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The endocrinology of perimenopause: need for a paradigm shift

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1. ABSTRACT

Perimenopause, rather than a time of declining estrogen, is characterized by three major hormonal changes that may begin in regularly menstruating women in their mid-thirties: erratically higher estradiol levels, decreased progesterone levels (in normally ovulatory, short luteal phase or anovulatory cycles), and disturbed ovarian-pituitary-hypothalamic feedback relationships. Recent data show that approximately a third of all perimenopausal cycles have a major surge in estradiol occurring *de novo* during the luteal phase. This phenomenon, named "luteal out of phase (LOOP)" event, may explain a large proportion of symptoms and signs for symptomatic perimenopausal women. Large urinary hormone data-sets from women studied yearly over a number of years in the Study of Women Across the Nation (SWAN) and in the Tremin data will eventually provide a more clear prospective understanding of within-woman hormonal changes. Predicting menopause proximity with FSH or Inhibin B levels is documented to be ineffective. Anti-Mullerian hormone levels may prove predictive. Finally, there is an urgent need to change perimenopause understandings, language and therapies used for midlife women's symptoms to reflect these hormonal changes.

2. PURPOSE, PERSPECTIVE AND DEFINITIONS

Current care of midlife women is often informed by outdated knowledge about the nature of perimenopause. Recent scientific reviews (1-4) have concluded that perimenopause is characterized by intermittently and sometimes dramatically high levels of estrogen, lower progesterone levels and disturbed hormonal feedback loops. This evidence is in contrast with assumptions of dropping or lower estrogen levels, and the casual use of the term "estrogen deficiency" as a synonym for perimenopause. Although we can easily link perimenopausal heavy flow with both high estrogen levels and inadequate progesterone-related endometrial effects (5), today this menorrhagia is commonly treated with oral contraceptives that make it worse (6), or with ablative surgeries of the endometrium or the uterus rather than with effective high dose long-cycle progesterone/progestins (7). Thus, although the major purpose of this review is to highlight current new knowledge of the changing endocrinology of perimenopause, we also want to contribute to improved clinical care, education and research.

Our perspective is a complex integration of several points of view—that of scientists studying the confusing endocrinology of perimenopause and women's

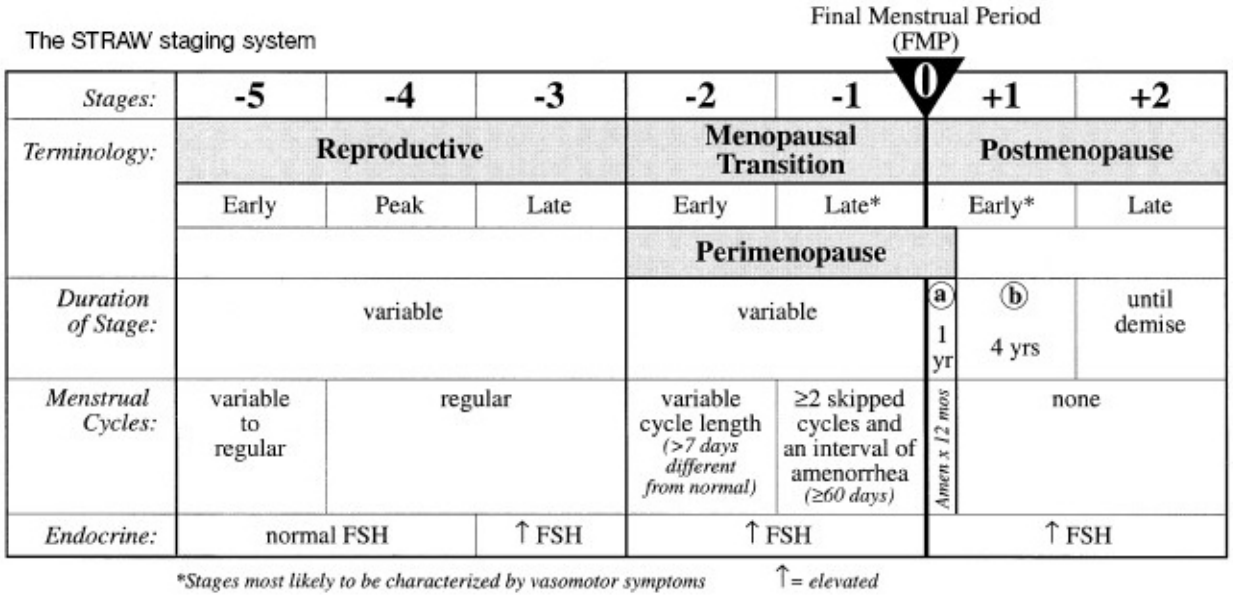

Figure 1. The Stages of Reproductive Aging Workshop (STRAW) classification of women's reproductive lives. Reproduced with permission from (10).

changing daily experiences over time, as investigators committed to knowledge translation from research into clinical care, and as educators trying to change concepts that may be prejudicial for women. One of us has also spent 40 years as a physician attempting to make the data gathered in a clinical setting speak a scientific language (8).

Taxonomy, or the naming of things, is fundamental for any field of science (9). We understand that definitions not only arise from but also create concepts that may prevent scientific advancement—for example, with the diagnosis of hysteria, which was formerly thought caused by the uterus flying throughout the body. There is a danger in prematurely naming incompletely understood phenomena, but it is a necessary part of the scientific process. However, clear definitions are essential for this paper and for our purpose. Therefore, building on the work performed by numerous investigators and the Stages of Reproductive Aging Workshop (STRAW; 10; Figure 1), we will create and justify definitions that fit with what we now know (see Table 1).

For the purposes of this review we define perimenopause as the entire transitional period from women's mature reproductive to a non-reproductive state. Thus, as shown in Figure 2, perimenopause begins when the estrogen levels have already begun to rise and progesterone levels have decreased but cycles continue to be regular (11). We have postulated a clinical definition of changes in women's experiences any three of which will make the diagnosis of perimenopause. It is likely that perimenstrual cyclic night sweats without daytime vasomotor symptoms is sufficient unique that it, alone, may be diagnostic. This clinical diagnostic tool (Table 2) needs to be validated against the final menstruation prospectively in a population-based sample. This diagnosis of perimenopause in women with regular cycles is controversial because all of the current taxonomies define the onset of women's midlife transition by decreases in the regularity or frequency of menstruation (10; 12; 13) yet by the onset of irregular cycles, women have usually experienced several years of hormonal changes typical of perimenopause and their associated symptoms.

Perimenopause ends, as adopted by STRAW, one year beyond the final menstrual flow (10). Thus, perimenopause as defined here encompasses part of the STRAW "late reproductive stage," the early and late menopause transition stages and one year beyond the final menstrual flow (Figure 2).

The end of perimenopause also defines the onset of what we prefer to call menopause (rather than postmenopause, which relies on the use of the word "menopause" to mean the retrospectively defined literal final menstrual period). This taxonomy avoids the inappropriate dual naming of the year following the last menstrual flow as both "postmenopause" and "perimenopause" that both the WHO and STRAW schema preserved (10; 14). Menopause, in our understanding, although it is also a hormonally complex and an experientially changing life phase, is the state within which women achieving it then permanently reside.

3. CHANGES IN OVARIAN STEROIDS DURING PERIMENOPAUSE

Before discussing the hormonal changes of perimenopause it is important to state clearly that our normal referent is the endocrinology of the premenopausal normally ovulatory cycle (15; 16). Ideally, all studies of perimenopausal hormonal changes would have a within-

Table 1. Reproductive Life Cycle Definitions

Premenopause – Women's life phase from the onset of menstruation until the beginning of perimenopause.

Perimenopause – This term encompasses the entire transitional period of women's reproductive aging from the onset of cyclic night sweats or other characteristic changes (see Table 1) in regularly menstruating women until one year past final menstruation. Perimenopause includes part of the Late Reproductive Age (as per Stages of Reproductive Aging Workshop, STRAW), all of Early and Late Menopausal Transition and the year following the last menstrual flow.

Menopause – The remainder of a woman's non-menstruating life, beginning one year following the last menstruation. (Note that this women's life phase is called by some, "postmenopause" to fit with the past use of the term "menopause" as the final menstrual period.)

Late Reproductive Age – as defined by STRAW, includes older regularly menstruating women (who in STRAW were required to have elevation of follicle stimulating hormone [FSH] levels—although these were not operationalized).

Early Menopausal Transition – as defined by STRAW, women over age 35 with variable menstrual cycle lengths (variability of 7 or more days) but who have not yet started skipping menstrual periods. The ReStage Collaboration has further operationalized this definition to having a difference in consecutive menstrual cycle lengths of at least 7 days, at least twice within a year.

Late Menopausal Transition – as defined by STRAW, women over age 35 who have skipped a menstrual cycle and have elevation of follicle stimulating hormone levels—although high FSH levels were not operationalized in STRAW. With the ReStage Collaboration analysis of prospective cohort data, a cycle of 60 days or longer is taken as the onset of the Late Menopausal Transition.

Table 2. Midlife women with regular menstrual cycles may have a diagnosis of perimenopause if they experience any three of the following experience changes.

1. New onset heavy and/or longer flow
2. Shorter menstrual cycles (∠25 days)
3. New sore, swollen or lumpy breasts
4. New mid-sleep wakening
5. Increased cramps
6. Onset of night sweats, in particular premenstrually
7. New or markedly increased migraine headaches
8. New / increased premenstrual mood swings
9. Weight gain without changes in exercise or eating

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center premenopausal control group that is similar in body mass index, racial mixture and dietary and activity variables.

3.1. Estradiol changes—the paradox of perimenopause

The word "menopause" is commonly used as inclusive of both women's midlife transitional phase and the stable non-reproductive phase. Because estradiol is truly low beginning about a year after the final menstrual flow, it is assumed that during perimenopause levels must be dropping. Teleologically, the functional requirement in perimenopause is to rid the ovary of hormonally responsive follicles that could be stimulated by FSH later in life (17). Anatomical studies have found an increased rate of recruitment of small follicles that undergo atresia—this starts about age 37 (17). At the same time estradiol levels become, on average, higher. Many of the symptoms of perimenopause are also associated with unusually high levels of estradiol. Thus perimenopause is a time during which estradiol levels become erratic and often high before eventually becoming lower than in reproductive-aged women.

Santoro and colleagues were the first to state the then-radical notion that estradiol levels were higher in perimenopause (18). This observation was based on a cross-sectional single cycle, daily urinary hormone study published in 1996 showing significantly higher levels especially during the luteal phase (Figure 3). This observation was confirmed by a meta-analysis comparing samples from premenopausal women to perimenopausal women within the same research center; average estradiol levels were statistically higher in perimenopausal women (4). Not one of the primary studies from which these data were extracted had the power to see significant differences or even noted these higher levels (4). Most remarkably, the cross-sectional analysis of data from an excellently designed, population-based study of perimenopausal women aged 45-55 was summarized as a "decrease in E2. . .levels" (19), despite abnormally high and hugely variable follicular phase serum estradiol levels (Figure 4). This inability to "see" data other than what is expected (20) appears to persist, especially about the higher estradiol levels of perimenopause.

The meta-analysis, previously mentioned, of follicular and premenstrual estradiol levels from studies published before 1998 showed that perimenopausal mean serum estradiol levels are 29% higher in the follicular phase and 22% higher in the premenstruum than in premenopausal women (4). We now know that estradiol levels are dramatically higher in some cycles and for some of the time (21). Although it is hard, yet, to put into a population perspective, in their prospective observational study, Hale and colleagues estimate that about a third of all menopausal transition cycles show evidence of "luteal out of phase" (LOOP) events, meaning, as shown in Figure 5, that a second, and usually higher estradiol peak appears after the normal midcycle estradiol peak (21). It is not yet known whether LOOP events are the primary explanation for the erratically higher estradiol levels of perimenopause.

3.2. Progesterone, ovulation and luteal phase changes in perimenopause

By contrast with the higher levels of estradiol, lower levels of progesterone characterize perimenopause. These lower levels arise through three mechanisms: 1) decreased progesterone production within normal-length ovulatory cycles; 2) shortened luteal phase lengths within ovulatory cycles; and 3) more frequently anovulatory cycles. The evidence about perimenopausal changes in ovulation and luteal phase lengths are sparser than the now extensive literature on the higher and erratic estradiol levels of perimenopause, and none are from population-based samples (22). Early observers such as Metcalf using once/week urinary pregnanediol excretions (PdG) documented that only 37% of irregular perimenopausal cycles were ovulatory (23). Likewise using classical (non-quantitative) basal body temperature, Doring showed that ovulatory cycles only occurred in 50% of cycles in women ages 46-50 (24), and Vollman by quantitative basal

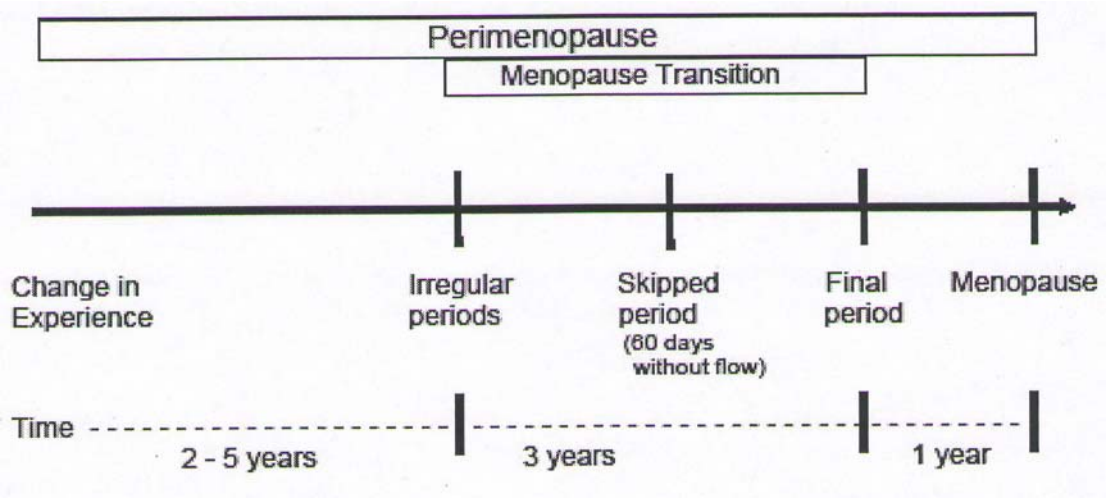

Figure 2. This figure illustrates women's reproductive aging and the midlife transition from reproductive to non-reproductive status, including definitions of perimenopause and menopause used in this review.

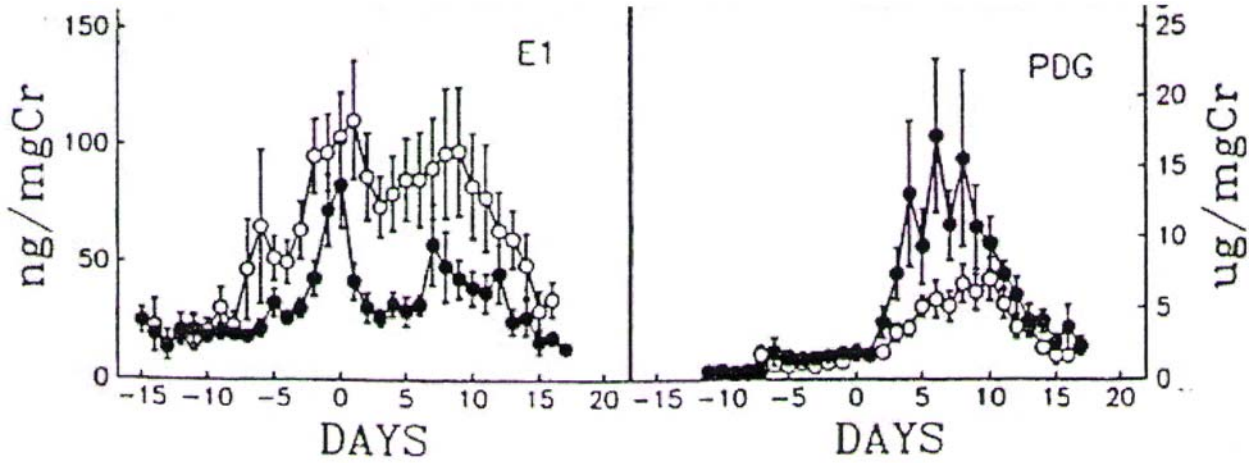

Figure 3. Daily urinary hormone data in a cross-sectional single-cycle study showing that urinary estradiol excretions are higher and progesterone excretions are lower in regularly cycling perimenopausal (open circles) compared with premenopausal (closed circles) women. Reproduced with permission from (51).

temperature (QBT) (25) noted ovulatory disturbances (meaning short luteal phases and/or anovulatory cycles) were significantly increased with increasing gynecological age over 35 years. Illustrative prospective QBT data that are valid against PdG, in one woman with regular cycles documented over more than 10 years showed that, in cycles that averaged 29±2 days long, only a single cycle out of a series of 14 had a short luteal phase length (8%) with no anovulatory cycles when she was in her mid-30s. However, 10 years later her regular cycles were shorter (27±2 d) but now 86% of cycles showed short luteal phases and 14% were anovulatory (22).

Several longitudinal studies have monitored ovulatory characteristics in perimenopause. Hale and colleagues from Australia (26) used thrice-weekly serum samples over a single cycle in a convenience sample comparing four groups: mid reproductive (controls), late reproductive, early menopausal transition, and late menopausal transition (26). They found lower progesterone levels in perimenopausal ovulatory cycles as well as higher estradiol levels (26). Other studies have used analysis of urinary hormone metabolites, which are more easily obtained, but absolute levels must be interpreted with caution, because of genetic variability in steroid metabolism (33).

Miro and colleagues presented the results of the British FREEDOM study (Fertility Recognition Enabling Early Detection Of Menopause), a convenience sample using daily first morning urines provided by 103 women prospectively studied over six to 18 months (27). Results showed that some women with increased urinary FSH levels but still regular cycles had higher PdG excretions than did women who were premenopausal, however, luteal phase lengths are not described (27). In

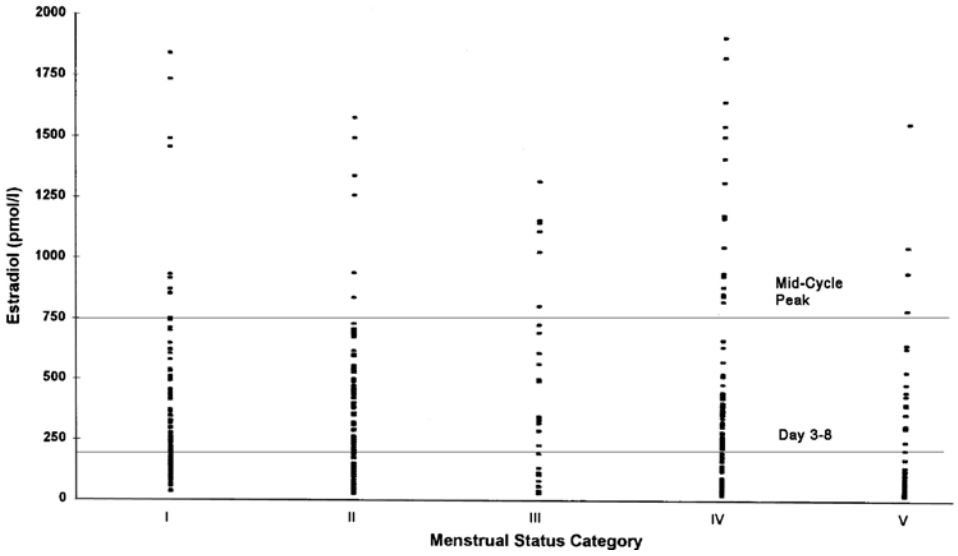

Figure 4. Serum estradiol levels from a cross-sectional population-based sample of women ages 45-55 organized by categories: I. no changes in cycle length or flow, II. changes in flow only; III. changes in cycle length only; IV. changes in both flow and cycle length; and V. those who were three to 12 months since the last menstruation. The figure is adapted from Burger and colleagues (19). Two added lines indicate the mid-follicular mean of estradiol levels and the mean midcycle peak estradiol levels as established in the same laboratory in premenopausal women.

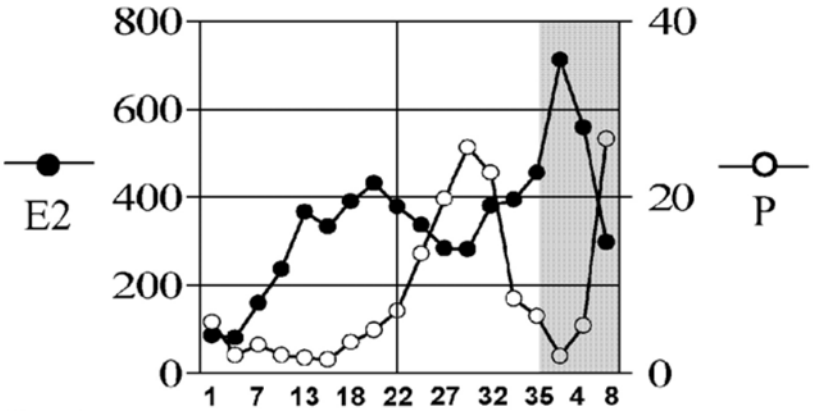

Figure 5. Aberrant and extremely high estradiol levels occur during the luteal phase of ovulatory perimenopausal cycles. These luteal out of phase (LOOP) events appear to occur in about one-third of cycles in the early and late menopausal transition stages of perimenopause. Reproduced with permission from (21).

general normal-length ovulatory cycles had higher PdG levels than "delayed" ovulatory cycles in what would be the early menopause transition by STRAW. In subsequent reproductive stages PdG decreased as estrogen excretions (E1G) increased (27).

The Study of Women Across the Nation (SWAN) prospectively followed a multiethnic cohort of over 3,000 women ages 42-52 from seven centers in the USA. Some were invited to join a daily hormone sub-study; of these, 840 collected daily first morning urines for 50 days/y. The majority of cycles (81%) met criteria for being ovulatory (28; 30). Women with ovulatory cycles were further separated into those who were still menstruating regularly (late reproductive age) and those who had skipped a menstrual period. Within ovulatory cycles, women in late menopausal transition had higher excretions of gonadotrophins, lower PdG and no difference in E1G (30). Anovulatory cycles were separated into three forms: normal midcycle peak of estrogen followed by an LH peak but not by PdG, a normal midcycle estrogen peak not followed by an LH peak, or no evidence of usual midcycle events suggesting that anovulation and low progesterone production were related to various kinds of hypothalamic-pituitary ovarian feedback disturbances (28). Of women starting with regular ovulatory cycles, having oligomenorrhea and anovulation (in data truncated at 50 days) was a strong predictor of being in the late perimenopause stage. In regular cycles, anovulation continued at about 10% of all cycles. However, within

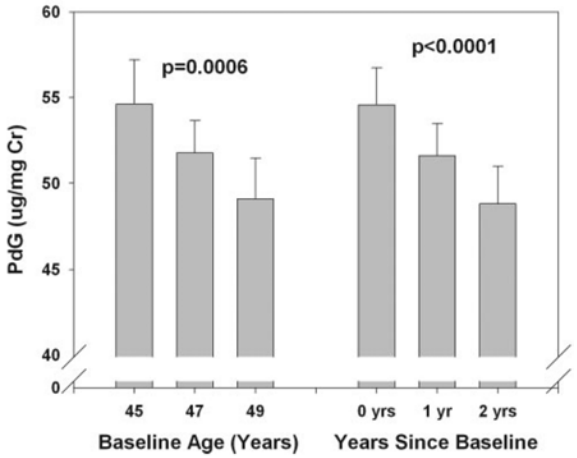

Figure 6. Urinary progesterone excretion (PdG) levels over time by age and years since baseline in the Study of Women across the Nation. Reproduced with permission from (29).

ovulatory cycles PdG levels decreased by about seven percent per year (29; Figure 6). Obesity and greater education were associated with lower PdG levels (29).

Finally, the Biodemographic Model of Reproductive Aging (BIMORA) study of the Tremin longitudinal menstrual cycle data collection in college-educated Caucasian women asked 156 women to collect daily first morning urines over six months (January to July) yearly for five years (31). Assessment of gonadal steroids primarily focused on reporting estrogen excretions that were not counterbalanced by PdG—this "unopposed" estrogen exposure increased during the menopausal transition because the 95th percentile for estrogen remained the same while ovulatory cycles and the amount of PdG were decreasing (32). This perimenopausal increased estradiol to progesterone ratio is similar to the observations made earlier by Metcalf and MacKenzie (34).

In summary, in perimenopause both older studies employing QBT and more recent studies monitoring serum and urinary hormones have found decreasing levels of progesterone within ovulatory cycles and a rising incidence of ovulation disturbances. Ovulatory cycle progesterone production decreases gradually but continuously with progress toward menopause. Estrogen production unopposed by appropriate progesterone production has been documented in one of the earliest (34) as well as one of the most recent studies of the endocrinology of perimenopause (32). In contrast to menopause, when both estrogen and progesterone are low, in perimenopause the two primary ovarian steroids are changing in opposite directions—estradiol levels higher and progesterone levels lower. These changed ovarian steroid hormone levels and ratio would be expected to increase women's risk for both endometrial (35) and breast cancer (36). It remains to be seen what contribution these changing steroid ratios make to women's midlife experiences and risk factors for subsequent menopausal health.

4. HYPOTHALAMIC-PITUITARY-OVARIAN FEEDBACK CHANGES OF PERIMENOPAUSE

Recent research has clarified that the primary hormonal changes of perimenopause result not only from the "aging ovary" but also from disruption of the usual positive and negative hormonal and paracrine feedback networks controlling the normal ovulatory menstrual cycle. The evidence for these changes in control mechanisms will now be briefly discussed.

4.1. Inhibin and control of perimenopausal follicle stimulating hormone (FSH)

We initially postulated that the higher estradiol levels in midlife women represented "perimenopausal endogenous ovarian hyperstimulation" (4). The term "endogenous" indicates that these changes occur from within a woman's reproductive system. The term "ovarian hyperstimulation" is used by analogy with that of ovulation induction for *in vitro* fertilization that can create extreme estradiol levels and medical emergencies. Higher estradiol levels normally act to suppress rising FSH levels; in perimenopause this feedback fails, particularly at the follicular-luteal transition.

The prime mover in the feedback disruptions that result in the hormonal changes of perimenopause is now confirmed to be Inhibin B. At the point at which each ovary contains fewer than 100 follicles (2), Inhibin B levels, made by small antral follicles, decline and no longer hold early cycle FSH level in check. This, in turn, leads to increased recruitment of follicles, each of which contributes to the increasing estradiol levels. Important prospective studies in a few women show decreases in Inhibins A and B and progesterone levels but maintained estradiol productions (37). That observation has been confirmed with sophisticated multiple linear regression studies of FSH and luteinizing hormone (LH) and their relationships with Inhibins A and B and their complex relationships with estradiol and progesterone (37; 38). These studies confirm the role of declining Inhibin B levels in allowing FSH to rise in the follicular phase. Elevated FSH, in turn, appears to stimulate the second estradiol peak called LOOP during the luteal phase (38). Because normally ovulatory progesterone levels may prevent a further cohort of follicles from becoming stimulated enough to cause a second mid-cycle like estradiol peak, this is further evidence of hypothalamic-pituitary-ovarian feedback disruption.

Although there are yet no clear feedback roles for anti-Mullerian hormone (AMH) in the feedback and control of perimenopausal changes, several studies from the same Australian group highlight the dropping levels of AMH across the perimenopausal transition (26; 38). Anti-Mullerian hormone is produced by granulosa cells from small follicles and levels are parallel with the number of remaining ovarian follicles as measured by antral follicle counts (on transvaginal ultrasound). Research suggests that AMH is highly reproducible at the same cycle phase (39), and is basically stable across the menstrual cycle (40). In addition, AMH levels decline over time in within-woman studies at ages 36 and 40 (41). It appears clear that lower

AMH levels provide a more reliable biomarker of approaching menopause than any other known measure (42). However, at the present moment whether or not AMH plays a role in the disturbed hormonal feedback loops in perimenopause is unknown (38).

4.2. Feedback loops, ovulation and the luteinizing hormone (LH) peak

The just discussed FSH changes relate to the control of estradiol in both the follicular phase, and also during the luteal phase in the form of LOOP events. However, there are additional changes in the control of ovulation and progesterone production that appear to relate more to the hypothalamic-pituitary-axis than to ovarian aging. An elegant description of SWAN daily urinary hormone data in cycles without evidence of luteal activity (anovulatory) shows that both estradiol and LH peaks can be normal but ovulation still not occur (28). One might speculate, given the strong negative associations between FSH (controlled for LH) and progesterone shown in the Australian analysis, that higher FSH levels might interfere with release of an egg and progesterone production (38). That phenomenon also can occur in premenopausal cycles but appears to be more common in perimenopause.

Additional perimenopausal feedback imbalances leading to anovulation involve disturbances of estradiol's positive feedback on LH such that a normal estradiol peak occurs but an LH peak does not follow (28). Finally, cycles may have no evidence of either an estradiol or an LH peak despite high follicular phase estradiol levels—there is also no ovulation (28). Thus there can be no doubt that the hypothalamus or pituitary can become insensitive to estradiol feedback resulting in anovulation.

5. ADDITIONAL PERIMENOPAUSE HORMONAL CHANGES—CORTISOL AND CATECHOLAMINES

To our knowledge there are no prospective studies of the autonomic and sympathetic system and cortisol stress hormone changes across the perimenopause. It is accepted that perimenopausal women are more likely than premenopausal women to report "mood swings" and various symptoms (tachycardia, chest pain, dry mouth, tingling, panic attacks) that are related to a stress response—further research should investigate whether associated hormones such as cortisol or Adrenocorticotrophic Hormone (ACTH) and/or sympathetic nervous system responses (such as norepinephrine) also show increases during perimenopause.

Moreover, the most symptomatic women in perimenopause even more commonly describe stress-related symptoms. Given this, it would be surprising if cortisol and catecholamine levels were not higher in symptomatic perimenopause, and higher levels of estrogen may be responsible. In an experimental study, healthy young men wore either a transdermal estradiol patch or placebo and 24-48 hours later were subjected to the Trier Social Stress Test (43). Those men wearing the estradiol patch experienced greater increases than controls in cortisol, ACTH and norepinephrine to the social stressors of the testing (43). Elevated endogenous estradiol is a potential mechanism to explain the experience women have of being less able to cope with stress than they were earlier in their lives. However, further changes in hypothalamic-pituitary responses may also play a role. Certainly women with disturbed sleep and vasomotor symptoms may experience greater stress hormone responses (as discussed below).

6. PERIMENOPAUSAL HORMONAL ORIGINS FOR COMMON EXPERIENCE CHANGES

There is a shared hope among physicians and midlife women that "a test" will tell them whether or not they are in perimenopause, if they are now menopausal (if they have had a hysterectomy, for example), or how close they are to becoming menopausal. Some physicians use the level of serum FSH level early in the cycle (say cycle day 3) as a test for perimenopause. For an individual woman, however, FSH is neither sensitive nor specific (44). There are hopes that the AMH will prove to be useful for deciding about proximity to menopause but further validation is needed.

The hypothesis that elevated perimenopausal estradiol levels were behind perimenopausal experiences was based on clinical observations of estrogen-associated experiences (increasingly heavy flow, increased premenstrual symptoms, mastalgia, fluid retention, weight gain) in cycles documented with the Daily Perimenopause Diary (45) and QBT (46). Cycle lengths tend to shorten in older, regularly menstruating women and the follicular phase becomes shorter (47). Shortened follicular phase lengths are associated with higher early cycle serum estradiol levels (16) and with higher urinary FSH levels in both follicular and late luteal phases (48).

6.1. Heavy menstrual flow

The best evidence linking symptoms to high estrogen comes from the analysis of very heavy flow (menorrhagia) (5). In a clinical study, 28 women over age 40 with heavy and/or heavy irregular flow were age-matched (± 2 years) with 28 women with regular cyclical bleeding. Estradiol and FSH levels were measured in a standardized way in all women showing that, although FSH levels were not different, estradiol levels were almost doubled in those with heavy flow (5). Twenty of the women with heavy flow had endometrial biopsies and 50% of these showed endometrial hyperplasia, also suggesting progesterone deficiency may have played a role in the heavy flow (5).

A recent quantitative study of the amount of flow during two consecutive menstruations in the Australian study by Hale and colleagues shows that flow increases in absolute amount and in variability from mid- to late-reproductive and across until the late menopausal transition (49). Flow was over 250 ml/menstrual period in women in the late perimenopause who experienced an ovulatory cycle with very high estradiol levels or the unique LOOP phenomenon (49). Thus two studies strongly associate

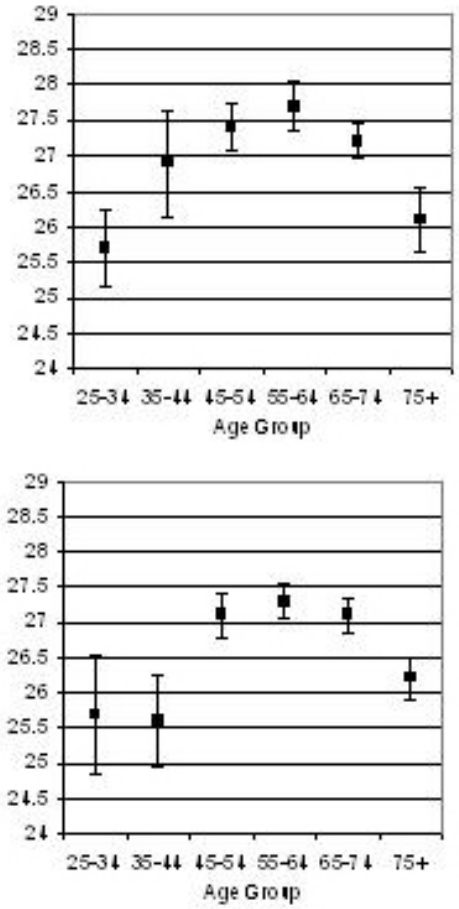

Figure 7. Body mass index (BMI) changes in men (left) and women (right) in the population-based Canadian Multicentre Osteoporosis Study. Note the gender difference in the pattern with a marked increase in the ages 45-55 decade for women. Reproduced with permission from (49).

higher estradiol levels with clinically and absolutely heavy menstrual flow (5; 49).

Although heavy flow in perimenopause is commonly attributed to fibroids, it is rare for this benign tumor, originating in the uterine muscle, to impinge on the endometrium. Rather heavy flow and fibroids co-occur because both are associated with higher estradiol and lower progesterone levels.

6.2 Increased premenstrual symptoms

We have previously suggested that the midlife increase in premenstrual symptoms is a result of the higher estradiol levels of regularly cycling women in very early perimenopause (50). Increased premenstrual symptoms also predict night sweats or hot flushes (51; 52). In healthy ovulatory young women (mean age 33), we found no hormonal relationship, however, with premenstrual mood symptoms (53). Although the exact combined hormonal and sociocultural etiologies of premenstrual symptoms are unclear, prospective within-woman data relate them to cycles with higher estradiol/lower progesterone levels (54) that are characteristic of the ovarian hormone changes in perimenopause. However, studies are inconsistent and contradictory, and the relationship between mood and hormones is not clear.

6.3. Weight gain

Whether or not the metabolic changes (weight, body mass index [BMI], waist circumference, blood pressure and cardiovascular adverse lipid changes) that increase in midlife women bear any relationship to the hormonal changes of perimenopause is currently unclear. The prospective daily urinary hormone study in SWAN found, however, that estradiol levels were not different in those with and without a diagnosis of the metabolic syndrome (29). What is quite clear, however, is that the BMI increases that occur in the population across ages 25-50 differ in men and women (55; Figure 7). Using prospective data from the randomly selected men and women in the 9243-strong Canadian Multicentre Osteoporosis Study, men have a gradual BMI increase after age 25 whereas women's BMI remains stable until it increases dramatically between ages 35-44 and ages 45-54. The majority of women ages 45-54 in the population will be in perimenopause, given that menopause occurs on average at age 52 in women without hysterectomy or ovariectomy (55). This is a strong suggestion that there are gender differences in the metabolic changes that occur during the 40s and 50s.

6.4. Night sweats/hot flushes

Although night sweats are often labeled as "estrogen deficiency symptoms", they are present in midlife women who continue to have regular menstrual cycles (and usually called "premenopausal" in surveys) (45). The initial large survey of hot flushes in women noted that seven women volunteered that their night sweats were cyclic and occurred around flow (56). In an observational study of Daily Perimenopause Diary© data from our laboratory, we observed not only that night sweats predominated over daytime hot flushes/flashes (vasomotor symptoms, VMS) but that they had a cyclic character with increased prevalence before or during menstruation (45). Whether night sweats occur in cycles with greater downward estradiol swings and higher average estradiol levels, as we postulate, is not currently known—we are currently performing a daily urine study to explore hormonal relationships with night sweats in very early perimenopausal women with regular cycles.

7. PERIMENOPAUSAL HORMONAL CHANGES AND FUTURE HEALTH RISKS

7.1. Cardiovascular disease

Heart diseases and stroke (together called cardiovascular disease or CVD) are considered by health experts to be the leading killer of women in North America although they don't enter most perimenopausal women's consciousness and predominantly occur for much older women. However, it is important to ask the question whether the hormonal changes of perimenopause increase or decrease the risks for menopausal CVD. If the notion were correct that estrogen treatment earlier rather than later

in menopause is protective against CVD, one could postulate that those with the highest perimenopausal endogenous estradiol levels would have the least subsequent CVD. Unfortunately, to date, no studies that have carefully characterized endogenous estradiol levels or tracked estradiol/estrogen treatment in perimenopause have subsequently observed the cohort for the development of CVD.

However, there are new data suggesting that lower perimenopausal progesterone levels may be related to subsequent CVD. Before sharing data from that study it is useful to remember there are mechanisms through which progesterone may decrease CVD. Intra-arterial progesterone compared with intra-arterial estradiol has been shown to equally improve endothelial function in a random-ordered vehicle-controlled experiment in 28 healthy women who were recently menopausal (57). Oral micronized progesterone also lowers blood pressure (58) and appears lipid neutral when given with estradiol (59). The strongest data relating progesterone to subsequent CVD are from a nested case control study from the Netherlands in which menstruating women of mean age 47 collected first morning urines for hormone levels on cycle day 22 of three consecutive cycles in 1982-86. All new myocardial infarctions among women in the same community were observed through 1991 to determine perimenopausal CVD risks (60). Forty-five women had acute myocardial infarction and in these versus controls, estrogen and testosterone excretions and other reproductive variables did not predict heart attacks over approximately eight years (60). However, those with lower progesterone levels and with probable anovulatory cycles tended to be more likely to have a heart attack during follow-up (smoking-adjusted odds-ratio: 1.3, 95% CI 0.3-3.7). With longer follow-up and an increased incidence of heart attack these data are likely to become stronger.

7.2. Breast and endometrial cancer

In contrast to CVD, midlife women are very concerned about breast cancer because most women have known someone who developed it or died from it. Given that two randomized controlled trials show that breast topical estradiol treatment stimulates and progesterone treatment inhibits human breast cell proliferation and cell division (61; 62), the increased frequency of perimenopausal days of estradiol unopposed by progesterone (32; 34) should increase breast cancer risk. Consistent with those data, higher perimenopausal progesterone levels in a case-control study were associated with a lower risk for breast cancer in the European Prospective Investigation into Nutrition and Cancer study (odds-ratio: 0.61, 95% CI 0.38, 0.98) (63). Finally, women in their 40s (mostly perimenopausal) are more likely than women in their 50s (mostly menopausal) to develop interval breast cancer between screenings (64; British Columbia Cancer Agency data). The strongest data suggesting that the lower progesterone levels of perimenopause may pose a breast cancer risk are from the large E3N cohort in which menopausal women treated with estradiol without progesterone had an increased breast cancer risk that did not occur when estradiol plus progesterone was the treatment (36).

Perimenopausal women appear little concerned about endometrial cancer, perhaps because it is less prevalent than breast cancer. Unopposed estrogen as a pharmacological therapy is a well recognized risk factor for endometrial cancer. Metcalf and MacKenzie (34) and O'Connor and colleagues (32) found that endogenous estrogen unopposed by progesterone was common in perimenopause. In addition, perimenopause has been identified as a "window of risk" for endometrial cancer (35). Further research is needed into whether perimenopausal exposure to high estradiol and low progesterone levels predicts subsequent risk for endometrial cancer.

7.3. Osteoporosis and fracture risks

Although the common belief has been, and still may be, that bone loss and fractures begin in women with estrogen deficiency who are menopausal, there is incontrovertible evidence that rapid bone loss begins in perimenopause (65-68). This is a paradox because of the higher estradiol levels earlier outlined. However, these observations fit perfectly with newer understandings of bone physiology—downward swinging estradiol levels release cytokines and increase RANKL that causes increased bone resorption. In a meta-analysis of spinal bone change observed in perimenopausal versus women early in menopause we documented a mean rate of bone loss of –1.8% per year in perimenopause that exceeded the rate of –1.2 % in early menopausal women (4).

Although it is predominantly bone resorption that determines bone loss and fracture (69), it has becoming increasingly clear that endogenous progesterone levels increase bone formation and contribute with estradiol to positive premenopausal bone change (70-72). An ongoing prospective study in Munich is documenting QCT spinal bone change prospectively (67). This group is now observing the prevalence of ovulatory cycles in relationship to bone change and showing greater bone loss in those with fewer normally ovulatory cycles (73). These data strongly suggest that the perimenopausal years—with swinging estradiol levels leading to increased bone resorption and lower progesterone levels causing less formation—set the stage for menopausal osteoporosis and fracture.

8. SUMMARY AND PERSPECTIVE

This review has presented evidence that demands a shift in the paradigm about perimenopausal changes. Perimenopausal women are not estrogen deficient; rather they have physiologically high and erratic levels of estrogen. Many of the clinical presentations of perimenopause are related to these high levels of estrogen, particularly heavy menstrual bleeding, breast tenderness and an increased response to psychological stressors. Moreover, perimenopausal estrogen is also poorly suppressible, because of impaired feedback mechanisms. The second ovarian hormone, progesterone, is largely ignored in the literature, but is clearly low compared with what was normal earlier in life. Lower progesterone levels or the abnormal ratio of estrogen and progesterone also likely causes many perimenopausal symptoms.

In the absence of relevant perimenopausal clinical trials, clinicians have extrapolated from studies of menopausal women to menstruating perimenopausal women whose hormonal circumstances are very different. The practice of prescribing estrogen (as menopausal hormone therapy, or as oral contraceptives) to perimenopausal women makes little physiological sense, and may cause harm. A few clinicians (including the first author) have instead prescribed progesterone as a monotherapy in perimenopause. Clinical trials have demonstrated that progesterone and progestins are effective therapies for heavy flow and progesterone improves sleep fragmentation. In clinical practice progesterone has also proved effective for many other issues in perimenopause, especially hot flushes. Clinical trials are needed to address other therapeutic uses of progesterone as a monotherapy in perimenopause.

The hormonal changes of perimenopause plus the onset of the reduced social status associated with aging in western culture make perimenopause a complex transition. However, it can also be a time of increased self-awareness and adaptation that can bring women feelings of improved self-worth. Should the perimenopausal changes that women notice not be explained and appropriately named, this can interfere with potential adaptation and resilience (74). There is urgent need for controlled trial research into therapies for the consequences of perimenopausal endocrine changes. A number of the current medical responses to perimenopausal symptoms and signs are no longer appropriate. For example, when a perimenopausal woman is told that she is "too young" to be having night sweats, or that she must be imagining things if she becomes symptomatic while she is still regularly menstruating, when her heavy flow is treated with hysterectomy rather than proven non-surgical strategies (7), when she is given therapies such as combined hormonal contraceptives with additional estrogen that add to her already erratically high endogenous estrogen, there may well be harm (6). Even within a purely clinical framework, the use of ineffective therapies or ones that make women feel worse have the potential to damage the clinician-patient relationship going into midlife and thus to decrease the potential for healthy aging. Within the broader context of women's lives and of recent perimenopausal endocrine research findings, there needs to be a paradigm shift.

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Abbreviations: LH, luteinizing hormone; FSH, follicle stimulating hormone; QBT, quantitative basal temperature; QCT, quantitative computed tomography (for bone density); AMH, anti-Mullerian hormone; ACTH, adrenocorticotrophic hormone; PdG, pregnanediol glucuronide; E1G, estrone glucuronide; STRAW, Stages of Reproductive Aging Workshop; FREEDOM, Fertility Recognition Enabling Early Detection Of Menopause; BIMORA, Biodemographic Observations in Reproductive Aging; LOOP, luteal out of phase; VMS, vasomotor symptoms (hot flushes/flashes and night sweats); CaMOS, Canadian Multicentre Osteoporosis Study; BMI, body mass index = kg/m^2

Key Words: Perimenopause, Estradiol, Progesterone, Inhibin B, LH, FSH, AMH, Menorrhagia, Cyclic VMS, LOOP, diagnosis, CVD, Breast Cancer, Endothelial Cancer, Osteoporosis, Menopause, Review

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