MINIREVIEW

Age-Related Changes in the Regulation of Luteinizing Hormone Secretion by Estrogen in Women

SUSANNA J. PARK,[1] LAURA T. GOLDSMITH, AND GERSON WEISS

New Jersey Medical School, Department of Obstetrics, Gynecology, and Women's Health, 185 South Orange Avenue, MSB E-506, Newark, New Jersey 07103

Despite the many studies that have been conducted using both primate and human models to understand the control of the menstrual cycle, there are many aspects of the hormonal dynamics of the menstrual cycle that are not understood. This Minireview summarizes the changes in estrogen regulation of luteinizing hormone (LH) secretion that occur throughout life in women from the time of maturation of the hypothalamic-pituitary axis resulting in the occurrence of the LH surge during puberty, through the reproductive years, to the changes in the regulation of the LH surge during premenopause and, subsequently, menopause. [Exp Biol Med Vol. 227(7):455–464, 2002]

Key words: estrogen; LH; puberty; gonadotropin control; menopause; reproductive development

Fetal to Puberty

Fetal. Neurons that synthesize gonadotropin releasing hormone (GnRH) are initially located in the olfactory placode (1). They migrate posteriorly to the hypothalamus by 6 weeks of gestation. GnRH is present in significant amounts in the fetal hypothalamus by 10 weeks of gestation (2). Initial development of the hypothalamic-pituitary portal system occurs by 60 days of gestation with interdigitation of capillaries in the mesenchymal tissue adjoining Rathke's pouch and the diencephalon. Due to the close proximity of the fetal hypothalamus and pituitary, hormones may be transmitted by diffusion, in addition to the portal route (2). By 19–20 weeks of gestation, the primary and secondary plexus of the portal system are completed and functional. GnRH, which is released from the fetal hypothalamus in a pulsatile manner, travels via the hypothalamic-pituitary stalk to the fetal pituitary where it stimulates the synthesis and pulsatile secretion of luteinizing hormone (LH). LH concentrations in fetal pituitary glands increase dramatically between 10–14 and 20–25 weeks of gestation (2). Thereafter, the LH content in fetal pituitary glands remains stable until late in gestation when there is a decrease in LH pituitary gland concentration. In the fetal circulation, LH concentrations are elevated until 25–29 gestational weeks, after which time circulating LH levels decrease, likely due to the developed ability of the hypothalamus and pituitary gland to respond to elevated levels of circulating estrogen (3).

Neonatal. Following delivery, fetal estrogen concentrations plunge due to the loss of maternal steroids. Estrogen levels remain low until puberty. This decrease in estrogen is accompanied by rising LH levels during the first 1–2 years of life. The increase in LH concentrations is attributed to reduced negative feedback by ovarian steroids. This theory is based on the observation that children with Turner's Syndrome, who have a deficiency of ovarian steroids, demonstrate relatively higher LH secretion than children with functioning ovaries (3). That is, children with normally functioning ovaries secrete minimal estrogen during childhood, which thus exerts a minimum negative feedback on gonadotropin secretion. However, children with Turner's Syndrome secrete no ovarian steroids, and thus there is no negative feedback on LH secretion. Therefore, due to the lack of estrogen inhibition on LH secretion, the LH levels of children who lack ovarian estrogen secretion are more elevated than those of children with functional ovarian steroid production.

This research was conducted while Dr. Susanna J. Park was a Pfizer/SWHR Scholar.
[1] To whom requests for reprints should be addressed at New Jersey Medical School, Department of Obstetrics, Gynecology, and Women's Health, 185 South Orange Avenue, MSB E-506, Newark, NJ 07103. E-mail: parksj@umdnj.edu

1535-3702/02/2277-0455$15.00

Juvenile Pause. The juvenile pause begins at 2–4 years of age and lasts until 10–12 years of age (3). By the start of this phase, LH concentrations are diminished despite concurrent decreased levels of estrogen. This decrease in LH levels is independent of ovarian steroid feedback. It is believed to be secondary to central nervous system inhibition, the mechanism of which is not well understood. However, certain disorders may give a hint to the underlying physiology. For example, children with Turner's Syndrome also demonstrate decreased LH levels during the juvenile pause, despite the lack of ovarian estrogen, which further suggests that the juvenile pause is not characterized by negative feedback inhibition by ovarian steroids upon LH secretion. Another disorder involves children with increased intracranial pressure (such as caused by hydrocephalus or subarachnoid cyst) who exhibit increased LH secretion with resultant precocious puberty. This can be reversed with a reduction of intracranial pressure (3). One can conclude that the elevated intracranial pressure impedes the central nervous system inhibition of gonadotropin secretion. This central nervous system inhibition may be related to GnRH. Studies in bilaterally ovariectomized infantile rhesus monkeys have shown that the decrease in LH in female infantile monkeys was associated with a slowing of LH pulse frequency, and presumably, of GnRH discharges, from one pulse per hour to one pulse every 4 hr (4). The reduced GnRH pulse frequency may be due to a number of factors such as an inhibitory synapse on the GnRH nerve terminal, attenuation of a pulse-generating signal at the GnRH cell body or the nerve terminal, or a desynchronizing input (4). However, no data has yet been generated to support which, if any, of these factors may be involved.

Puberty. The age range during which puberty occurs is 8.5–13 years (5). Precocious puberty is defined as the development of secondary sexual characteristics prior to 7.5 years of age. Delayed puberty is defined as the absence of secondary sexual characteristics by age 14.

Thelarche (breast development) is usually the first sign of puberty. By Tanner stage 3 or 4 of breast development, pubarche (pubic hair development) is noted. However, the converse may occur, that is, pubarche may be the first sign of puberty, with thelarche occurring when pubic hair development is Tanner stage 3 or 4. The growth spurt (average 25 cm in females) takes place when breast development is Tanner stage 2 or 3. The mean age of peak velocity is 12 years. Axillary hair growth occurs when breast development is Tanner stage 3 or 4. The final stage of puberty is menarche (the first menstrual period). The average time from the first sign of puberty to menarche is 2.3 years (range 6 months–5.75 years) (5).

Nocturnal LH pulses. Prior to the appearance of the first secondary sexual characteristic, there is an increase in nocturnal levels of LH that occurs within 1 hr of the onset of sleep (6). This nocturnal increase in LH activity is primarily due to an increase in LH pulse amplitude (7). With the onset of daylight hours, the elevated nocturnal LH levels decrease to their original values. In prepubertal girls, the LH pulses during sleep are predominantly irregular. With more advanced stages of puberty, the nocturnal LH pulses become more regular and of greater magnitude (6). As puberty progresses, the nocturnal LH pulses persist into the daylight hours, in addition to the continued further amplification of the nocturnal LH pulsatile activity. The increase in LH throughout the day results in a gradual increase in circulating LH concentrations with each stage of puberty, which stimulate an increase in ovarian estrogen production, resulting in the sequential appearance of the secondary sexual characteristics (8). Nocturnal LH secretion discontinues after the first ovulation (9).

In humans, the nocturnal increase in LH pulse amplitude is not associated with darkness, but rather, it is associated with rapid eye movement (REM)-non-REM sleep cycles. This was proven by blindfolding an awake adolescent and demonstrating a lack of an increase in LH activity (10). Alternatively, arousal of an adolescent during sleep resulted in a decrease in LH pulse secretion. Furthermore, reversing the time of sleep from nighttime to daytime also reversed the incidence of increased LH activity such that it occurs during the sleeping hours (11).

Diurnal pattern of estrogen secretion. The change in the pattern of LH secretion during puberty is reflected in the circulating estrogen levels. The elevated nocturnal LH levels stimulate ovarian estrogen secretion such that estrogen concentrations are most significantly elevated between 0600 hr and 1000 hr (12, 13). Estrogen levels lessen for the remainder of the day. This diurnal rhythm in estrogen secretion is seen since the time of early puberty and is associated with the first clinical signs of puberty. The diurnal rhythm becomes more striking as development progresses through the stages of puberty such that there is a steady increase in estrogen levels with further development of secondary sexual characteristics with each advanced stage of puberty (5, 14). By late puberty, circulating estrogen levels achieved are compatible with those seen during the early follicular phase of the adult menstrual cycle (4). The diurnal rhythm of estrogen secretion promptly ends 1 year after menarche.

LH surge. The LH surge is a hallmark of the maturation of the hypothalamic-pituitary axis. The LH response to exogenous estrogen has been assessed by many investigators during different stages of pubertal development to investigate the functional differences of the hypothalamic-pituitary-ovarian axis during different phases of sexual maturation. One such study conducted in sexually immature rhesus monkeys demonstrated that an LH response to exogenous estrogen could only be elicited in postmenarcheal monkeys (15). A study conducted in girls, however, yielded disparate results. Presl *et al.* (16) investigated the occurrence of LH surges in response to exogenous estrogen. None of the girls in the first three developmental stages (prepubertal, early puberty, or midpuberty) responded with an LH surge. In contrast, all the premenarcheal girls demonstrated

an LH surge following the exogenous estrogen; in two of the five girls, the LH surges were similar to that seen in normal ovulatory adult women. This and other studies demonstrate that the ability to have an LH surge requires a degree of maturation of the hypothalamic-pituitary-ovarian axis, which is achieved by mid- to late puberty.

Ovulation. Occasional spontaneous LH surges have been reported in premenarcheal girls (17). Postmenarcheal girls demonstrate LH surges similar to those in adult women, but not all LH surges result in ovulation, as documented by inadequate luteal phase lengths and insufficient progesterone levels (18). In a study performed by Metcalf *et al.* (19), in the first menstrual year, only 44.6% of menstrual cycles were ovulatory. This number increased to 83.3% by 5 years postmenarche. The concept that regular ovulatory menstrual cycles are not established for approximately 5 years concurs with other studies (20).

The onset of puberty. The precise mechanism that initiates puberty is not known. The stimulation of the onset of puberty is likely GnRH dependent. The occurrence of nocturnal LH pulses prior to the first clinical sign of puberty provides evidence that the GnRH pulse generator is functionally active during the prepubertal phase of development. GnRH pulse frequency increases at the onset of puberty and remains elevated throughout the pubertal period (21). The significance of GnRH to the initiation of puberty is demonstrated by the ability of GnRH pulsatile treatments to induce puberty in children with delayed or arrested puberty (22).

An increase in pituitary sensitivity to GnRH with pubertal development may be another component to the onset of puberty. When exogenous GnRH is administered during the prepubertal phase, there is minimum LH response. In contrast, when GnRH is administered at the time of anticipated puberty, there is a marked increase in LH levels in response to the exogenous GnRH. This LH response signifies the onset of puberty within the next 6–12 months (3).

There are two main theories to explain the mechanism responsible for the onset of puberty. The first is that the central inhibition of GnRH on LH secretion (independent of the negative feedback of gonadal steroids) that occurs during the juvenile pause is removed such that there is an increase in GnRH pulsatile secretion, thus triggering the onset of puberty (9). Therefore, puberty is initiated by the activation of the hypothalamic mechanisms that control the pulsatile release of GnRH.

The second theory is called the "gonadostat hypothesis," (initially proposed by Dohrn and Hohlweg), which states that during the transition from the juvenile pause to puberty, the hypothalamus and pituitary become less sensitive to the negative feedback of ovarian estrogen such that LH secretion increases. This results in the nocturnal LH pulses, thereby activating the pubertal phase of development. This hypothesis, however, implies that the quiescence of gonadotropins during the juvenile pause is due to an increased sensitivity of the hypothalamus and pituitary gland to estrogen such that the minimal amounts of estrogen are enough to suppress LH secretion. Grumbach *et al.* (21) support this hypothesis based on the findings of the ability to further decrease the low levels of gonadotropin secretion by administration of small amounts of ovarian steroids during the juvenile pause. This implies that the hypothalamic-pituitary unit is highly sensitive to the feedback effect of ovarian steroids during the juvenile pause. Thus, the sensitivity of the brain to the negative feedback of ovarian steroids is altered. The hypothalamus becomes increasingly more resistant to the negative feedback of estrogen such that the pituitary secretes increasing levels of LH triggering the onset of puberty.

Although data exists to support each theory, there is no widely accepted conclusion to explain the mechanism responsible for the onset of puberty. Thus, the development of the hypothalamic-pituitary-ovarian axis during puberty consists of the maturation of the negative feedback system on gonadotropin secretion *in utero* and culminates in the occurrence of the LH surge, the positive feedback system.

Reproductive Years

Brief Overview of the Menstrual Cycle *Follicular phase.* In general, the menstrual cycle, which lasts 21–35 days, results in the development and release of a mature egg for fertilization. During the follicular phase of the menstrual cycle, follicle-stimulating hormone (FSH) stimulates the differentiation and proliferation of granulosa cells in ovarian follicles from approximately 1 million to ≥50 million cells. This marked increase in cell number is due to the FSH-stimulated transcription of genes that encode growth factors, such as insulin-like growth factor 1 (IGF-1), that function in both a paracrine and autocrine fashion (23). As the granulosa cells secrete both estrogen and progesterone, the less mature FSH-dependent follicles become atretic. The dominant follicle, which is selected by the mid-follicular phase, secretes increasing amounts of estrogen, which exerts a negative feedback on FSH and LH secretion.

During the mid-follicular phase, granulosa cells acquire LH receptors. LH inhibits FSH-induced follicular growth, but continues to stimulate granulosa cell differentiation. In addition, LH stimulates the secretion of androgen by the theca interna cells. *In vitro* studies have shown that IGF-1 and inhibin, both granulosa-derived factors, can synergistically increase the production of androgens by the theca cells (24). These androgens then diffuse via the lamina basalis into the adjacent granulosa cells where the androgens are converted to estrogen through aromatization via the enzyme aromatase. IGF-1 acts synergistically with FSH to increase the expression of this enzyme, thereby increasing estrogen concentrations (25). Less than 1% of the LH receptors need to be occupied to achieve maximal response (26).

During the early and mid-follicular phase, estradiol levels are low. These low levels of estrogen inhibit the secretion of LH (negative feedback). By the late follicular phase, estrogen concentrations are noticeably elevated as a result

of estrogen production by the granulosa cells. In a comparison of the relation of the estrogen peak to the LH surge, the estrogen peaks occurred up to 1 day prior to the LH surge; none occurred after the LH surge (27). However, elevated serum estrogen concentrations must be maintained at the time of the initiation of the LH surge. In addition, approximately 12 hr prior to the LH surge, there is also a slight increase in serum progesterone levels (28).

Superimposed on negative feedback of estrogen on LH secretion, a positive feedback of estrogen on LH secretion occurs, which is known as the midcycle LH surge. The LH surge arises once serum estrogen levels surpass a set threshold for a certain period of time. The LH surge is the trigger for ovulation (29). Ovulation occurs 24–36 hr after the estrogen peak and 10–12 hr after the LH surge (28). The midcycle LH surge marks the beginning of the luteal phase.

Luteal phase. The corpus luteum secretes major quantities of estrogen such that there is a smaller secondary rise of estrogen during the luteal phase. However, this secondary rise of estrogen does not result in an LH surge due to a refractory period that exists after the midcycle LH surge. In addition, the increased levels of progesterone during the luteal phase inhibit the estrogen-induced occurrence of an LH surge (30).

Estrogen levels decrease to early follicular levels by the end of the luteal phase. LH levels decrease to concentrations similar to those seen during the follicular phase of the menstrual cycle. If fertilization does not take place, luteolysis occurs with subsequent reduction in serum progesterone concentrations. FSH levels increase to stimulate the proliferation of new granulosa cells with a consequent rise in serum estrogen concentrations. The menstrual cycle starts anew.

Pulsatile Secretion of Gonadotropins. Circulating concentrations of LH are maintained by secretion in a rhythmic, pulsatile manner—approximately one pulse every hour—named "circhoral" by Knobil following his studies in rhesus monkeys (31). Similar pulsatile patterns of gonadotropin secretion occur in humans (32, 33). LH secretion is influenced by the pulsatile secretion of GnRH from the arcuate nucleus of the median eminence of the hypothalamus, which is transmitted to the anterior pituitary via the infundibular stalk. Each pulse of LH from the pituitary is coincident with a pulse of GnRH from the hypothalamus (34). Pulsatile secretion of GnRH essential to normal female reproductive function is well established. Continuous, nonpulsatile administration of exogenous GnRH in hypothalamic amenorrheic women results in a decline in circulating levels of gonadotropins (35). Continuous GnRH stimulation results in downregulation of GnRH receptors, thereby preventing further GnRH stimulation of LH secretion and, consequently, a decline in serum levels of gonadotropins. However, resumption of pulsatile GnRH infusion restores normal serum gonadotropin concentrations because pulsatile GnRH stimulation maintains the GnRH receptors on the pituitary gland, thereby allowing for further GnRH stimulation.

During the follicular phase of the menstrual cycle, the frequency of LH pulses is approximately one pulse every 60–90 min. Markedly elevated concentrations during the midcycle LH surge is a result of an increase in both LH pulse amplitude and frequency (up to one pulse every 15–20 min) (34). During the luteal phase of the cycle, LH levels diminish to concentrations similar to those prior to ovulation. This is achieved through a balance of decreased LH pulse frequency (one pulse every 4 hr) and an increase in pulse amplitude, thereby maintaining LH concentrations. By the start of the new menstrual cycle, the follicular phase frequency of LH pulse secretion is reestablished (36).

Negative and Positive Feedback of Estrogen on Gonadotropin Secretion. Much of the knowledge of the negative and positive feedback control of gonadotropin secretion was learned from studies conducted using rhesus monkeys.

Negative feedback of estrogen. The negative feedback of estrogen on gonadotropin secretion was demonstrated by the prompt decrease in serum concentrations of gonadotropins in response to exogenous estrogen in ovariectomized monkeys (37). This effect could not be demonstrated with the administration of progesterone during the follicular phase in ovariectomized monkeys (38). Therefore, it was concluded that estradiol was an important ovarian regulator of gonadotropin secretion in the rhesus monkey. Studies in humans have confirmed that gonadotropin secretion is similarly regulated (39).

Positive feedback of estrogen—the LH surge. The LH surge is not the result of desensitization developed in LH receptors as a consequence of sustained negative feedback of estrogen. This theory was invalidated by the inability of an estrogen antagonist (which would block the negative feedback of estrogen thereby mimicking the escape from the sustained negative feedback of estrogen) to elicit an LH surge (40). Rather, rising estrogen levels precede the LH surge. However, a causal relationship between these two hormones in primates was not established until the study conducted by Yamaji *et al.* (41). In this study, subcutaneous injections of estradiol benzoate were administered to achieve late follicular circulating estrogen levels. Maintenance of these levels elicited LH surges similar to the spontaneous preovulatory LH surges observed during the primate menstrual cycles. Further in-depth studies of the positive control of estrogen on gonadotropin secretion were conducted by the Knobil laboratory in ovariectomized rhesus monkeys (38). Estrogen was administered by placement of subcutaneous Silastic capsules, a solid-state solvent that releases estrogen in a controlled manner such that stable circulating estrogen levels can be easily maintained. Following an initial decrease in gonadotropin secretion (negative feedback effect of estrogen), an LH surge indistinguishable from that occurring spontaneously was elicited (38). By varying the number of Silastic capsules implanted and the duration of implantation, it was concluded that the positive feedback of estrogen on gonadotropin secretion was depen-

dent on both a threshold concentration (>100 pg/ml) and time component (36–42 hr) of circulating estrogen exposure in rhesus monkeys (42). Once these threshold limits were surpassed, further increases in circulating estrogen concentration or prolonged exposure to estrogen did not alter the magnitude of the LH surge response. However, increasing or decreasing the circulating concentrations of estrogen did affect the promptness (earlier or later, respectively) of the LH surge. The LH surge was advanced by 12 hr when plasma estrogen concentrations achieved by the Silastic capsules were of supraphysiological levels. The LH surge was delayed by 12 hr when the plasma estrogen concentrations achieved by the Silastic implants were of lower, but adequate, magnitude (100–200 pg/ml).

Additionally, Knobil *et al.* (38) showed that circulating estrogen concentrations must be maintained until the LH surge was initiated by demonstrating that premature removal of the Silastic estrogen-containing capsules resulted in incomplete or complete lack of an LH surge.

Similar studies of the ability to elicit estrogen-induced gonadotropin surges in women have been conducted. One of the first studies that showed a causal relationship between estrogen and LH in humans was conducted by Nillius and Wide (43). Following a negative feedback effect of an intramuscular injection of 1 mg of estradiol benzoate on LH secretion, an LH peak was induced 48–72 hr following the injection in these amenorrheic and oligomenorrheic women. No ovulation followed the LH peak, which was most likely due to the fact that the follicles were not mature enough for ovulation. Indisputable evidence that circulating estrogen is the factor responsible for inducing an LH surge was confirmed in other studies (44–48).

However, the presence of the ovaries in these experiments brings into consideration the possibility of endogenous ovarian steroid hormone production or other ovarian factors that may have affected the gonadotropin responses to the exogenous estrogen. In light of this, March *et al.* (49) studied the positive feedback roles of estrogen and progesterone in women in a manner that was similar to the conditions of the rhesus monkeys in Knobil's experiments (49). The three women in March's study had regular menstrual cycles and were scheduled to undergo total abdominal hysterectomy and bilateral salpingo-oophorectomy for chronic pelvic infections. During the surgery and at 6-month intervals thereafter, one 25-mg estradiol pellet was inserted subcutaneously. These estradiol pellets achieved circulating estradiol levels comparable with those of mid-follicular phase estrogen levels. About 9–15 months postoperative, each women underwent a series of experiments involving the intramuscular injection of estradiol benzoate in gradually increasing dosages twice daily for 4 days. Exogenous progesterone was administered via a progesterone-impregnated vaginal ring. The protocol consisted of the administration of estradiol benzoate alone, progesterone alone, and a combination of estradiol benzoate with varying concentrations of progesterone and varying times of administration of progesterone in relation to the estradiol benzoate. When circulating estrogen levels alone were elevated, an LH surge was observed. The LH surge was of greater magnitude and occurred earlier when the rise in circulating estrogen levels was followed by a rise in serum progesterone levels. However, an LH surge could not be elicited when circulating progesterone levels alone were elevated, or when serum progesterone and estrogen levels rose concurrently. This study confirmed the obligatory role of estrogen in the induction of an LH surge in women.

Site of feedback actions of estrogen ***Negative feedback*** The site of negative feedback is thought to be at both the hypothalamus and pituitary. Initially, a hypothalamic site of action was suggested based on studies showing a reduction or cessation of pulsatile LH secretion after administration of opiates, barbiturates, α1-adrenergic antagonists, and dopamine antagonists in ovariectomized rhesus monkeys (36). Consequently, Ferin *et al.* (36) demonstrated blockage of LH pulses when estrogen was injected directly into the hypothalamus in monkeys. These data suggested a neural site of action for negative feedback for estrogen.

However, there is also evidence for the pituitary as a site of negative feedback on LH secretion. The Knobil laboratory imposed bilateral radio frequency hypothalamic lesions in ovariectomized rhesus monkeys such that endogenous GnRH secretion was blocked ("hypophysiotropic clamp"). Exogenous GnRH was then infused in a pulsatile manner to maintain a functioning hypothalamic-pituitary axis with resultant pulsatile LH secretion. The administration of exogenous estrogen resulted in a decrease in LH secretion (50).

To address the question of the site of feedback actions of estrogen in women, Thompson *et al.* (51) performed a study on women with secondary amenorrhea. Simultaneous with the exogenous GnRH treatment, exogenous estradiol benzoate was administered to these women such that late follicular phase circulating estrogen levels were achieved. This resulted in a decrease in gonadotropin concentrations. That is, the ability to reproduce the negative feedback effect of estrogen on gonadotropin secretion in spite of a nonfunctioning hypothalamus provided compelling evidence of a pituitary site of action.

Positive feedback. Similar to the negative feedback, there is likely more than one site of action of estrogen on positive feedback of gonadotropin secretion. Nakai *et al.* (50) demonstrated that the pituitary gland was not only the main site of negative feedback, but also of positive feedback. This was concluded when, subsequent to the negative feedback of estrogen on gonadotropin secretion, continuation of the exogenous estrogen resulted in gonadotropin surges similar to those occurring during the normal primate menstrual cycle (50). Moreover, further evidence against a hypophyseal site of action was the inability of β-adrenergic blocking agents (propranolol), scopolamine, and sodium pentobarbital anesthesia to abolish LH surges in monkeys, as they did in rodents (38).

In contrast, however, studies in many species have also shown that estrogen stimulates GnRH secretion, thereby implicating the hypothalamus as another site for positive feedback action of estrogen (34). In summary, studies have shown that both the hypothalamus and the pituitary gland serve as sites for negative and positive feedback of estrogen on LH secretion.

Perimenopause

Defining the Perimenopause. At present, the World Health Organization (WHO) defines the perimenopause as the "period immediately before the menopause (when the endocrinological, biological, and clinical features of approaching menopause commence) and the first year after menopause" (52). According to the Massachusetts Women's Health Study, one of the largest longitudinal studies that investigated a method for defining the perimenopause based on self-reported data in 1550 women over 5 years, the two items that best define the inception of the perimenopause is increased menstrual irregularity or 3–11 months of amenorrhea (53). The perimenopause can be divided into early and late perimenopause. The early perimenopause encompasses the time from the first disruption of regular menstrual cycles to less than 3 months of amenorrhea. Amenorrhea of 3–11 months duration is classified as late perimenopause (54).

However, these definitions of the perimenopause do not clearly define the inception of the perimenopause. The definition is further complicated by the current use of similar words with slight variations in definitions (i.e., climacteric and premenopausal). In an effort to address the need for a more consistent nomenclature, the Stages of Reproductive Aging Workshop (STRAW) was held in July 2001 to create a staging system (similar to puberty) for reproductive senescence. The staging system proposed is based upon menstrual cyclicity and endocrine changes. Symptoms were not considered a criteria for staging because of their highly variable frequency and quality, and their subjective nature.

Seven stages were established; five that precede, and two that follow the final menstrual period.

Reproductive interval: stages –5 to –3. Stage –5, early; stage –4, peak; and stage –3, late. There is no clear demarcation between the stages. The duration of this phase is variable.

Menstrual cyclicity. Stage –5 is variable to regular; stages –4 to –3 are regular.

Endocrine changes. Circulating FSH levels are normal during stages –5 to –4. During stage –3, there is an increase in early follicular plasma FSH (>2 SD above mean FSH levels in women ages 25–30); this is the first measurable sign of reproductive aging. During stage –3, circulating early follicular estradiol levels can be either normal or elevated.

Menopausal transition: stages –2 to –1. Stage –2, early and stage –1, late. The duration of this phase is variable. This phase ends with the final menstrual period.

Menstrual cyclicity. Stage –2 is characterized by regular cycles but variability in cycle length (changes by ≥7 days); stage –1 is characterized by ≥2 skipped menstrual cycles and at least one episode of amenorrhea lasting ≥60 days.

Endocrine changes. Plasma FSH concentrations continue to increase. LH levels gradually increase, and estrogen and progesterone levels decrease. The levels of each of these hormones are highly variable.

Duration and/or amount of menstrual flow are not criteria for staging because they are highly variable during the menopausal transition.

Postmenopause: stages +1 to +2. Stage +1, early and stage +2, late. The duration of this phase depends on the stage. Stage +1 can be subdivided into: (a) the first 12 months after the final menstrual period, thus, it lasts 1 year; and (b) the subsequent 4 years. Stage +2 ends with the woman's death.

Menstrual cyclicity. Women are amenorrheic.

Endocrine changes. Elevation of plasma FSH concentrations.

Based on this staging system, the perimenopause begins with stage –2 and ends 12 months after the final menstrual period (stage +1a). Though this staging system will undergo further revisions, it is hopeful that it will become accepted as the new system of defining reproductive aging in women.

The perimenopause period may last 2–8 years, with a median duration of 3.8 years (55). It usually occurs while women are in their 40's; the median age of inception of perimenopause is 47.6 years. Smoking and unilateral oophorectomy are associated with an earlier age of onset of the perimenopause; conversely, factors that delay the age of onset of the perimenopause include higher parity and later menarche (56).

Clinical Symptoms. The perimenopause is characterized by menstrual changes (irregular frequency and duration, hypermenorrhea, oligomenorrhea, and anovulation), vasomotor instability (hot flushes, night sweats, and sleep disturbances), psychological/cognitive disturbance (worsening premenstrual symptoms, depression, irritability, poor concentration, and forgetfulness), sexual difficulties (decreased vaginal lubrication, decreased libido, dyspareunia, and vaginismus), somatic symptoms (headache, dizziness, palpitations, and breast pain and enlargement), growth of uterine fibroids, and progression of endometriosis symptoms (57–59).

Alterations in the Hypothalamic-Pituitary-Ovarian-Axis. Changes in the female reproductive axis begin as early as the mid-30's, at which time there is an accelerated loss of the quantity of ovarian follicles and a decrease in the quality of the remaining ovarian follicles (60). Despite these changes, menstrual cycles continue to be regular. By the 40's, however, the changes in the hypothalamic-pituitary-axis during the perimenopause become clinically apparent as the occurrence of menstrual cycle ir-

regularities. During the early perimenopause, there is shortening of the follicular phase and thus, shortening of the entire menstrual cycle by as much as 3–7 days (61). With the progression of the perimenopause, there is increasing irregularity of the menstrual cycle due to anovulation and luteal phase defects. Intermenstrual periods become longer, resulting in an increasing incidence of abnormal uterine bleeding patterns. Such menstrual cycle irregularities of the perimenopause is almost a mirror image of the menstrual irregularities following menarche (62).

One of the difficulties in characterizing the hormonal changes of the perimenopause is the significant fluctuations in hormone levels from one menstrual cycle to the next that occur during this phase (63). This may account for many of the conflicting results in various studies.

Pattern of LH secretion. It is believed that the early perimenopause is characterized by a monotropic rise in FSH; that is, while there is a rise in FSH, LH levels remain low until prior to menopause, at which time there is a rise in LH concentrations (61, 64–67). However, in contrast, other studies have shown an increase in circulating LH, in addition to circulating FSH, during the perimenopause (68–71). This elevated circulating LH may be associated with decreased ovarian LH receptors (72).

In order to better characterize these contradictory results, Reame *et al.* (73) conducted a study involving an intensive sampling protocol in which samples were taken every 10 min for 8 hr during the late follicular, midluteal, and late luteal phases in perimenopausal women ages 40–50 years. They demonstrated that in addition to the elevations in FSH, there were elevations in mean LH concentrations and LH pulse amplitude during the late luteal phases in perimenopausal women (73).

Changes in the secretory patterns of LH during the perimenopause were also demonstrated by Matt *et al.* (74). They studied pulsatile LH secretion in 39- to 49-year-old women who had regular menstrual cycles. An intensive sampling paradigm consisting of blood draws every 10 min for 8 hr during the mid- to late follicular phases was employed. Using the *Cluster* analysis to detect episodic perturbations in circulating hormones, they demonstrated an increase in LH interburst interval, suggesting decreased LH pulse frequency, and prolonged LH pulse duration in the perimenopausal women compared with those in younger women. They did not detect a change in LH amplitude in the perimenopausal women compared with that in younger women. These data suggest that alterations in LH secretion occur during the perimenopause.

Despite elevated LH levels during the early perimenopause, the menstrual cycles of perimenopausal women can be ovulatory (75). This suggests that during the perimenopause, there may be an alteration of the usual feedback mechanisms that regulate the menstrual cycles during the reproductive years.

Pattern of estrogen secretion. It was believed that the perimenopause was a time of estrogen deficiency due to a depletion of ovarian follicles (64, 61, 65). However, more recent studies have shown otherwise. Oscillations between episodes of hypo- and hyperestrogenemia have been observed during the perimenopause (76, 70). Investigation of the pattern of estrogen secretion during the perimenopause was conducted by Santoro *et al.* (71). In this study, the perimenopausal group consisted of two subgroups of women: the first group was six regularly cycling women $\geq$47 years in age in whom daily first morning urine collections for 6 months were assessed; the second group was composed of five women, ages 43–47 years, who underwent daily circulating and urine hormone measurements for one menstrual cycle. Hormone levels in these two groups were compared with those of three different groups of women: 11 normally cycling women 19–38 years in age (control group), five women $\leq$40 years in age with premature ovarian failure, and five menopausal women ages 54–79 years. The 6-month duration of the study was a relatively long period of observation, which allowed the assessment of the significant cycle to cycle fluctuations in hormone levels characteristic of the perimenopause. Results demonstrated that estrogen levels were elevated during both the follicular and luteal phases of the perimenopause. The hyperestrogenemia during the perimenopause suggests that despite the reduction in ovarian quantity and quality that precede the perimenopause, perimenopausal ovaries retain the ability to produce adequate estrogen. This provides data that contradict the theory that the hormonal changes of the perimenopause is due to only a deficiency of ovarian function. Elevated estrogen concentrations during the perimenopause account for some of the increased incidence in gynecological pathologies, such as increased growth of uterine fibroids, increased incidence of endometrial hyperplasia, increased occurrence of dysfunctional uterine bleeding, and progression of endometriosis symptoms that occur during the perimenopause. The results of this study also demonstrate that despite the hyperestrogenemia during both the follicular and luteal phases, some of the women continued to have ovulatory menstrual cycles. Furthermore, elevations in circulating estradiol did not appear to have a marked inhibitory effect on either FSH or LH secretion; that is, the perimenopause is a state of hypergonadotropinemia and hyperestrogenemia.

Despite the elevated estrogen levels during the perimenopause, perimenopausal women continue to experience climacteric symptoms (77). Thus, the onset of climacteric symptoms cannot be attributed to estrogen deficiency. It is more likely that the climacteric symptoms are related to unstable estrogen circulating concentrations.

Interestingly, transitory postmenopausal episodes (elevated FSH and LH, and decreased estrogen) have been a common feature seen in studies investigating the hormonal patterns in perimenopausal women (76, 71). These occasional patterns of hypergonadotropinemia with hypoestrogenemia were interspersed with ovulatory and anovulatory menstrual cycles (71). These transitory postmenopausal

episodes became more common with proximity to the menopause.

Etiology of the Endocrinology of the Perimenopause. The mechanisms that regulate the hypergonadotropin and hyperestrogen hormonal milieu of the perimenopause are not well understood. The changes that occur during the perimenopause may be more complex than just ovarian failure; that is, increased ovarian follicular atresia may be the result of changes in the neuroendocrine environment that originate in the central nervous system.

Studies of the role of the neuroendocrine environment during the perimenopause were conducted by Wise *et al.* (78, 79). In their studies of the rat model, they noted that middle-aged rats exhibited a change in LH secretion (decreased amplitude and frequency) and a significant decline in the number of activated GnRH neurons, despite the fact that the rodents were cycling regularly.

The role of the central nervous system in the neuroendocrine changes of the perimenopause in women can be observed by investigating the effect of a single depot estradiol benzoate injection, previously shown to elicit an LH surge in young regularly cycling women, upon the LH surge response in perimenopausal women (47). Because this method provides for adequate circulating estrogen necessary to elicit a LH surge, it replaces the ovarian role in the LH surge mechanism. However, this method requires a functioning hypothalamic-pituitary axis and, therefore, allows for examination of the response of the central nervous system to the exogenous estrogen.

In a preliminary study, we employed this method to investigate whether perimenopausal women have an altered LH surge mechanism (80). We studied eight perimenopausal (ages 45–50) women and a control group of nine younger (ages 25–33) women. All women had regular menstrual cycles and were not on any hormonal therapy. After obtaining serum on Days 2 and 3 of the menstrual cycle to document baseline hormone levels, 4 mg of E_2B in oil was administered i.m. Serum was obtained every 12 hr for 4 days and was assessed for estradiol, progesterone, LH, and FSH. An LH surge was defined as a 3-fold increase above baseline levels. Baseline levels of estrogen, progesterone, and LH were similar between the two groups. Baseline levels of FSH were markedly elevated in the perimenopausal women (16.3 ± 3.48 mIU/ml [means ± SEM]) above those in controls (5.17±0.62 mIU/ml). Estradiol levels achieved after injecting E_2B were similar in both groups and were similar to or greater than normal midcycle estradiol levels. All women exhibited an initial decrease in LH and FSH levels in response to the E_2B challenge. However, although seven of nine young women exhibited an LH surge to the E_2B challenge, an LH surge was evident in only one of eight perimenopausal women, which was a significant difference in proportions (two-tailed $P = 0.015$, Fisher's exact test). These data demonstrated that the central LH surge mechanism is altered in perimenopausal women. Although baseline steroid and LH levels and the E_2B challenge were the same, older women generally failed to respond to E_2B with an LH surge. These data demonstrated that perimenopausal changes involve mechanisms other than ovarian hypofunction. Complex central differences that alter the response to a standard estrogen challenge mark the perimenopausal transition. These results are currently being verified in a study with an increase in the number of participants. We hypothesize that the hormonal differences in the perimenopausal women are due to decreased sensitivity to estrogen. Interestingly, alteration of central nervous system sensitivity to LH secretion by estrogen occurs during puberty as well.

Menopause

Defining Menopause. The menopause is the age at the final menstrual period, after which a woman experiences 12 consecutive months of amenorrhea. Thus, menopause is designated retrospectively. The average age of menopause is 51.3 years. Smoking has shown to be associated with an earlier age at menopause, the median decrease in age at onset of menopause in smokers is 1.5–2.0 years (55). An earlier age at menopause is also associated with menstrual cycle length. Women whose mean cycle length was <26 days became menopausal 1.4 years earlier than those whose cycles were between 26–32 days in duration, and 2.2 years before those with cycles >32 days (62). A delayed age at menopause is also associated with higher parity and age at hysterectomy without oophorectomy (81).

Patterns of LH and Estrogen Secretion. In a recent study, prematurely menopausal women had decreased estrone excretion compared with that in perimenopausal women (71). Similarly, the hormone levels of menopausal women were characterized by lower estrone conjugate excretion and elevated LH compared with those in perimenopausal women. In menopausal women, circulating estradiol is decreased by more than 90% and LH levels are increased 4- to 5-fold compared with those in younger, reproductive-aged women (82). The menopausal elevated LH levels are maintained by continued secretion of LH in a pulsatile manner, with high amplitude and LH pulse frequency of approximately every 1–2 hr (32).

Conclusions

In summary, the estrogen regulation of LH secretion throughout reproductive life in women begins with the maturation of the hypothalamic-pituitary-ovarian axis *in utero*, advances to the development of the LH surge during puberty, climaxes with the ability to reproduce during the reproductive years, and culminates in the reversal of the development of the hypothalamic-pituitary axis. That is, the sequential development of the negative feedback system followed by the positive feedback system (LH surge) prior to the reproductive years is reversed after the reproductive years by the loss of the LH surge mechanism during the perimenopause and loss of the negative feedback mechanism during the menopausal years. Alteration of the central

nervous system sensitivity to LH secretion by estrogen defines, to some extent, prepubescent as well as the perimenopausal hormonal changes.

1. Schwanzel-Fukuda M, Pfaff DW. Origin of luteinizing hormone-releasing hormone neurons. Nature **338:**161–164, 1989.
2. Kaplan SL, Grumbach MM, Aubert ML. The ontogenesis of pituitary hormones and hypothalamic factors in the human fetus: maturation of central nervous system regulation of anterior pituitary function. Rec Prog Horm Res **32:**161–234, 1976.
3. Styne DM. Physiology of puberty. Horm Res **41:**3–6, 1994.
4. Plant T. Puberty in primates. In: Knobil E, Neill JD, Eds. The Physiology of Reproduction (2nd ed). New York: Raven Press,, pp453–485, 1994.
5. Weiss G, Goldsmith LT. Puberty and pediatric and adolescent gynecology. In: Scott JR, DiSaia PJ, Hammond CB, Spellacy WN, Eds. Danforth's Obstetrics and Gynecology (7th ed). Philadelphia: JP Lippincott Co., pp611–619, 1994.
6. Apter D, Butzow TL, Laughlin GA, Yen SSC. Gonadotropin-releasing hormone pulse generator activity during pubertal transition in girls: pulsatile and diurnal patterns of circulating gonadotropins. J Clin Endocrinol Metab **76:**940–949, 1993.
7. Jakacki RI, Kelch RP, Sauder SE, Lloyd JS, Hopwood NJ, Marshall JC. Pulsatile secretion of luteinizing hormone in children. J Clin Endocrinol Metab **55:**453–458, 1982.
8. Lee PA, Xenakis T, Winer J, Matsenbaugh S. Puberty in girls: correlation of serum levels of gonadotropins, prolactin, androgens, estrogens, and progestins with physical changes. J Clin Endocrinol Metab **43:**775–784, 1976.
9. Terasawa E, Fernandez DL. Neurobiological mechanisms of the onset of puberty in primates. Endocr Rev **22:**111–151, 2001.
10. Boyar RM, Finkelstein J, Roffwarg H, Kapen S, Weitzman E, Hellman L. Synchronization of augmented luteinizing hormone secretion with sleep during puberty. N Engl J Med **287:**582–586, 1972.
11. Kapen S, Boyar RM, Finkelstein JW, Hellman L, Weitzman ED. Effect of sleep-wake cycle reversal on luteinizing hormone secretory pattern in puberty. J Clin Endocrinol Metab **39:**293–299, 1974.
12. Boyar RM, Wu RHK, Roffwarg H, Kapen S, Weitzman ED, Hellman L, Finkelstein JW. Twenty-four-hour estradiol patterns in pubertal girls. J Clin Endocrinol Metab **43:**1418–1421, 1976.
13. Norjavaara E, Ankarberg C, Albertsson-Wikland K. Diurnal rhythm of 17β-estradiol secretion throughout pubertal development in healthy girls: evaluation by a sensitive radioimmunoassay. J Clin Endocrinol Metab **81:**4095–4102, 1996.
14. Jenner MR, Kelch RP, Kaplan SL, Grumbach MM. Hormonal changes in puberty: IV. Plasma estradiol, LH, and FSH in prepubertal children, pubertal females, and in precocious puberty, premature thelarche, hypogonadism, and in a child with a feminizing ovarian tumor. J Clin Endocrinol Metab **34:**521–530, 1972.
15. Dierschke DJ, Weiss G, Knobil E. Sexual maturation in the female rhesus monkey and the development of estrogen-induced gonadotropic hormone release. Endocrinology **94:**198–206, 1974.
16. Presl J, Horejsi J. Stroufova A, Herzmann J. Sexual maturation in girls and the development of estrogen-induced gonadotropic hormone release. Ann Biol Anim Biochem Biophys **16:**377–383, 1976.
17. Hayes A, Johanson A. Excretion of follicle-stimulating hormone and luteinizing hormone in urine by pubertal girls. Pediat Res **6:**18–25, 1972.
18. Penny R, Parlow AF, Olambiwonnu NO, Frasier SD. Acta Endocrinol **84:**729–737, 1977.
19. Metcalf MG, Skidmore DS, Lowry GF, Mackenzie JA. Incidence of ovulation in the years after the menarche. J Endocrinol **97:**213–219, 1983.
20. Treolar AE, Boynton RE, Behn BG, Brown BW. Variation of the human menstrual cycle through reproductive life. Int J Fertil **12:**77–126, 1967.
21. Grumbach MM, Styne DM. Puberty: ontogeny, neuroendocrinology, physiology, and disorder. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, Eds. Williams Textbook of Endocrinology (9th ed). Philadelphia: WB Saunders Co., pp1509–1625, 1998.
22. Stanhope R, Brook CGD, Pringle PJ, Adams J, Jacobs HS. Induction of puberty by pulsatile gonadotropin releasing hormone. Lancet **2:**552–555, 1987.
23. Adashi EY, Resnick CE, D'Ercole AJ, Svoboda ME, Van Wyk JJ. Insulin-like growth factors as intraovarian regulators of granulosa cell growth and function. Endocrine Rev **6:**400–420, 1985.
24. Hillier SG, Yong EL, Illingworth PJ, Baird DT, Schwall RH, Mason AJ. Effect of recombinant inhibin on androgen synthesis in cultured human thecal cells. Mol Cell Endocrinol **75:**R1–R6, 1991.
25. Erickson GF, Garzo VG, Magoffin DA. Insulin-like growth factor 1 regulates aromatase activity in human granulosa and granulosa luteal cells. J Clin Endocrinol Metab **69:**716–724, 1989.
26. Chappel SC, Howles C. Reevaluation of the roles of luteinizing hormone and follicle-stimulating hormone in the ovulatory process. Hum Reprod **6:**1206–1212, 1991.
27. Korenman SG, Sherman BM. Further studies of gonadotropin and estradiol secretion during the preovulatory phase of the human menstrual cycle. J Clin Endocrinol Metab **36:**1205–1209, 1973.
28. Hoff JD, Quigley ME, Yen SSC. Hormonal dynamics at midcycle: a reevalution. J Clin Endocrinol Metab **57:**792–796, 1983.
29. Yussman MA, Taymor ML. Serum levels of follicle stimulating hormone and luteinizing hormone and of plasma progesterone related to ovulation by corpus luteum biopsy. J Clin Endocrinol Metab **30:**396–399, 1970.
30. Pohl CR, Richardson DW, Marshall G, Knobil E. Mode of action of progesterone in the blockade of gonadotropin surges in the rhesus monkey. Endocrinology **110:**1454–1455, 1982.
31. Dierschke DJ, Bhattacharya AN, Atkinson LE, Knobil E. Endocrinology **87:**850–853, 1970
32. Yen SSC, Tsai CC, Naftolin F, Vandenberg G, Ajabor L. Pulsatile patterns of gonadotropin release in subjects with and without ovarian function. J Clin Endocrinol Metab **34:**671–675, 1972.
33. Filicori M, Santoro N, Merriam GR, Crowley WF. Characterization of the physiological pattern of episodic gonadotropin secretion throughout the human menstrual cycle. J Clin Endocrinol Metab **62:**1136–1144, 1986.
34. Karsch FJ. Central actions of ovarian steroids in the feedback regulation of pulsatile secretion of luteinizing hormone. Annu Rev Physiol **49:**365–382, 1987.
35. Southworth MB. Matsumoto AM, Gross KM, Soules MR, Bremner WJ. The importance of signal pattern in the transmission of endocrine information: pituitary gonadotropin responses to continuous and pulsatile gonadotropin-releasing hormone. J Clin Endocrinol Metab **72:**1286–1289, 1991.
36. Hotchkiss J, Knobil E. The menstrual cycle and its neuroendocrine control. In: Knobil E, Neill JD, Eds. The Physiology of Reproduction (2nd ed). New York: Raven Press, pp711–749, 1994.
37. Karsch J. Dierschke DJ, Weick RF, Yamaji T, Hotchkiss, Knobil E. Positive and negative feedback control by estrogen on luteinizing hormone secretion in the rhesus monkey. Endocrinology **92:**799–804, 1973.
38. Knobil E. On the control of gonadotropin secretion in the rhesus monkey. Rec Prog Horm Res **30:**1–46, 1974.
39. Yen SSC, Tsai CC, Vandenberg G, Rebar R. Gonadotropin dynamics in patients with gonadal dysgenesis: a model for the study of gonadotropin regulation. J Clin Endocrinol Metab **35:**897–904, 1972.
40. Ordog T, Goldsmith JR, Chen MD, Connaughton MA, Hotchkiss J, Knobil E. On the mechanism of the positive feedback action of estradiol on luteinizing hormone secretion in the rhesus monkey. J Clin Endocrinol Metab **83:**4047–4053, 1998.
41. Yamaji R, Dierschke DH, Hotchkiss J, Bhattacharya AN, Surve AH,

Knobil E. Estrogen induction of LH release in the rhesus monkey. Endocrinology **89**:1034–1041, 1971.
42. Karsch FJ, Weick RF, Butler WR, Dierschke DJ, Krey LC, Weiss G, Hotchkiss, Yamaji T, Knobil E. Induced LH surges in the rhesus monkey: strength-duration characteristics of the estrogen stimulus. Endocrinology **92**:1740–1747, 1973.
43. Nillius SJ, Wide L. Induction of a midcycle-like peak of luteinizing hormone in young women by exogenous oestradiol-17β. J Obstet Gynaecol Br Commonw **78**:822–827, 1971.
44. Yen SSC, Tsai CC. Acute gonadotropin release induced by exogenous estradiol during the mid-follicular phase of the menstrual cycle. J Clin Endocrinol Metab **34**:298–305, 1972.
45. Monroe SE, Jaffe RB, Midgley AR. Regulation of human gonadotropins. XII. Increase in serum gonadotropins in response to estradiol. J Clin Endocrinol Metab **34**:342–347, 1972.
46. Shaw RW, Butt WR, London DR, Marshall JC. The oestrogen provocation test: a method of assessing the hypothalamic-pituitary axis in patients with amenorrhoea. Clin Endocrinol **4**:267–276, 1975.
47. Weiss G, Nachtigall LE, Ganguly M. Induction of an LH surge with estradiol benzoate. Obstet Gynecol **47**:415–418, 1976.
48. Liu JH, Yen SCC. Induction of midcycle gonadotropin surge by ovarian steroids in women: a critical evaluation. J Clin Endocrinol Metab **57**:797–802, 1983.
49. March CM, Goebelsmann U, Nakamura RM, Mishell DR. Roles of estradiol and progesterone in eliciting the midcycle luteinizing hormone and follicle-stimulating hormone surges. J Clin Endocrinol Metab **49**:507–513, 1979.
50. Nakai Y, Plant TM. Hess DL, Keogh EJ. Knobil E. On the sites of the negative and positive feedback actions of estradiol in the control of gonadotropin secretion in the rhesus monkey. Endocrinology **102**:1008–1014, 1978.
51. Thompson IE, Argania J. Taymor M. Effects of estrogen and progesterone on pituitary response to stimulation by luteinizing hormone-releasing factor. J Clin Endocrinol Metab **37**:152–155, 1973.
52. WHO Scientific Group. Research on the Menopause in the 1990's: A Report of the WHO Scientific Group. World Health Organization, Geneva, Switzerland **866**:1–79, 1996.
53. Brambilla DJ, McKinlay SM, Johannes CB. Defining the perimenopause for application in epidemiologic investigations. Am J Epidemiol **140**:1091–1095, 1994.
54. Association of Professors of Gynecology and Obstetrics. Barbieri RL, Berga SL, Chang RJ, Santoro NF, Eds. Managing the Perimenopause. APGO Educational Series on Women's Health Issues, Washington DC, 2001.
55. McKinlay SM. The normal menopause transition: an overview. Maturitas **23**:137–145, 1996.
56. Hardy R, Kuh D. Reproductive characteristics and the age at inception of the perimenopause in a British national cohort. Am J Epidemiol **149**:612–620, 1999.
57. Nachtigall LE. The symptoms of perimenopause. Clin Obstet Gynecol **41**:921–927, 1998.
58. Peterson DD, Schmidt RM. Longitudinal and cross-sectional analysis of Health Watch data with a subset of perimenopausal women and match control. J Geront **54A**:B160–B170, 1999.
59. North American Menopause Society. Clinical challenges of perimenopause: consensus opinion of the North American Menopause Society. Menopause **7**:5–13, 2000.
60. Bopp BL, Seifer DB. Oocyte loss and the perimenopause. Clin Obstet Gynecol **41**:898–911, 1998.
61. Sherman BM, West JH, Korenman SG. The menopausal transition: analysis of LH, FSH, estradiol, and progesterone concentrations during menstrual cycles of older women. J Clin Endocrinol Metab **42**:629–636, 1976.
62. Richardson SJ. The biological basis of menopause. Bailliere's Clin Endocrinol Metab **7**(1):1–16, 1993.
63. Hee J, MacNaughton J, Bangah M, Burger HG. Perimenopausal patterns of gonadotropins, immunoreactive inhibin, oestradiol and progesterone. Maturitas **18**:9–20, 1993.
64. Sherman BM, Korenman SG. Hormonal characteristics of the human menstrual cycle throughout reproductive life. J Clin Invest **55**:699–706, 1975.
65. Reyes FI, Winter JSD, Faiman C. Pituitary-ovarian relationships preceding the menopause. Am J Obstet Gynecol **129**:557–564, 1977.
66. Lee SJ, Lenton EA, Sexton L, Cooke ID. The effect of age on the cyclical patterns of plasma LH, FSH, oestradiol and progesterone in women with regular menstrual cycles. Human Reprod **3**:851–855, 1988.
67. Klein NA, Battaglia DE, Fujimoto VY, Davis GS, Bremner WJ, Soules MR. Reproductive aging: accelerated ovarian follicular development associated with a monotropic follicle-stimulating hormone rise in normal older women. J Clin Endocrinol Metab **81**:1038–1045, 1996.
68. Adamopoulos DA, Loraine JA, Dove GA. Endocrinoogical studies in women approaching the menopause. J Obstet Gynaecol Br Commonw **78**:62–79, 1971.
69. Metcalf MG, Livesey JH. Gonadotropin excretion in fertile women: effect of age and the onset of the menopausal transition. J Endocrinol **105**:357–362, 1985.
70. Shideler SE, DeVane GW, Kalra PS, Benirschke K, Lasley BL. Ovarian-pituitary hormone interactions during the perimenopause. Maturitas **11**:331–339, 1989.
71. Santoro NS, Brown JR, Adel R, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. J Clin Endocrinol Metab **81**:1495–1501, 1996.
72. Vihko KK, Kujansuu E, Morsky P, Huhtaniemi I, Punnonen R. Gonadotropins and gonadotropin receptors during the perimenopause. Eur J Endocrinol **134**:357–361, 1996.
73. Reame NE, Kelch RP, Beitins IZ, Yu M, Zawacki CM, Padmanabhan V. Age effects on follicle-stimulating hormone and pulsatile luteinizing hormone secretion across the menstrual cycle of premenopausal women. J Clin Endocrinol Metab **81**:1512–1518, 1996.
74. Matt DW, Kauma SW, Pincus SM, Veldhuis JD, Evans WS. Characteristics of luteinizing hormone secretion in younger versus older premenopausal women. Am J Obstet Gynecol **178**:504–510, 1998.
75. Papanicolaou AD, Loraine JA, Dove GA, Loudon NB. Hormone excretion patterns in perimenopausal women. J Obstet Gynaecol Br Commonw **76**:308–316, 1969.
76. Metcalf MG, Donald RA, Livesey JH. Pituitary-ovarian function in normal women during the menopausal transition. Clin Endocrinol **14**:245–255, 1981.
77. Ushiroyama T, Ikeda A, Ueki M. Evidence for attenuation of gonadotropin pulse frequency in hypergonadotropic women with estradiol secretion in the menopausal transition. Psychoneuroendocrinology **24**:85–97, 1999.
78. Scarbrough K, Wise PM. Age-related changes in the pulsatile pattern of LH release precede the transition to estrous acyclicity and depend upon estrous cycle history. Endocrinology **126**:884–990, 1990.
79. Lloyd JM, Hoffman GE, Wise PM. Decline in immediate early gene expression in gonadotropin-releasing hormone neurons during proestrus in regularly cycling, middle-aged rats. Endocrinology **134**:1800–1805, 1994.
80. Park SJ, Goldsmith LT, Reinert A, Skurnick JH, Castracane VD, Weiss G. Perimenopausal women are deficient in an estrogen positive feedback on LH secretion mechanism. The 82nd Annual Endocrine Society Meeting, Toronto, Canada, Abstract #248, June 2000. Bethesda, MD: The Endocrine Society Press.
81. Greendale GA, Soers M. The menopause transition. Endocrinol Metab Clin North Am **26**(2):261–277, 1997.
82. Burger HG. The endocrinology of the menopause. J Steroid Biochem Mol Biol **69**:31–35, 1999.