Menarche, menses, and menopause: a brief review

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■ Reproductive maturation, the menstrual cycle, and the transition to postreproductive life are complex processes. Detailed understanding of reproduction underlies logical patient management. Greater understanding of physiology has brought about better control of ovulatory problems and the beginnings of a logical approach to other problems such as androgen excess, where two complex systems overlap.
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OVER a period of 40 years between menarche and menopause, the reproductive organs of normal women undergo repeated series of sequential changes that form the menstrual cycle. The target organs (endometrium, fallopian tubes, cervix, vagina, and breasts) and many nontarget organs are influenced by the steroid hormones produced in the temporary endocrine gland formed in the dominant follicle. The interaction between the follicular apparatus producing steroid hormones and the hypothalamic-pituitary unit producing gonadotropins is complex, with a dynamic reciprocity not found in other endocrine systems (*Figure 1*). The ovum matures over 2 to 3 weeks from an inert state that has lasted many years to be released at a time when sperm transport is facilitated and to be transferred to the uterus as an embryo when the endometrium is prepared for nidation. The corpus luteum has the ability to involute, making way for the next dominant follicle if pregnancy does not occur. It can also survive and grow as a functioning unit for several weeks if pregnancy does occur.

Extensive reviews of menarche,[1] the menstrual cycle,[2–4] and menopause[5] have been published. This paper is a brief account of the endocrine physiology of the menstrual cycle and of the beginning and end of the reproductive cycles.

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MENARCHE

At birth, the normal human ovary contains about 2 million oocytes with follicles in various stages of development, including mature antral follicles.[6] During childhood, the ovary is active but not stimulated sufficiently to produce significant quantities of sex steroids.[7] The hypothalamic-pituitary-ovarian axis is functional in the fetus, but GnRH (gonadotropin-releasing hormone)-gonadotropin secretion is suppressed shortly after birth and remains suppressed during childhood.[8] It remains unclear exactly how the suppression is controlled in the human; it is conceptualized as a structural or functional "gonadostat" that is highly sensitive to circulating sex steroids. Presumably, it is mediated by currently unidentified inhibitory neurotransmitters suppressing the normal activity of GnRH-producing cells.

The beginning of puberty is associated with increased

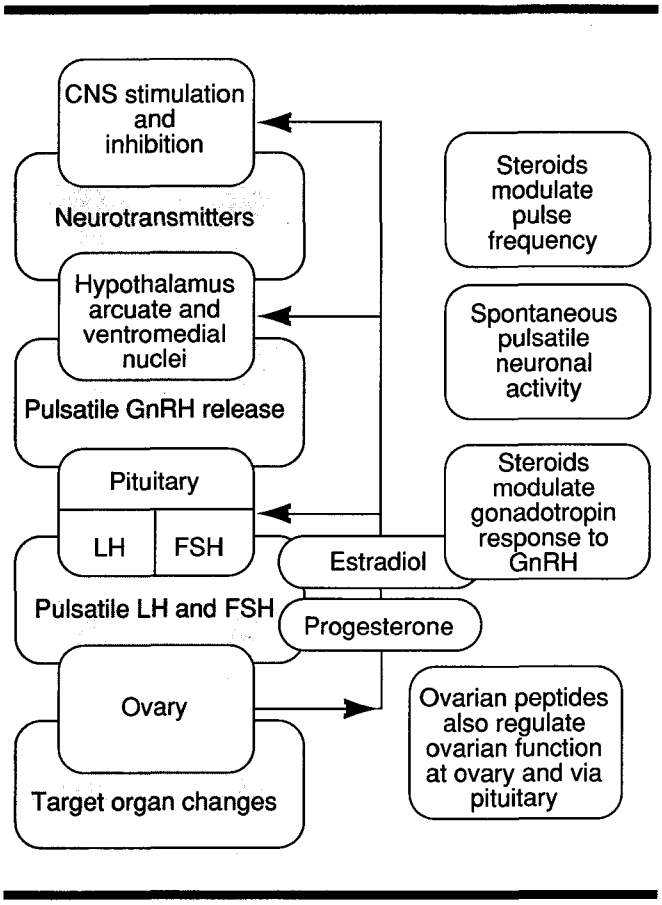

FIGURE 1. Interaction of the components of the hypothalamic-pituitary-ovarian axis.

GnRH activity, and gonadotropin release becomes pulsatile.[9] The pattern of gonadotropin responses to exogenous GnRH also changes during maturation. Initially, the follicle stimulating hormone (FSH) response is relatively greater, but as puberty advances, this is replaced by the adult pattern of greater luteinizing hormone (LH) response.[10] The pattern of change in gonadotropin response probably reflects both steroid feedback at the pituitary level and the changing GnRH pulsatile release as the hypothalamus matures.[7] The attainment of puberty in women is associated with an increased blood level of biologically active gonadotropins, which increases relative to levels measured by usual radioimmunoassay methods.[11] The increase in biologically active gonadotropins in turn leads to follicular development in the ovary and a consequent increase in circulating gonadal steroids. The increasing levels of circulating sex steroids produce development of the secondary sexual characteristics.

In childhood and up to the prepubertal period, estrogen acts at the level of the hypothalamus to suppress LH release (negative feedback). At the time of puberty, the hypothalamic "gonadostat" loses sensitivity and so allows the increase in biologically active gonadotropins that, in turn, furthers estrogen production.[7] When the serum levels of estrogen are sufficiently high for a sufficient length of time, a positive-feedback mechanism is stimulated, resulting in a surge of LH.[12,13] When the system reaches total maturity, the ovum is released for fertilization.

It is clear that the ovary plays only a passive role in this maturation process, responding solely to the stimuli from the central unit. When the system is mature enough to elicit an ovarian response and to respond normally to signals from the developing follicular apparatus, the axis is ready for ovulatory cycles. This may not take place for some time following menarche, so that initially anovulatory cycles are the rule.[13] Menarche occurs when the estrogen levels are sufficient to stimulate endometrial development. It has no particular physiological significance since it is merely a step on the way to full maturity, but it does have considerable sociological and psychological significance and tends to be remembered.

Reproductive maturation in the human, as in other mammals, occurs when the individual has reached a size and stage of development commensurate with a high likelihood of successful reproduction.[14] The average age of menarche in North America is 12.5 years, some 2 years after breast development begins and 6 to 8 years after the androgen levels begin to increase.[15] Information collected over the last century suggests that the mean age of menarche has steadily decreased in the developed world.[16]

The timing of sexual maturation and the onset of menstrual periods in women may be influenced by a number of factors, including genetic and ethnic background, socioeconomic status, number of siblings, season, climate, altitude, and general health. Kirkwood et al[14] have suggested that the various factors influence pubertal development and menarche predominantly by altering the nutritional status of the prepubertal child and the adolescent. More girls now enter puberty at an earlier age, but the earliest age of menarche has remained unchanged.[17] In general, menarche has corresponded with physical size rather than chronological age; thus young women achieve menarche at the same physical size as their mothers but at an earlier age.[16] These and other observations provided the basis for the evolution of the critical-body-composition theory for the initiation of menarche.[18] While many criticisms

have been made of the critical-body-fat theory,[14,19] it remains likely that some form of metabolic or nutritional threshold is involved in menarche. However, it is also clear that menarche is a late event in a maturational process that began several years before with a slow increase in androgen levels. The increase in adrenal androgens—a process termed "adrenarche"—precedes by several years any significant change in circulating sex steroids and in some species seems a prerequisite for continuing reproductive maturation.[20] In humans and the great apes, the sequence of events is characteristic, but adrenarche does not seem necessary to the continuing developmental process.[20,21]

NORMAL MENSTRUAL CYCLE

The cyclic shedding of the uterine lining results from complex interactions of the hypothalamus, pituitary, ovaries, and endometrium. The events of an idealized 28-day cycle are summarized in *Figure 2*. As indicated previously, the total complement of follicles is laid down in the ovary during intrauterine life.[6] The ovarian events of the menstrual cycle include selection of the dominant follicle, follicular maturation, ovulation, luteinization of the follicle, and luteolysis. As the corpus luteum fails, a new dominant follicle is being recruited. Little is known of the recruitment except that the dominant follicle seems to develop, perhaps by chance, from a cohort of follicles in the ovary that has been dormant during the previous cycle and is dependent upon the characteristic pattern of gonadotropin secretion as described by Fritz and Speroff.[2] Morphological and biochemical changes during follicular maturation are characterized by increased oocyte size, increased numbers of granulosa cells in the follicle, acquisition of FSH and other receptors (including estradiol, androgen, gestagen, prolactin, and prostaglandin receptors) on the membrane or in the cytosol of the granulosa cells, increased LH-mediated androgen synthesis in the theca cells, and increased FSH-mediated conversion to estradiol in the granulosa cells.[3] Estradiol is maintained within the follicle and secreted into the systemic circulation. High systemic levels suppress FSH release. The high intrafollicular levels of estradiol in the dominant follicle protect it when serum FSH levels are suppressed.

Ovulation occurs when the physical maturation of the follicle is complete. The process is dependent upon the LH surge, which is also responsible for resumption of meiosis in the oocyte and luteinization of granulosa cells (to provide an increase in progesterone, which is in part responsible for the LH surge), as well as local prostaglandin and enzyme synthesis necessary for the release of the ovum.[22] Luteinization is characterized by increased cell size from 12–14 μm to 30–40 μm, an increased cytoplasmic-nuclear ratio, and the acquisition of cytoplasmic granules and fat droplets.[23] Functionally, the changes lead to increasing progesterone production and a secondary increase in estradiol manufacture.[24] Luteinization begins following exposure of the mature follicle to high levels of LH, and the corpus luteum needs continuing basal LH support.[22] The FSH receptors decrease, and the cyclic adenosine monophosphate response to FSH decreases. A local "luteinizing inhibitor" and high local levels of estrogen prevent significant luteinization before follicular rupture. Luteolysis, the degeneration of

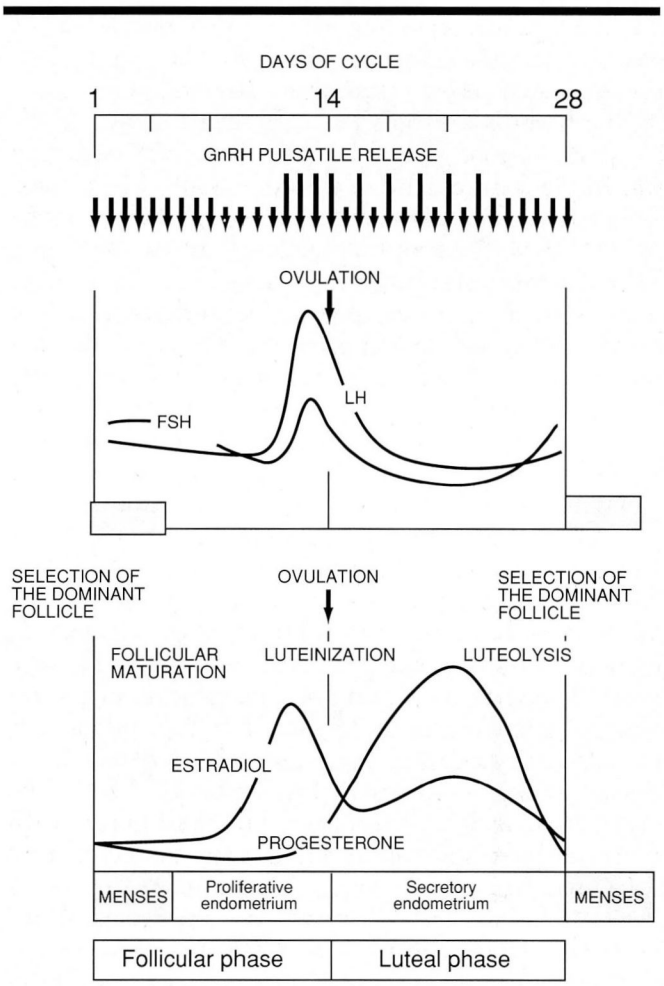

FIGURE 2. Integration of functional and hormonal events of the menstrual cycle.

the functioning corpus luteum, is poorly understood but seems to involve luteolytic effects of estrogen production mediated perhaps through prostaglandins.[25]

The hormonal variations of the menstrual cycle are better understood than the molecular events occurring within the follicle. Late in the cycle, GnRH is released in a pattern of moderate pulses occurring regularly at 90- to 120-minute intervals.[8] Together with the declining levels of sex steroids, GnRH induces an increase in serum FSH that, in turn, is involved in the selection of the dominant follicle and is responsible for its continuing maturation.[4] Following FSH induction of aromatase in granulosa cells, the dominant follicle progressively increases estradiol output, initially inhibiting FSH levels with negative feedback and later causing a surge of LH and FSH with positive feedback.[26] Small amounts of progesterone appear to be secreted just prior to ovulation and augment the estradiol-induced increase in LH and FSH.[27] The inhibition of FSH in the middle and late follicular phases of the cycle inhibits growth of nondominant follicles that may be developing. The LH surge leads directly to ovulation and luteinization of the remaining granulosa cells. The luteinized granulosa cells manufacture progesterone and are also responsible for the secondary rise in estradiol in the luteal phase of the cycle. If there is no pregnancy, luteolysis occurs with decreasing sex hormone levels, leading to endometrial shedding. At the same time, the dominant follicle for the next cycle is being selected by the late-cycle FSH increment. The gonadotropin levels fluctuate in response to changes in the amplitude and frequency of GnRH pulses modulated by circulating sex steroid levels.[8]

The stimulus to initiate a menstrual cycle is the pattern of GnRH pulses seen in the late luteal phase and in the early follicular phase of the cycle.[8] Since GnRH cannot be measured, the pulsatile release of LH is used as a bioassay. A longer half-life makes it more difficult to detect pulsatile change in FSH except in postmenopausal women where FSH pulses are apparent.[28]

Marshall et al[8] suggested that the pattern of moderate GnRH pulses with a periodicity of 90 minutes is responsible for the increase in FSH that produces maturation of the dominant follicle. Although the LH levels fluctuate in response to GnRH, there is little cyclic change in mean LH levels. As estrogen levels increase in the follicular phase of the cycle, the GnRH pulsatile release decreases so that frequent, small LH oscillations are seen.[8,29] FSH levels fall. However, the dominant follicle maintains its ability to secrete estrogens, and circulating estrogen levels continue to increase. It is only in the late follicular phase of the cycle, when the pulses of GnRH increase in amplitude and the pituitary is sensitized by high levels of estrogen, that positive feedback occurs with the LH surge following peak estradiol levels. Pulses that are irregular in size and frequency occur throughout the luteal phase of the cycle, suppressing the gonadotropins until, with the falling levels of sex steroids, the pattern of moderate, regular pulses is resumed and the FSH levels begin to increase. This stimulates a new cohort of follicles to develop for the selection of the new dominant follicle.[8,29,30]

Neurotransmitter involvement at the hypothalamic level has been demonstrated in the human. It is clear that dopamine and endogenous opiates act as variable inhibitors throughout the menstrual cycle.[31,32] Norepinephrine probably functions as a stimulatory neurotransmitter, although this is unclear from the human evidence.[33] Many other substances such as thymosin, insulin, and a range of neuropeptides influence the release of GnRH, but their significance remains unclear.[34]

The menstrual cycle is considered normal if the time from the beginning of one cycle to the beginning of the next is between 21 and 35 days. Alteration of this pattern can occur with a disorder situated entirely within the hypothalamic-pituitary-ovarian-endometrial axis (either structural or functional) or may reflect a systemic disorder.

In general, regular menstrual cycles have been regarded as a sign of health, and the loss of a regular cycle has been looked upon as a symptom of disease. The possibility that life-threatening disorders can present with abnormalities of menstruation makes an understanding of the normal menstrual cycle and its abnormalities essential.[35]

MENSTRUAL-CYCLE CHANGES IN WOMEN IN THE LATE REPRODUCTIVE AGE

The regulation of the hypothalamic-pituitary-gonadal axis changes during the years immediately prior to menopause.[36] Intermenstrual intervals and duration and quantity of menstrual flow become increasingly variable.[37] An increased ovarian resistance to gonadotropins presumably results from a reduced number of oocytes, since gonadotropin binding does not seem to be reduced in the ovaries of women in the immediate premenopausal years.[38] An alteration in ovarian sensitivity can be observed as early as 6 to 8 years before cessation of the menstrual cycles, as there is a striking increase in FSH levels throughout the cycle while LH usually remains in the normal range.[39] Serum estradiol

and progesterone indicate the cyclic fluctuations necessary for normal hypothalamic-pituitary interaction, but there is some dispute as to when levels of the individual sex steroid hormones begin to decline.[39,40] The only characteristic marker for imminent menopause is the elevation of serum FSH levels, which may occur several years before menopause. The patterns of abnormal bleeding that occur during the premenopausal period doubtless reflect the reductions in sex steroid levels and anovulatory cycles common at this time.[5]

GONADOTROPINS IN POSTMENOPAUSAL WOMEN

The change in reproductive hormones in the perimenopausal period is gradual so that the diagnosis of menopause—the final period—is a retrospective one that of necessity is at least 12 months after the actual event. Following the final menstrual period, the serum levels of both FSH and LH are elevated.[41] Following menopause, the serum FSH levels are much higher than those of LH. The FSH/LH ratio rarely exceeds unity during reproductive age, but it is much increased in postmenopausal women. Roughly equivalent amounts of each hormone are produced by postmenopausal women. The high serum FSH levels result from a longer half-life and decreased metabolic clearance.[42,43] An increase in gonadotropins is apparent within 96 hours of castration, although it may take several weeks for the hormones to reach final menopausal values.[44,45] Replacement of gonadal steroids significantly reduces gonadotropin levels but not to levels normally found in women in the reproductive age group.[46] This has generally been explained by the production of inhibin-like substances by the ovary but may alternatively reflect a final, further decrease in the sensitivity of the hypothalamic-pituitary unit to circulating steroids, analogous to that which occurs at puberty. The increased serum gonadotropin levels persist throughout the postmenopausal years, but there is debate as to whether there is the same intensity of elevation.[47] The levels may decline with time to values 40% to 50% of those seen in the immediate postmenopausal period, although other studies have described relatively consistent levels persisting until even 100 years of age.[47–49]

Since the interactive relationship of the hypothalamus and pituitary with the ovary has ended, there is no menstrual variation in the gonadotropin levels and no circadian variation.[28] Pulsatile patterns are maintained and even exaggerated with increased frequency and amplitude. The pulse frequency of 10 to 20 minutes compares to 90 to 100 minutes in the early follicular phase of the menstrual cycle. The opiate modulation of the frequency of pulsatile activity during reproductive life disappears after the menopausal transition, perhaps because of decreased circulating sex steroid levels.[50] In the short term, minute-to-minute oscillations of LH and FSH, unrelated to each other, and a synchronous "sine-wave" activity with a periodicity of 120 min, have also been described, but the physiological significance remains unclear.[51] The increased pulse frequency and amplitude presumably result from increased GnRH production. Reports of increased GnRH in blood and urine are difficult to evaluate.[52,53] Administration of GnRH results in both LH and FSH level increases.[54] The LH response to GnRH is greater than that of FSH, a finding similar to that reported in reproductive age women.[54] Although the gonadotropin increment in response to GnRH is greater in absolute terms in postmenopausal than in reproductive-age women, there is no difference when the increase is expressed in relative terms as percent change over baseline values. Estrogen administration reduces the gonadotropin response to GnRH, as may be anticipated from the effect on basal levels.[55] In appropriate circumstances, both estrogens and progestins are capable of inducing a gonadotropin increment similar but not identical to the midcycle surge. LH pulses are synchronous with objectively measured hot flashes, a finding that suggests a common hypothalamic mechanism for both.[56,57]

In summary, the levels of LH and FSH are elevated in postmenopausal women. Manipulation of the hypothalamic-pituitary unit suggests that the system is physiologically normal although all the changes may not be due solely to the decrease in circulating sex steroids.

SEX STEROID LEVELS IN POSTMENOPAUSAL WOMEN

In postmenopause, the quantity and type of estrogens produce change. Cytological studies indicate that 90% of postmenopausal women are hypoestrogenic while 8% to 10% still retain an estrogenic smear.[58] Total urinary estrogens are reduced but remain relatively constant for about 10 years after menopause.[59] After this time, there is a progressive reduction to relatively low levels in advanced age.

Prior to menopause, the major circulating estrogen is estradiol, which is produced substantially by the developing follicle and reaches very high levels during the pre-ovulatory surge. Following menopause, the predominant estrogen is estrone, present in quantities twice that of estradiol.[60] This reflects the production rates of 40 μg per day for estrone (produced mainly by peripheral

conversion of androstenedione) and 6 μg per day for estradiol (produced substantially by peripheral conversion of testosterone).[61] Comparable production rates during the reproductive age are 80 μg to 500 μg per day for estradiol and 80 μg to 300 μg per day for estrone. The binding of estradiol to sex-hormone-binding globulin reduces clearance and maintains the circulating level at slightly higher values than would be anticipated from the production rates.[62]

The ovary retains the capacity to manufacture both androgenic and estrogenic steroids into the postmenopausal period. The ovarian contribution to the androgen pool is substantial, but the direct contribution to the estrogen pool is relatively insignificant.[63–65] Most circulating estrogen is formed from androgen precursors.[66] It is interesting that conversion rates of androstenedione to estrone seem to vary inversely with serum androstenedione levels.[66,67] In vitro studies of the ovary suggest also that the stroma in the postmenopausal ovary can elaborate androgens, androstenedione, and testosterone, as well as dehydroepiandrosterone, but fails to aromatize the androgens to estrogens.[68] Evidence has also suggested that the cortex and medulla predominantly manufacture androstenedione and testosterone, respectively.[69–72]

Several clinical problems commonly occur in perimenopausal and postmenopausal women due in major part to declining levels of sex steroids. Other factors such as age, intercurrent illness, psychological adjustment, social status, and possibly nutritional status are also important. The expected lifespan of the average woman now reaching menopause in North America is 86 years, so the problems of postmenopausal women will assume greater importance in time to come.

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