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Endocrinology of the Menopause

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Abstract

In women, age-related changes in ovarian function begin in the mid-thirties with decreased fertility and compensatory hormonal changes in the hypothalamic-pituitary-gonadal axis that maintain follicle development and estrogen secretion in the face of a waning pool of ovarian follicles. The menopause transition is characterized by marked variability in follicle development, ovulation, bleeding patterns and symptoms of hyper- and hypoestrogenism. The menopause, which is clinically defined by the last menstrual period, is followed by the consistent absence of ovarian secretion of estradiol.

Keywords

ovary; hypothalamus; pituitary; menopause; estradiol; follicle stimulating hormone

Menopause is a signal event in a woman's life that marks the end of reproductive competence. While the age-related loss of vaginal bleeding in women has been described throughout history, the studies of Block, published in 1952, documented the dramatic decrease in the number of follicles within the ovary as a function of age¹, demonstrating that the loss of both germ cells and the hormone-producing cells that support them is key to the the loss of menstrual function in women. Menopause is defined retrospectively by the final menstrual period and occurs at an average age of 51. However, the process of reproductive aging is gradual, begins much earlier than the final menstrual period, and can be conceptualized as encompassing: 1) an initial period in which compensatory changes in the hypothalamus, pituitary and ovary help to maintain both reproductive competence and gonadal hormone secretion; 2) a period characterized by marked variability in follicle development, ovarian secretion and consequent symptomatology leading up to the final menstrual period; and 3) stable and low ovarian hormone secretion. In the following chapter these three phases of reproductive aging will be discussed on the background of a discussion of normal reproductive cycle function and the changes that occur at all levels of the reproductive axis with aging.

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Reproductive Function in Normal Women

Regular reproductive cycles are established within the first 1–3 years after the first menstrual period in normal women². Although cycles between 25 and 35 days (from the first day of menses in one cycle to the first day of menses in the subsequent cycle) are considered normal³, cycle-to-cycle variability in an individual woman is considerably smaller ($\pm$ 2 days).

Normal menstrual cycle function requires tightly integrated interactions between the hypothalamus, pituitary and ovary while the endometrium serves as a gonadal steroid end organ and clinical marker of reproductive cycles (Figure 1). Estradiol secretion from developing follicles causes follicular phase proliferation of the endometrium. After ovulation, the combination of progesterone and estradiol produces the secretory changes that prepare the endometrium for implantation if conception occurs. In the absence of pregnancy, the function of the corpus luteum declines, hormonal support of the endometrium is lost and menses results (for review see Hall et al ⁴).

At the beginning of each cycle, increasing levels of FSH are necessary for recruitment of a new cohort of follicles while restraint of FSH is required to ensure that only a single follicle reaches the preovulatory stage to ensure optimum pregnancy outcomes for women. Estradiol secretion from developing follicles contributes to the negative feedback control of FSH, acting at both the hypothalamus and, to a lesser degree, the pituitary. Ovarian secretion of inhibin B and inhibin A provide an additional level of control through selective inhibition of FSH at the pituitary. In the late follicular phase, rising levels of estradiol result in generation of the preovulatory LH surge that is necessary for ovulation. The LH surge requires ongoing pulsatile GnRH secretion, but is otherwise fully dependent on the marked augmentation of gonadotropin responses to GnRH that occur at the level of the pituitary in response to the exponential rise in estradiol secretion from the dominant follicle⁴.

Progesterone secretion from the corpus luteum is maintained by LH secretion and inhibits GnRH pulse frequency^{5,6}. In the early and mid- luteal phase, slow-frequency GnRH pulses are hypothesized to increase synthesis of FSH over that of LH, as has been shown in animal models,⁷ although secretion of FSH is inhibited by estradiol and probably inhibin A. In the late luteal phase, the loss of this negative feedback from the waning corpus luteum⁸ results in a preferential rise in FSH over LH. Increased hypothalamic GnRH secretion, made possible by the loss of progesterone and estradiol negative feedback, is also necessary during the luteal-follicular transition to achieve levels of FSH that are adequate for the next wave of follicular recruitment⁹.

Ovarian Aging in Women

In women, the finite pool of resting follicles in the ovary reaches its maximum in neonatal life. Thereafter, there is a steady decline due to atresia such that, at birth, only one million follicles remain with a further reduction to 250,000 by the time of puberty (for review see Gougeon et al¹⁰). During and after puberty, follicles will leave the pool of resting follicles by activation of further growth or by degeneration. Rising levels of FSH provide a critical

stimulus for recruitment of resting follicles into the growing follicle pool while antimüllerian hormone (AMH), produced in granulosa cells from small growing follicles, restrains this effect of FSH within the ovary¹¹. Throughout early reproductive life the number of growing follicles is highly correlated with the size of the resting pool. However, between the ages of 30 and 35, the percentage of growing follicles increase^{12–14} and the trajectory of follicle loss is accelerated until the pool of resting follicles is reduced to between 100 and 1000 when there is cessation of reproductive cycles¹⁵. Age-related changes in oocyte quality parallel the decrease in follicle number with reported decrease in fertilization and conception rates and higher rates of pregnancy loss. Chemotherapy, radiation and smoking are all factors that accelerate follicle loss through damage to the oocyte and/or dividing granulosa cells^{16–19}.

However, one of the most powerful predictors of age at menopause is family history, with twin studies estimating that a remarkable 44–85% of the variance in age at natural menopause is heritable^{20–22}. At least 17 genes functioning in diverse pathways including hormonal regulation, DNA repair, and immune function have been associated with the age at natural menopause in genome wide association studies (GWAS)^{23–26}. There is further evidence of gene-environment interactions²⁷ raising the possibility that the wide range in age at menopause in normal women will be found to result from such interactions.

The Hypothalamus and Pituitary Changes with Repductive Aging

Response to the Loss of Ovarian Feedback

During normal reproductive life, the ovarian hormones and peptides restrain gonadotropin secretion through mechanisms that are operative at both the hypothalamus and pituitary. At the hypothalamus, progesterone has a profound inhibitory effect on LH, and therefore GnRH, pulse frequency. Estradiol does not appear to influence pulse frequency in women, but does decrease the overall quantity of GnRH secretion and thus the amount of GnRH secreted with each pulse. At the level of the pituitary, estradiol decreases the gonadotrope response to GnRH, with an effect that is greater for FSH than LH while inhibin B plays an additional pituitary role in the selective inhibition of FSH over LH.

The earliest hormonal evidence of ovarian aging is the selective increase in FSH that results from decreasing levels of inhibin B, a marker of granulosa cell number. With a further decrease in ovarian function and the loss of ovulatory cycles, GnRH pulses occur more frequently²⁸ while declining levels of estradiol permit increases in both GnRH²⁹ and in the gonadotropin responses to GnRH³⁰. Autopsy studies confirm an increase in GnRH expression in the medial basal hypothalamus after menopause³¹ and suggest that this effect is mediated by an increase in the stimulatory neuropeptides, neurokinin B and kisspeptin, and a decrease in the inhibitory neuropeptide, dynorphin³². Finally, the half-life of LH and FSH disappearance is prolonged in postmenopausal women as a result of alterations in the isoform composition of these two glycoprotein hormones with the loss of estradiol^{33, 34}. Taken together, declining levels of ovarian steroids and peptides with ovarian aging result in a 15-fold increase in FSH and a 10-fold increase in LH in postmenopausal women in the early years after their LMP³⁵.

Potential Roles of the Hypothalamus and Pituitary in Menopause

In rodents, ovaries from old donors undergo folliculogenesis and ovulation when transplanted to young ovariectomized hosts³⁶, providing evidence for a central contribution to reproductive failure with aging in rodents. Further studies have pointed to the importance of age-related alterations in estrogen positive feedback on GnRH secretion as at least one contributing mechanism³⁷. An important question is whether similar central mechanisms contribute to reproductive failure in women.

Studies in younger and older postmenopausal women suggest that there are effects of aging on the hypothalamus and pituitary that are independent of the loss of steroid feedback. After menopause there is a 30–40% decrease in LH and FSH between the ages of 50 and 75^{35, 38}. Underlying these gonadotropin changes are complex effects of aging on GnRH secretion with a 22% decrease in GnRH pulse frequency³⁹ that is partially compensated by a 14% increase in the overall amount of GnRH secreted over that due to the loss of ovarian function alone²⁹. There are also age-related effects at the pituitary with a 30% decrease in both LH and FSH responses to GnRH in older compared to younger postmenopausal women³⁰.

Estrogen negative feedback at the hypothalamic level remains intact in older compared with younger postmenopausal women; low-dose estrogen administration is associated with a significant decline in circulating levels of LH, FSH and FAS and a parallel decrease in the overall amount of GnRH, with no effect on pulse frequency²⁸. Addition of progesterone decreased pulse frequency in postmenopausal women with a concomitant decrease in overall amount of GnRH, neither of which effects differed with aging^{28, 29}. The effect of estrogen negative feedback on the LH response to GnRH is not influenced by aging although the FSH response to GnRH is attenuated with aging³⁰.

Several studies have suggested that sensitivity to estrogen positive feedback may be lost with aging in women^{40, 41} as it is in rodents⁴². An LH surge and increased progesterone were not evident in a small percentage of women who collected daily urine samples for variable periods of time during the menopause transition, despite similar peak late follicular phase estradiol levels⁴³. In further studies, a controlled and graded steroid infusion paradigm that recreated early and late follicular phase levels of estradiol in younger and older postmenopausal women demonstrated attenuation of the LH surge with age in the face of identical preovulatory patterns of estradiol was attenuated with age⁴⁴. There is now ample evidence for the overriding importance of increased pituitary responsiveness to GnRH in generation of the LH surge in women and thus, attenuation of the steroid induced-surge with aging is quite consistent with the decrease in pituitary responsiveness to GnRH with aging described earlier⁴⁵.

Integration of Hormonal Changes with Aging in Women

Our clinical and mechanistic understanding of the process of ovarian aging has progressed dramatically since the classic studies of Block in the 1950's demonstrated follicle loss across the reproductive lifespan in women¹ and markers of ovarian aging have also changed. FSH levels are increased in older women even before their FMP⁴⁶ and for many years the selective rise in FSH on day 3 of the menstrual cycle was the only clinically available

marker of fertility potential. Although the discovery of inhibin B elucidated its critical roles in ovarian negative feedback on FSH and as a marker of ovarian aging^{47, 48}, measurement of inhibin B was unable to serve as a better marker of fertility potential than FSH itself⁴⁹. However, since that time anti-mullerian hormone (AMH) has been established as an unexpected marker of the number of ovarian follicles and AMH and antral follicle count have been used as prognostic markers in infertility programs (for review see Broekmans et al⁵⁰). Our understanding of these new ovarian factors has not only contributed to fertility prognosis, but has also provided important insights into the integrated changes that occur with reproductive aging.

Maintenance of Follicle Development and Estrogen Secretion in Early Ovarian Aging

The existence of compensatory hormonal and intra-ovarian mechanisms that are operative in the early stages of ovarian aging is evidenced by continued follicle development and maintenance of estradiol levels well beyond the time at which other markers indicate declining ovarian function^{51–54}. The age-related decrease in the number of follicles in the ovary reviewed above is reflected in the number of antral follicles seen on ultrasound⁵⁵, in declining levels of AMH¹² which is expressed only in small growing follicles¹¹, and in decreased levels of inhibin B which is constitutively secreted from granulosa cells in FSH-dependent growing follicles⁵⁶.

Inhibin B plays an extremely important role as a gonadal feedback modulator of FSH secretion in early ovarian aging with declining levels of inhibin B associated with increasing FSH^{48, 57}. Higher levels of FSH drive increased recruitment of follicles into the growing pool, the percentage of growing follicles increases^{13, 14} and, as indicated above, there is an increase in the rate of follicle loss¹⁵. It is likely that increased FSH is responsible both for the increased rate of spontaneous dizygotic twinning in older women⁵⁸ and for the increased follicular phase estradiol levels in early reproductive aging even in the absence of development of more than one preovulatory follicle⁵⁹. AMH restrains the stimulatory actions of FSH on recruitment of primordial follicles into the growing pool¹¹ and on the FSH-dependent stimulation of aromatase⁶⁰. Upregulation of aromatase in older cycling women is suggested by an increase in the ratio of serum levels of estrone to androstendione in the follicular phase in regularly cycling women 35 compared with their younger counterparts⁶¹ and increased aromatase expression in granulosa cells aspirated from the dominant follicle in older compared with younger normal women.

Taken together, these data support that hypothesis that lower levels of AMH in conjunction with elevated levels of FSH drive the accelerated depletion of the resting follicle pool after age 35, that these hormonal and autocrine/paracrine changes are important for maintaining estradiol levels in the face of ovarian function and serve to extend fertility and maintain reproductive cycles and estrogen levels early in reproductive aging.

Hormonal Variability of the Menopause Transition

With ongoing follicle loss, the compensatory mechanisms described above are no longer adequate and cycles become irregular, signifying the onset of the menopause transition. Large scale cohort studies describe the overall hormonal changes, characterized by the

reciprocal relationship between decreasing inhibin B and increasing FSH levels early on and a later decline in estradiol that may not reach its nadir until one to two years after the FMP^{52, 62, 63}.

However, these aggregate changes do not reflect the marked variability in hormone levels that occur between women and within an individual woman (Figure 2) from month to month over the two to five years of the menopause transition. Estrogen levels may fluctuate between undetectable and many times normal for variable periods of time with these anovulatory hormonal patterns interspersed with ovulatory cycles⁶⁴. While the inconsistent estrogen response to FSH is not well understood, there is evidence of a mismatch between the progressively decreasing and scattered follicles in the ovary and their blood supply; Doppler studies indicate reduced ovarian blood supply in the aging ovary^{65, 66} and there are higher levels of vascular endothelial growth factor (VEGF), a marker of tissue hypoxia, in older reproductive aged women⁶⁷.

FSH levels are dramatically increased when estrogen levels are low due to the loss of steroid and inhibin feedback at the pituitary, and also because of a marked decrease in gonadotropin clearance in the face of hypoestrogenism³⁴. Age related slowing of GnRH pulse frequency would also favor synthesis and secretion of FSH over LH^{7, 39}. Prior to the complete loss of ovarian follicles, consistently increased FSH levels will drive follicle development and estrogen synthesis and secretion to levels that may be many times higher than ever seen in normal cycles⁶⁴.

In the year before the FMP, 60–70% of cycles are either anovulatory or have prolonged follicular phases^{68, 69} consistent with hormonal data indicating that a significant number of increases in estradiol are not followed by an LH surge and an increase in progesterone. Generation of a preovulatory surge requires a highly specific pattern of increasing estrogen levels over an adequate duration^{70, 71}, both of which are likely to be altered in the face of asynchronous FSH and ovarian function⁴³. Attenuation of the pituitary response to GnRH with aging⁴⁵ may further contribute to the abnormal cycle dynamics or the perimenopause. Irregular bleeding patterns, varying breast tenderness, hot flashes, sleep disturbance and possible mood changes are a frequent accompaniment of the variability in hormonal patterns in the menopause transition.

Stability of Hormone Secretion after Menopause

In the first one to two years after the FMP, occasional follicle development is evident in individual women. Consistent with these observations, epidemiologic studies using sensitive estradiol assays⁵⁴ demonstrate a further decrease from the FMP to the estradiol nadir two years later. Thereafter, estradiol levels remain low and stable. FSH levels also remain stable between two and eight years after the FMP⁵⁴, but decline over time such that FSH decreases by approximately 30% by approximately age 75, as does LH⁷². While women are no longer bothered by irregular bleeding and breast tenderness, hot flashes may persist for up to 7 years after the FMP⁷³ and with prolonged hypoestrogenism, genitourinary syndrome of menopause (GSM) may emerge as a new clinical symptom.

Clinical Assessment of Reproductive Aging and Menopause

In 2001, the first Stages of Reproductive Aging Workshop (STRAW), utilized the findings from important cohort studies of women across the menopause transition, based primarily on changes in menstrual bleeding patterns and qualitative changes in FSH, and introduced standardized terminology referenced to the final menstrual period⁷⁴. This staging system provided a critical scaffold for further studies and was updated a decade later (STRAW+10) to incorporate the results of longitudinal studies across the menopause transition and studies of fertility in older women⁷⁵. FSH cut-off levels are now possible because of international standardization of this measure. AFC and AMH have been limited to qualitative descriptors as these measures have not been standardized across centers and are used primarily in infertility populations and particularly in women over 35⁷⁶.

Addition of changes in estradiol to this schema permits us to understand the the clinical symptoms of changes in menstrual cyclicity, vasomotor symptoms and GSM, which will be discussed in Chapter 2 in the context of evolving hormonal changes with progressive loss of ovarian function (Figure 3).

Conclusions

Reproductive aging in women is primarily due the progressive, and ultimately accelerating, loss of ovarian follicles. The associated decline in inhibin B secretion from the ovaries results in the loss of negative feedback on FSH. Within the ovary, low levels of AMH serve to facilitate FSH-stimulated follicle growth and estrogen synthesis and secretion. With further follicle loss, these compensatory hormonal mechanisms are no longer adequate, follicle development becomes unpredictable before further loss of ovarian function results in the stable but very low estradiol levels that characterize the postmenopause.

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Key Points

- Menopause is defined by the final menstrual period, but this diagnosis can only be made retrospectively after a year of amenorrhea.
- Reproductive aging in women is largely due to the loss of ovarian function, which is marked by decreased levels of inhibin B and anti-mullerian hormone (AMH).
- In the early stages of reproductive aging, there is an increase in FSH, as inhibin B levels decline, which serves to maintain folliculogenesis and estradiol secretion.
- With further loss of ovarian function, these compensatory changes are not always sufficient and result in marked variability in cycle dynamics and in estradiol and FSH levels.
- Estradiol levels stabilize at very low levels after the final menstrual period.

Figure 1 –.

The hormonal, follicular, and endometrial (Endo) dynamics of the normal menstrual cycle from the late luteal phase through menses and the beginning of a new cycle of follicle development, ovulation, and corpus luteum function and decline. inhibin B (Inh_B) inhibin A (Inh_A) From Hall JE. Neuroendocrine control of the menstrual cycle. In: Strauss JF, Barbieri RL, editors. Yen and Jaffe's Reproductive Endocrinology, 7th Edition. Philadelphia, PA: Elsevier Publishing, pp 141–156; 2013, with permission.

Figure 2 –.

Daily urine samples over 6 months in a perimenopausal woman indicate marked variability in the pattern of LH, FSH, estrone conjugates (E1C) and progesterone diglucuronide (PDG). The dashed line in the upper panel indicates the upper limit of normal for FSH in young women while the dotted line in the lower panel indicates the upper limit of normal E1C in young women. Shaded bars indicate cycles in which levels of PDG are consistent with ovulatory cycles. Data from Santoro N, Brown JR, Adel T, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. *J Clin Endocrinol Metab* 1996; 81(4): 1495–501.

	REPRODUCTIVE		MENOPAUSE TRANSITION		POST MENOPAUSE		
	Peak	Late	Early	Late	Early		Late
PRINCIPAL CRITERIA							
Menstrual Cycle	Regular	Subtle Changes	Variable Length	Interval of Amenorrhea $\geq$ 60 d			
SUPPORTIVE CRITERIA							
<i>Endocrine</i>							
FSH	low	variable	high variable	high >25 IU/L	high variable	stable	
AMH	low	low	low	low	low	very low	
Inhibin B		low	low	low	low	very low	
Antral Follicle Count	low	low	low	low	very low	very low	
Estradiol	normal	normal	normal	highly variable	stable	low stable

Figure 3 –.

Qualitative changes in estradiol superimposed in relation to the STRAW+10 system for reproductive aging⁷⁵ reflect the result of initial compensatory changes that preserve folliculogenesis and estrogen secretion and the progressive loss of compensation (graded arrow) with marked hormonal variability leading up to the final menstrual period, followed by low and stable estrogen secretion.