

The average age of onset of menstruation is between 12 and 13. The menstrual cycle is usually irregular, reflecting anovulatory cycles, for the first 6 months to a year after menarche. It will take an average of 2 years after menarche before regular ovulatory cycles are achieved. Menarche is often delayed in gymnasts, distance runners, and ballet dancers. Some theories propose that this is due to an insufficient percent body fat that may be required for menstrual cycles. However, it is unclear whether it is the percent body fat or the exercise and stress on the body that interfere with menarche.

THE MENSTRUAL CYCLE

The hypothalamus, pituitary, ovaries, and uterus are all involved in maintaining the menstrual cycle (Fig. 18-4). During the **follicular phase**, release of FSH from the pituitary results in development of a primary ovarian follicle. The ovarian follicle produces estrogen, which causes the uterine lining to proliferate. At midcycle,