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Ovarian Aging and the Perimenopausal Transition

The Paradox of Endogenous Ovarian Hyperstimulation

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The purpose of this review is to put into a useful clinical context the changing over time of basic ovarian–pituitary–hypothalamic relationships during perimenopause. "Perimenopause" means changes in ovarian hormones, feedback relationships, and clinical experiences beginning in women ages 35–50 with regular flow and ending 1 yr after the final menstrual flow. A key observation must be explained—estradiol levels are increased in perimenopause. Inhibin B levels are lower and activin may be higher in midlife, menstruating women. These changes probably cause higher follicular phase FSH levels—"endogenous ovarian hyperstimulation" results. The positive estradiol feedback on LH is also disturbed—midcycle LH peaks and midluteal slow-frequency, high-amplitude LH pulses are less frequent. In addition to higher levels, estradiol receptors may increase in tissues of symptomatic women. Despite hyperstimulation of follicles, progesterone levels and luteal phase lengths are paradoxically decreased —reasons probably include LH peak disruptions and estrogen-stimulated greater corticotrophin-mediated reproductive suppression. In summary, disturbed feedback relationships causing higher and unpredictable estrogen and lower progesterone levels occur throughout perimenopause, especially during regular cycles. Prospective, population-based research is needed to systematically relate these feedback hormonal changes to clinical characteristics and to allow a diagnosis of perimenopause in regularly cycling midlife women.

Key Words: Perimenopause; estradiol; FSH; LH; inhibin; activin; progesterone; ovarian hyperstimulation.

Introduction

The purpose of this review is to highlight the known changes in hypothalamic–pituitary–ovarian feedbacks (HPOF) and their resulting gonadal steroid changes during the transition from premenopausal ovulatory cycles to perimenopause. My perspective is that of a clinical scientist and physician. Midlife women experience a confusing complexity of largely unexplained experience changes. For purposes of this review, based on previous work *(1–3)*, perimenopause is defined to begin when women experience typical changes in their experiences—such as premenstrual breast tenderness and night sweats and with mid-sleep wakening—despite maintaining regular flow *(2)*. Perimenopause ends and menopause begins when a woman has been 1 yr since her final menstrual flow, although about 5% of women over 53 will experience a further spontaneous menses *(4,5)* and up to 10% if they are 45–49 *(6)*. If flow is preceded by breast tenderness and other high-estrogen signs, these suggest that the flow is not due to endometrial pathology.

This review may give rise to some controversy. First, the concept of declining estradiol levels through the menopausal transition *(7)* is firmly entrenched. And this paradigm has a way of obscuring reality *(8)*. Estradiol levels are clearly higher in perimenopause than in young adulthood—data are consistent from a meta-analysis of observational data, follicular phase levels in a population-based cohort aged 45–55, and a single cycle comparative study in older and younger regularly cycling women *(1,8,9)*. Second, for many gynecologists, regular cycles are, by definition, ovulatory—irregular cycles are considered synonymous with anovulation *(10)*. This review will show that anovulation and short luteal phase cycles commonly occur in regularly cycling perimenopausal women *(3)*. Data show that flow onset does not require dropping progesterone levels *(11)*, and also that 5–10% of regularly menstruating women across *all* reproductive life phases are non-ovulatory *(12)*. Finally, this review will indicate the difficulties with the Stages of Reproductive Aging Workshop definition of the onset of the menopausal transition *(13)*.

Results

This section details a series of variably expressed hypothalamic–pituitary–ovarian feedback changes that occur during perimenopause: changes in ovarian protein levels including decreased inhibin B levels, probably later decreased inhibin A levels, and possibly higher activin A levels; vari-

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able but disturbed feedback suppression of FSH by estradiol; and decreased consistency of estrogen-related positive feedback with erratic LH midcycle peaks and decreased midcycle slow-frequency, high-amplitude LH pulsatility. Gonadal steroid levels and experiences change as a result of these feedback loop changes.

This review will not attempt to discuss other possible hypothalamic influences on perimenopause. These include changes in melatonin levels *(14)* that could relate to the sleep disturbances that are common in perimenopause *(15)*. Each of the feedback changes documented in perimenopausal women will be followed by the known and postulated hormonal and clinical implications. Overall, the results of these fundamental changes in hypothalamic–pituitary–ovarian feedback loops are changes in the ovulatory menstrual cycle pattern of estradiol secretion, increases in ovarian estradiol production, more rapid loss of primary ovarian follicles, and an increase in disturbances of ovulation including short luteal phase cycles and anovulation. It is also likely that higher estradiol levels up-regulate target tissue estradiol receptors. Finally, this review will touch on genetic influences on the expression of feedback and gonadal steroid changes in women's perimenopausal health experiences.

Changes in Ovarian Regulatory Proteins— Inhibins, Activins and Follistatin

Although research on "inhibin," a pleomorphic ovarian and testicular protein, began over 30 yr ago, only recently have the two major, discrete types in women, inhibin B relating to the ovarian follicle pool *(16)* and inhibin A relating to LH and luteal phase events *(17)*, been sufficiently studied and characterized to be of clinical usefulness *(18,19)*.

Inhibin B levels, stimulated by FSH, normally increase early in the menstrual cycle to inhibit further FSH-related recruitment of follicles *(20)*. However, follicular-phase inhibin B levels are lower in regularly menstruating midlife women—this change is associated with higher FSH and estradiol levels *(21)*. There are negative correlations between inhibin B levels and FSH and estradiol *(20)*. Furthermore, inhibins, not well characterized by type, also appear to act as intragonadal paracrine regulators *(22)*.

Inhibin A levels are not as well characterized but decreases appear to occur later in perimenopause *(23,24)*, although some authors have shown small increases in follicular phase levels in older women *(25)*. Inhibin A appears to be important in regulation of events relating to ovulation, and to decrease over time *(17,23)*. More recent data show no difference in inhibin A levels in ovulatory and non-ovulatory cycles as women transitioned to menopause *(10)*. It remains entirely mysterious why both inhibin A and B levels appear to decrease in older, menstruating women. It is possible that the older follicles remaining in perimenopause were ones initially buried deeper in the ovary and something about this environment causes less capacity to secrete the inhibins.

In addition to the effects of inhibins, other ovarian proteins such as activin and follistatin are important in the net changes in ovarian control during perimenopause. Reame and colleagues have postulated that the net effect of inhibitory peripheral inputs (inhibins, estradiol, follistatin) and stimulatory inputs (activin and GnRH) cause the changes in early follicular FSH levels *(25)*. They have shown that activin A levels are higher although follistatin and free follistatin are not different in the follicular phases of women averaging age 44 compared with women aged 30 *(25)*.

Changes in FSH Feedback Control and Levels

Follicle-stimulating hormone (FSH) is secreted in pulses by the anterior pituitary under the influence of gonadotrophin-releasing hormone with direct inhibitory feedback by estradiol and inhibin B and stimulatory actions of activin A. The STRAW definition of the menopausal transition onset specifies that cycle-day 3 FSH levels are increased, in addition to cycle irregularity of ±7 d. Both population-based cross-sectional *(7)* and prospective data *(24)* show that FSH levels increase during perimenopause. The key question is—What is an increased FSH level? Based on prospective, population-based data from 150 women sampled in the early follicular-phase yearly over 6 yr, Burger and colleagues concluded, "there is no single reliable hormonal marker of menopausal status for an individual woman" *(24)*. In addition, the usual premenopausal follicular-phase FSH normal range is wide, often has a middle gray zone, or it overlaps the menopausal range. For example, in a cohort sampled yearly over 4–9 yr before menopause, serum FSH levels averaged from weekly samples over 4 wk were 13.1 (2.3–75) in prolonged cycles compared with 6.7 (2.2–20.7) IU/L in regular ovulatory cycles *(10)*. The big picture is that FSH levels increase with age or across perimenopause—the primary reason appears to be inconsistent or decreased estradiol suppression. That, in turn, is probably related to lower levels of inhibins and perhaps higher activins.

However, it appears to take very little elevation of FSH, only into the 15–20 IU range, to produce heavy flow, endometrial thickening and hyperplasia, multiple moderate-sized ovarian cysts, and estradiol levels over 2000 pmol/L *(26)*. Hence, levels seen commonly in both ovulatory and non-ovulatory cycles from midlife women are sufficient to cause ovarian hyperstimulation.

Changes in LH Feedback Control and Levels

It is known that when FSH levels are already higher, LH levels may remain normal in the perimenopausal transition *(21)*. However, some studies show LH levels are also statistically higher in older women *(27)* and higher in those with greater estrogen excretion levels *(28)*. The most important changes in LH appear to relate to the dynamics of the midcycle LH peak. Although data remain preliminary, exog-

enous estrogen appears to unreliably produce an LH peak in older women *(29)*. Also, although estradiol levels were not significantly different, cycling women ages 40–50 appeared to lack the slow-frequency, high-amplitude LH pulsatility characteristic of the luteal phase *(27)*. Therefore, changes in positive and perhaps also the negative feedback control of LH appear to occur in perimenopause.

Changes in Estradiol Feedback and Levels

The net effects of the early follicular phase, rising FSH levels discussed earlier, perhaps lower paracrine intraovarian suppression of follicles by a dominant follicle, and impaired suppression of FSH by estradiol, is that more recruited follicles cause higher levels of estradiol production within ovulatory cycles *(9)*. The highest levels appear to occur at the extremes of the menstrual cycle *(9,10)* so levels tend to be high during flow.

Higher *premenstrual* estradiol levels in midlife women are associated with heavy flow *(30–32)* and with abnormal proliferation of the endometrium *(31)*. The symptom of heavy flow causes about 25% of perimenopausal women to seek medical help *(33,34)* and commonly occurs, if not before, as cycles change from being regular to irregular *(35)*. Part of the pathophysiology of abnormal vaginal bleeding may be that endometrial estradiol receptors are up-regulated in women with heavy flow *(36)*. Finally, in an epidemiological sample of 900 women from Rotterdam, estrogen receptor genotypes related to the age at menopause, risk for and age at hysterectomy *(37)*. The mean age at hysterectomy was younger than, on average, irregular cycles start and before perimenopause is conventionally diagnosed *(13,38)*.

High estradiol levels before flow may also explain premenstrual front-of-breast tenderness that is commonly reported in regularly cycling women who may also have cyclic night sweats *(2)*. Often perimenopause presents as increasing "premenstrual syndrome" with increased mood, fluid, appetite, and breast tenderness symptoms before flow *(39)*. High estradiol levels have also been shown experimentally to amplify stress hormone responses to situational stress *(40)*. It is possible, although other feedback effects are less efficient, that higher estradiol-related corticotrophin-releasing hormone causes suppressive effects on pituitary control of the ovary *(41)*. These hypothalamic responses to high estradiol may account for the feelings of being out of control, palpitations, and chest pressure some perimenopausal women experience.

Changes in Ovulation and Progesterone Levels

Ovulation and premenstrual endocrinology of perimenopause are less well understood than early follicular phase changes. The major epidemiological prospective study of hormonal levels did not measure premenstrual levels *(42)*. Nevertheless, weekly overnight urines for pregnanediol, in three cycles per woman in 31 women considered to be in the menopausal transition, showed that only 52% of cycles that were 18–260 d apart (median 29) were ovulatory *(43)*. The longer cycles were significantly less likely to be ovulatory than the ones of normal length *(43,44)*. In general, short luteal phase cycles and lower progesterone levels occur, even in regularly cycling women in their mid–late 40s *(3)*. This means that the ratio of estradiol to progesterone levels increases *(45)*. These ovulatory changes may result from the disturbed positive feedback of estradiol on LH *(29)*.

Discussion

In perimenopause, FSH increases early in the follicular phase as a result of net positive change as inhibition decreases and stimulation increases. This lack of normal inhibition of FSH probably leads to increased follicle numbers and the increased incidence of dizygotic twinning in older women *(46)*, the more rapid depletion of follicles in autopsy studies *(47)*, and higher estradiol levels *(1,9)*. In turn, higher estradiol levels are associated with heavy flow *(31)* in some perimenopausal women and menstrual problems in 32% of menstruating midlife women *(48)*, as well as increased endometrial thickness *(49)* and proliferative histology *(31)*. Higher estradiol levels, through hypothalamic effects, also appear to increase cortisol and catecholamine responses to situational stresses *(40)*. Premenstrual symptoms increase, perhaps as a consequence, and in turn predict more difficult hot flush/night sweat symptoms later in perimenopause *(50)*.

Ovulation, although commonly present, is often not normal in amount or duration of progesterone *(3,9)*. The definite trend is for the ratio of estradiol to progesterone to increase *(45)*. These perimenopausal hormonal changes likely have major, although poorly understood, effects on women's experiences.

The effect of the decreased coordination of feedback loops in perimenopause is that high estradiol levels may and often co-exist with elevated gonadotrophin levels. Therefore, exogenous estrogen levels may not reliably suppress endogenous estradiol. These data suggest that symptomatic treatment of heavy flow, vasomotor symptoms, premenstrual symptoms, and sleep disturbances should avoid estrogen. However, progesterone may be effective perimenopausal therapy—it is a steroid that is relatively or absolutely low in perimenopause.

Medroxyprogesterone has been shown to help heavy flow *(51)* and to treat hot flushes *(52)*. Oral micronized progesterone, another treatment option, improves sleep *(53)* and helps premenstrual symptoms *(54)*.

Before we will understand relationships between perimenopausal hormonal and symptom changes, every endocrine study needs to carefully characterize each participant. Symptomatic regularly cycling older women need be prospectively observed to document which of their experiences

predicts the subsequent onset of menopause—this study must be of at least 6 yr's duration to adequately characterize this long process. Sociodemographic characteristics *(48)*, weight and waist circumference changes, cycle intervals, and length of flow also need to be documented. Using an instrument like the Daily Perimenopause Diary *(2)*, patterns of breast tenderness, stretchy cervical mucus, hot flushes/night sweats, mood symptoms, and sleep across normal and long intermenstrual intervals can be characterized. Finally, there is need for other prospective population-based studies of perimenopause that include measures of progesterone and luteal-phase lengths.

In summary, the complex, interactive and always variable endogenous ovarian hyperstimulation with ovulation disturbances characteristic of perimenopause is much better known now than two decades ago. However, we still need to integrate the endocrinology with symptoms and to be able to define the onset of perimenopause when cycles are regular and estradiol levels have already increased.

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