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Review

The perimenopausal woman: Endocrinology and management

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ABSTRACT

This review focuses on the endocrine and physiological features of the transition to menopause, known as the menopausal transition or the perimenopause. The updated 2011 Stages of Reproductive Aging workshop (STRAW) system is presented with a discussion of the new subdivisions within stages −3 (late reproductive age) and +1 (postmenopause) and incorporation of FSH and other biomarkers in the supportive criteria. Ovarian follicle reserve and ovarian follicle dynamics are also discussed in terms of the changes that occur with reproductive aging, and the dramatic effect these changes have on the hypothalamic-pituitary-gonadal feedback system. Topics include the disruption of normal ovulatory function and related hormone secretion patterns, abnormal uterine bleeding, and the changes that occur in bone and the cardiovascular system. The review concludes with a discussion of management strategies.

This article is part of a Special Issue entitled 'Menopause'.

Contents

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1. Introduction

From a practical and clinical standpoint, a woman may be termed perimenopausal if at an appropriate age (usually ≥45), she experiences menstrual cycle changes and symptoms suggestive of the approach of menopause. The experience that officially meets the criteria for entry into the perimenopause or menopause transition is the onset of variable length menstrual cycles [see below for the specific menstrual criteria of the Stages of Reproductive Aging Workshop (STRAW) system]. Several years before this in late reproductive age, many women experience a discernible decrease in cycle length (mean cycle length of 25–26 days instead of 28–29 days) [1–3], then once they enter the perimenopause, cycle length can vary between about 14 and 50 days [4–6]. Such variable length cycles prior to menopause however are not the rule and between 15% and 25% women report very little change in their menstrual cycles before cessation of bleeding [7–9].

The majority of women experience at least mild symptoms along with changes in the menstrual cycle in late reproductive age and the menopause transition [10–14]. Even prior to the early perimenopause, just over half of women begin to experience symptoms such as headache, joint aches or stiffness, back pain, waking at night, night sweats, hot flushes and difficulty concentrating [13,15]. Breast tenderness is common but becomes less prevalent with progression to the final menstrual period (FMP) [15,16]. In a large British cohort, around 10% women experienced severe vasomotor symptoms (VMS) before the perimenopause and with the onset of perimenopause up to 30% reported severe VMS. Vasomotor symptoms usually worsen with progression from early to late perimenopause before subsiding 1–3 years after the menopause [12].

In the following sections, the 2011 revisions to the STRAW staging system are presented, followed by a review of the normal female reproductive cycle in terms of ovarian and endocrine function and a description of the changes which occur as menopause approaches, Particular attention will be given to the endocrine features and ovarian dynamics underlying the progression from regular cycles, to variable length and irregular cycles and then finally to the cessation of cycles.

2. Stages of Reproductive Aging Workshop (STRAW) criteria: an update

The World Health Organization (WHO) has held two working groups on menopause since 1980 to review the state of menopause research, including clarification of the nomenclature for women's reproductive aging and to propose 'stages' of reproductive aging. In this early WHO definition, the term "menopause" described the stage that begins 12 months after the FMP (also termed "postmenopause") and the "perimenopause" as the time of onset of symptoms of approaching menopause and up to a year following the FMP [17]. The WHO staging nomenclature was revised at the 2001 Stages of Reproductive Aging Workshop (STRAW) [18] and then further revised ten years later, at the STRAW + 10 ReSTAGE Collaboration (Fig. 1) [19]. The STRAW and now the STRAW + 10 are internationally recognized staging systems for characterizing reproductive aging and providing a consistent classification of reproductive status in midlife women for use in clinical and research settings.

Menstrual cycle patterns are the principal criteria employed in both the STRAW and STRAW + 10 systems and in both, the FMP is the central reference '0' point for '−' and '+' stages. Subjective data such as menstrual flow changes or hot flushes and night sweats were considered too subjective and variable (particularly between ethnic groups) to be included in the criteria. Vasomotor symptoms have however since been included in the STRAW + 10 criteria as 'supportive criteria'. While it was advised that the STRAW system was not applicable to smokers, obese (BMI >30) or underweight (BMI <18) women, and intense exercisers, these exclusions were abolished from the STRAW + 10 criteria. While neither STRAW nor STRAW + 10 used age as a criterion, at the ReSTAGE meeting, it was recommended that the STRAW + 10 criteria not be used in women under 40 years of age with suspected primary ovarian failure (4 months amenorrhea and 2 menopause-range FSH levels taken a month or more apart), because reproductive aging in these individuals has been found to be highly variable compared to normal individuals. The Re-STAGE meeting also recommended that STRAW + 10 would not be reliable or applicable in women with a history of hysterectomy or ablation, PCOS, chemotherapy or chronic disease such as HIV and AIDS.

The 2001 STRAW system included five stages prior to (−5 to −1), and two stages after the FMP (+1 and +2). In the updated 2011 STRAW + 10 system, stage −3 (late reproductive age) was further divided into −3b and −3a, and stage +1 was further divided into +1a, +1b and +1c. Stage −3b is characterized by regular menstrual cycles and normal early follicular phase FSH levels and stage −3a, by shortened cycle length (but not meeting stage −2 criteria, early menopause transition) and elevated early follicular phase FSH levels. The criterion for stage −1 was unchanged in the updated STRAW + 10, and it begins after the observation of at least one episode of amenorrhea lasting 60 days or more. For early postmenopause, both +1a and +1b were estimated to last about 12 months each (based on the fact that there are ongoing changes in FSH and estradiol levels for at least 24 months after the FMP), and +1c represents the period of hormonal stabilization, estimated to last 3–6 years. In addition, the criteria for stage −2, the definition for entry into the early menopause transition was refined as the onset of menstrual cycle length variability with a persistent difference of 7 days or more in the length of consecutive cycles, with the persistence being defined as at least one recurrence within 10 cycles of the first variable length cycle.

Although FSH measurements are known to be unreliable (particularly with the onset of the perimenopause), and thus of limited use as 'diagnostic criteria' in the reproductive stages, the ReSTAGE acknowledged recent data from large cohorts such as the SWAN [20] and improved assay standardization, and included elevated early follicular phase FSH levels as a supportive criterion for entry into stages −3a and −2. FSH levels of >25 IU/L were also included as a supportive criterion for entry into stage −1, the late perimenopause. Although AMH and AFC were considered to be promising reproductive aging biomarkers, their use in the STRAW system will remain limited until the widespread availability of standardized assays. 'Low' AMH levels were included in the new STRAW + 10 system as a supportive criterion from stages −3b, +1a&b and 'very low' levels were included as a supportive criterion in stages +1c. The definitions of 'low' and 'very low' however were not provided in terms of quantitative levels. Inhibin B was included in the system as a supportive criterion in a similar way to AFC.

3. Reproductive aging and ovarian reserve

Central to the pathophysiology of the perimenopausal experience is the decline in number of ovarian follicles. Underlying this decline, is a complex dynamic of ovarian follicle activity and hormone production [21]. The standard in vivo or clinical method of estimating ovarian reserve is an ultrasonographic measurement of antral follicle count (AFC) [22]. Unlike hormone levels, the AFC is relatively unaffected by menstrual cycle phase [23],

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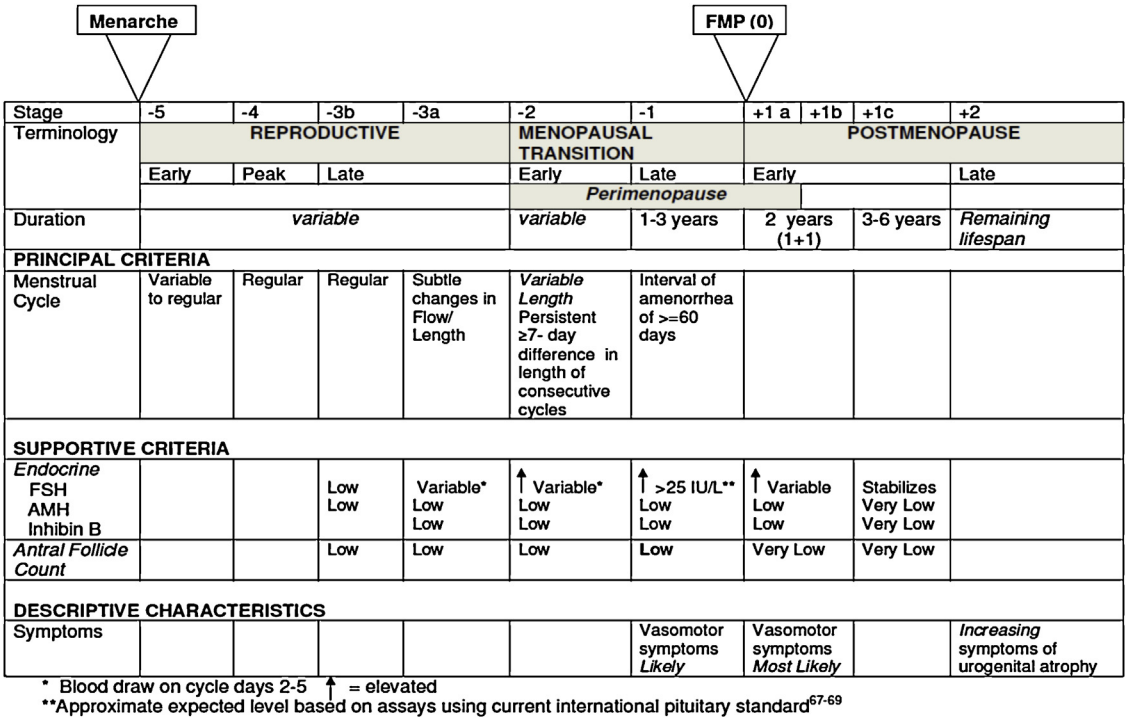

Fig. 1. The 2011 Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women.

is relatively easy to measure given the appropriate equipment and technician skills and has become a recognized and practical measure of ovarian reserve. A recent small study of 63 women categorized according to the menstrual criteria within the STRAW system ($N = 8$, 16, 33, 6 in STRAW stages −4, −3, −2 and −1, respectively) showed a clear progressive decline in AFC across the STRAW stages (Fig. 2) [24]. It has since been included into the updated STRAW + 10 system as a supportive criterion for stages −3 to −1.

Estimation of ovarian reserve in the research setting involves a histological examination of ovarian tissue and includes measurements of primordial, intermediate and primary follicles, all of which constitute estimations for the total nongrowing follicle (NGF) pool. Our current understanding of human ovarian reserve presumes that the ovary establishes several million NGFs at around five months of gestational age. By the age of thirty, the NGF population has already decreased to around 12% of the initial reserve and by forty, it is only 3% [25]. By age 50–51 at menopause, the NGF pool is almost deplete (<1500). Several studies have reported the number of NGFs at different ages in humans [22,26,27] and constructed mathematical models of the decline in NGF with age [22,28]. These studies suggest an increased rate of loss of NGFs around the age of 37 years when the NGF pool has been reduced to about 25,000 [27–30]. The increased rate has been thought due to elevated levels of FSH, but this remains unclear given functional FSH receptors are not present on primordial follicles [31]. The role of gonadotropins in the initial recruitment of primordial follicles remains unclear, as does the diminishing inhibitory influence from a depleting number of growing follicles [32]. Anti-Müllerian hormone (AMH), a member of the transforming growth factor-beta (TGF-β) superfamily of growth factors [33] is an intra-ovarian regulator of folliculogenesis and also plays a key role. It is produced by ovarian granulosa cells of pre-antral and small antral follicles and exerts a negative or inhibitory influence on the primordial to primary follicle transition [34].

4. Ovarian and hormonal mechanisms: the reproductive age menstrual cycle

The human menstrual cycle involves a highly regulated chain of neuro-endocrine phenomena which are initiated and maintained in the arcuate nucleus in the hypothalamus, the master gland for reproduction. The GnRH pulse generator within the hypothalamus is under the influence of a number of regulatory mechanisms that create a dynamic balance between excitatory and inhibitory signals. Glutamate and norepinephrine generate major excitatory signals, while GABA and endogenous opioids generate inhibitory signals [35]. Recently discovered factors, such as the RF-amide superfamily [kisspeptins, 26/43RFa, gonadotropin-inhibiting hormone (GnIH), RF-releasing peptides (RFRP)] also play a role [35]. From the time of puberty onward, the GnRH pulse generator communicates with the pituitary gland through the pulsatile secretion of gonadotropin releasing hormone (GnRH), which in turn communicates with the ovaries through the secretion of FSH and LH. At each level of this communication system, multiple neuroendocrine molecules orchestrate precise positive and negative feed-back loops, to ensure regular opportunities for fertilization. The ovary is a unique endocrine organ given its primary response to hormonal stimulation (ovulation) is complex, taking around 28 days to complete in the absence of pregnancy and results in the secretion of a multitude of steroidal and non-steroidal hormones that form the all important feed-back communication system that is so critical to maintaining the menstrual cycle.

Detailed ultrasonographic studies in animals [36–38] and humans [39–43] demonstrate that follicle development occurs in distinct developmental waves where cohorts of primary follicles (<2 mm) grow to at least the antral follicle stage (4–5 mm) or further (12–15 mm diameter). Normal cycling mid-reproductive age women have two or three developmental waves per cycle [39] occurring at precise intervals relative to ovulation. Only one developmental wave per cycle results in ovulation and this ovulatory wave typically emerges between days 2 and 10 of an existing

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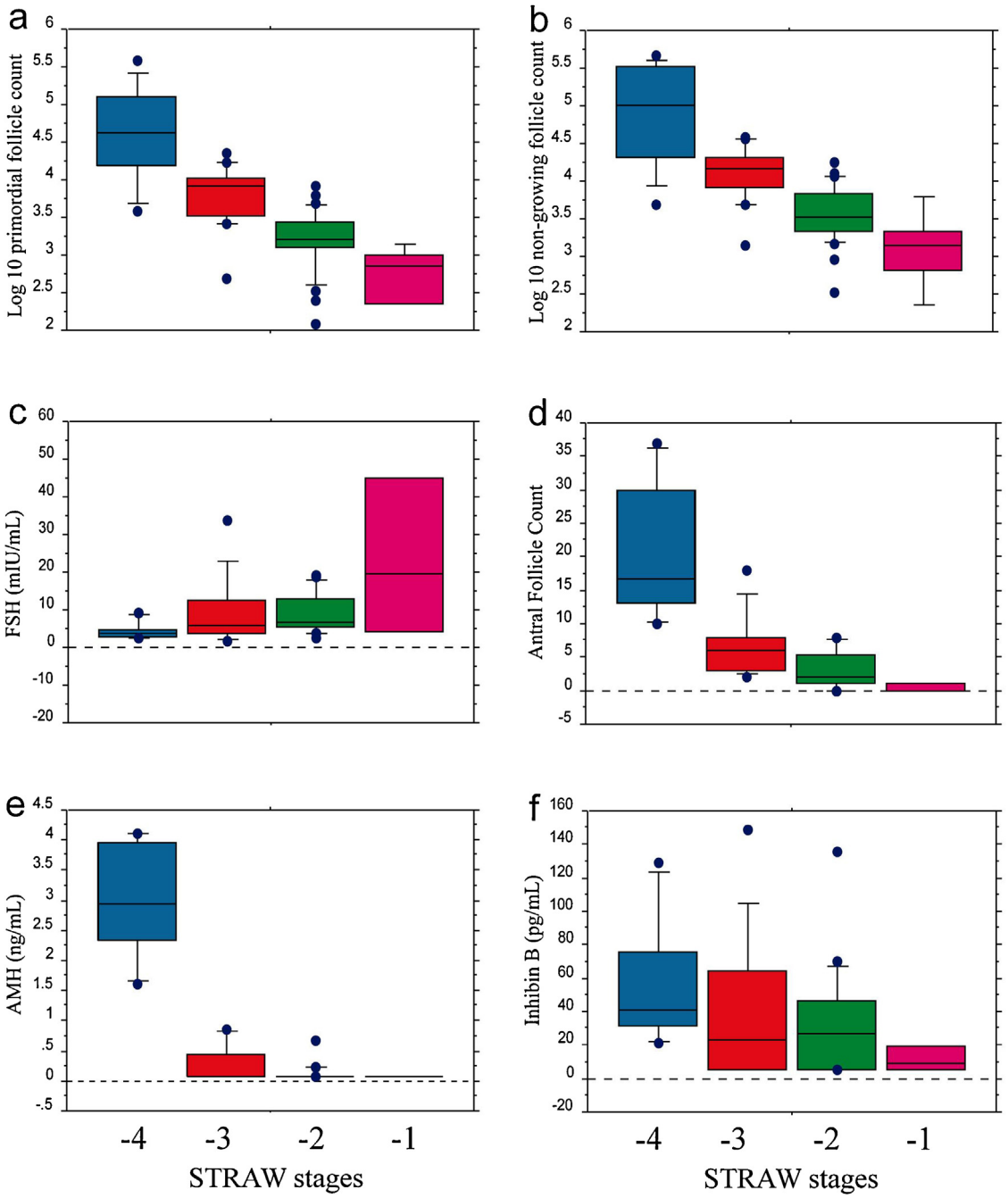

Fig. 2. Box plots of log10-transformed ovarian primordial and nongrowing follicle counts, total ovarian antral follicle counts, and biomarkers of ovarian reserve for STRAW stages −4 through −1. (A) Log10 primordial follicle count: $P < 0.0001$ between all stages except −2/−1, where $P = 0.0074$. (B)Log10 nongrowing follicle count: $P < 0.0001$ between all stages except −2/−1, where $P = 0.015$. (C) FSH: $P = 0.0036$ between stages −4 and −1; all others are not significantly different. (D) Antral follicle count: $P < 0.0001$ between all stages except −3/−2, −3/−1, and −2/−1, which are not significantly different. (E) AMH: $P < 0.0001$ between all stages except −3/−2, −3/−1, and −2/−1, which are not significantly different. (F) Inhibin B: ANOVA not significant ($P = 0.23$). STRAW, Stages of Reproductive Aging Workshop; FSH, follicle-stimulating hormone; AMH, antimullerian hormone; ANOVA, analysis of variance.

menstrual cycle [40]. All follicles in the other 'anovulatory waves' undergo atresia. The emergence of the follicular waves is preceded by small elevations in FSH (e.g.: 3–8 IU/L) but the role of these elevations in the follicle wave dynamics remain unclear. AMH is also likely to play a role in follicle wave development, but this is yet to be clarified .

Follicle growth in the early follicular phase (day 4–6), is under the control of FSH which stimulates the granulosa cells of antral follicles to produce estradiol and inhibins A&B. The resulting rise in estradiol is accompanied by a rise in inhibin B, which in turn inhibits FSH production. As FSH starts to fall in the mid-follicular phase, luteinizing hormone (LH) starts to rise. With dominant follicle selection, estradiol levels quickly rise and peak over 3–5 days and this is accompanied by a mid-cycle peak in both inhibin A&B levels. The dominant follicle is able to secrete increasing amounts of estradiol despite the rising estradiol and falling FSH. In response to the rapid rise in estradiol, the pituitary responds by releasing a surge of LH which in turn triggers ovulation. An increase in pituitary sensitivity to GnRH (and thus the quick rise in estradiol) is key to generation of the midcycle LH surge. Although the

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LH peak is the most important trigger for ovulation, the smaller peak (4-fold compared to 10-fold increase) in FSH [44,45], the small rise in progesterone [46,47] and the rise in inhibin A [48] also contribute to either oocyte maturation (FSH particularly) or ovum release. Throughout the luteal phase, the corpus luteum is the major source for estradiol, progesterone and inhibin A. If pregnancy doesn't occur, the corpus luteum regresses and this leads to a 2–4 days rapid decline in estrogen and progesterone at the end of the cycle, which in turn leads to endometrial shedding and menstruation.

Regardless of whether 2 or 3 follicle waves develop during a single menstrual cycle, one of the waves always develops during the mid-luteal phase [49]. It has been postulated that the rise in progesterone and estradiol during the luteal phase normally prevents these luteal phase waves from developing further through negative feedback at the level of the pituitary and hypothalamus. Ovarian AMH and inhibins A&B are also likely to play a role in inhibiting the progression of follicle development during the luteal phase, but the mechanisms remain unclear.

5. Ovarian and hormonal mechanisms: the approach of menopause

As primordial follicle numbers fall to a critically low level (<1000) with advancing reproductive age, levels of key components of the feed-back system also fall. As a result, a series of endocrine changes occur which disrupts the normal cyclical ovarian hormone secretion and ovulatory patterns. Given the highly coordinated interplay of ovarian, pituitary and hypothalamic hormones governing the normal menstrual cycle, this disruption is usually complex and involves a transition from predominantly normal ovulatory cycles, to predominantly abnormal ovulatory or anovulatory cycles until the final menstrual period [50]. In the perimenopause, around 20% of cycles that are 40 or less days long are anovulatory, but this increases to 80% in cycles that are more than 40 days in length [51–53].

In late reproductive age while cycles remain regular, there is a monotropic rise in early cycle FSH and women often experience slightly shorter cycles (by 2–4 days) due to a shorter follicular phase [54–58]. The changes in FSH cannot be explained by a fall in estradiol levels, because in fact many studies suggest that estradiol levels remain unchanged [59–61] or are slightly elevated in late reproductive age [62–64]. The rise in FSH has instead been attributed to a fall in antral follicle production of inhibin B which decreases in advancing reproductive age [62,65] with the AFC [66,67]. It has been hypothesized that the initial endocrine change associated with entry into the perimenopause is due primarily to the declining AFC which in turn underlies changes in feedback mechanisms regulating the ovarian-pituitary axis [68,69]. The hypothesis is based on a cycle-type classification system that was developed to distinguish late reproductive age and perimenopausal menstrual cycles where the relationship between inhibin B and FSH changed from being similar to mid-reproductive age cycles to those characterized by a critically low inhibin B level and chronically elevated FSH [69].

In late reproductive age, AMH is also reduced 2–10 fold compared to mid-reproductive age women [68,70] and although AMH is known to decrease FSH sensitivity in small antral follicles [71,72], its adverse or otherwise effects on ovulatory function in late reproductive age are unknown. Although higher follicular phase FSH is unlikely to change the timing or the interval between follicle waves, it may play a role in causing earlier dominant follicle selection [2]. Because of its minimal within-cycle variation [23,68,73], AMH can be useful in late reproductive age fertility assessments and predicting length of time to menopause [70,74,75]. It should be noted however that as menopause approaches, AMH may show marked within-cycle variation owing to the variable and limited follicle development during the follicular and luteal phases of the cycle [68].

By the early perimenopause with the onset of variable length cycles [19], AMH has dropped to almost undetectable levels [70] and inhibin B has dropped further, reflecting the diminishing NGF pool (now ~1000). The continued fall in inhibin B releases the inhibition on pituitary output of FSH, resulting in increasingly lengthy and higher elevations in FSH [62]. With residual ovarian follicles in the early perimenopause, ovulatory cycles still predominate [76,77] but high sustained FSH leads to an increase in cycle length variability by causing a combination of normal length ovulatory cycles, superimposed ovulatory cycles (LOOP or luteal out-of-phase cycles) [6] and variable length anovulatory cycles [78]. Fig. 3 illustrates hormonal data from our serum study of 77 women, where the most advanced reproductive age cycles are represented by the type 3 cycles. Compared to the earlier reproductive aged type 1 and 2 cycles, the type 3 cycles were characterized by highly variable estradiol levels on day 1–4 of the cycle in addition to variable and elevated levels during the luteal phase. Both of these characteristics are features of LOOP cycles and are associated with significantly elevated FSH and LH, low AMH and low luteal phase progesterone.

By the early perimenopause, minor elevations in LH are evident [77,79,80], but the significance of this is poorly understood. It may be caused by the fall in inhibin B [81] and could be associated with changes in sensitivity to both steroid hormones and gonadotropins at the level of the hypothalamus and pituitary [82]. The more dramatic changes in FSH and AMH may adversely affect the ability of the dominant follicle to release at the time of ovulation. Ovulatory cycle estradiol and progesterone levels appear unaffected during the early perimenopause and are similar to those in mid-reproductive age ovulatory cycles [60,83]. However when ovulatory cycles become superimposed on each other as occurs in LOOP cycles, markedly high levels of estradiol can occur [6]. Although data from the large SWAN cohort suggest that there may be a decline in estradiol with increasing age [84], the hormone sampling was only performed in the early follicular phase and the ovulatory status of the sampling cycles was unknown. The lower estradiol levels may therefore reflect the increased capture of anovulatory cycles. Most available urinary data from large and small cohorts suggest that both luteal phase and mean cycle progesterone levels decline with advancing reproductive age [20,52,80,85–87] and this concurs with a single serum study which showed a decline in luteal phase progesterone across the menopause transition [83].

In the late perimenopause, where longer cycles (≥60 days) predominate, 60–70% cycles are anovulatory. In terms of the steroid hormone secretion patterns, when ovulatory cycles do occur, the cycle may appear normal [60], superimposed on one another [6] or have an elongated follicular phase referred to as a lag phase [86]. While the early perimenopause is characterized by disturbances in the timing and regulation of ovulation, the late perimenopause is characterized by paucity of ovulation secondary to the underlying ovarian follicle depletion. In the British longitudinal FREEDOM study of daily urinary hormones in 112 women aged 30–58 years, elongated ovulatory cycles were associated with low pregnanediol glucuronide (PdG) and high estrone excretion in the luteal phase [86]. This was similar to a smaller earlier study that found low estrone and high FSH excretion during the follicular phase of elongated cycles, followed by high estrone (2–3 × normal) and low PdG excretion during the luteal phase [87]. In the late perimenopause, although AMH has fallen to undetectable levels, inhibin B often remains detectable, especially if there is still remaining follicle activity [24,68,70]. Both gonadotropins are markedly elevated and demonstrate significant cyclical variation. FSH levels can be at their most unreliable during the late perimenopause. The role that very

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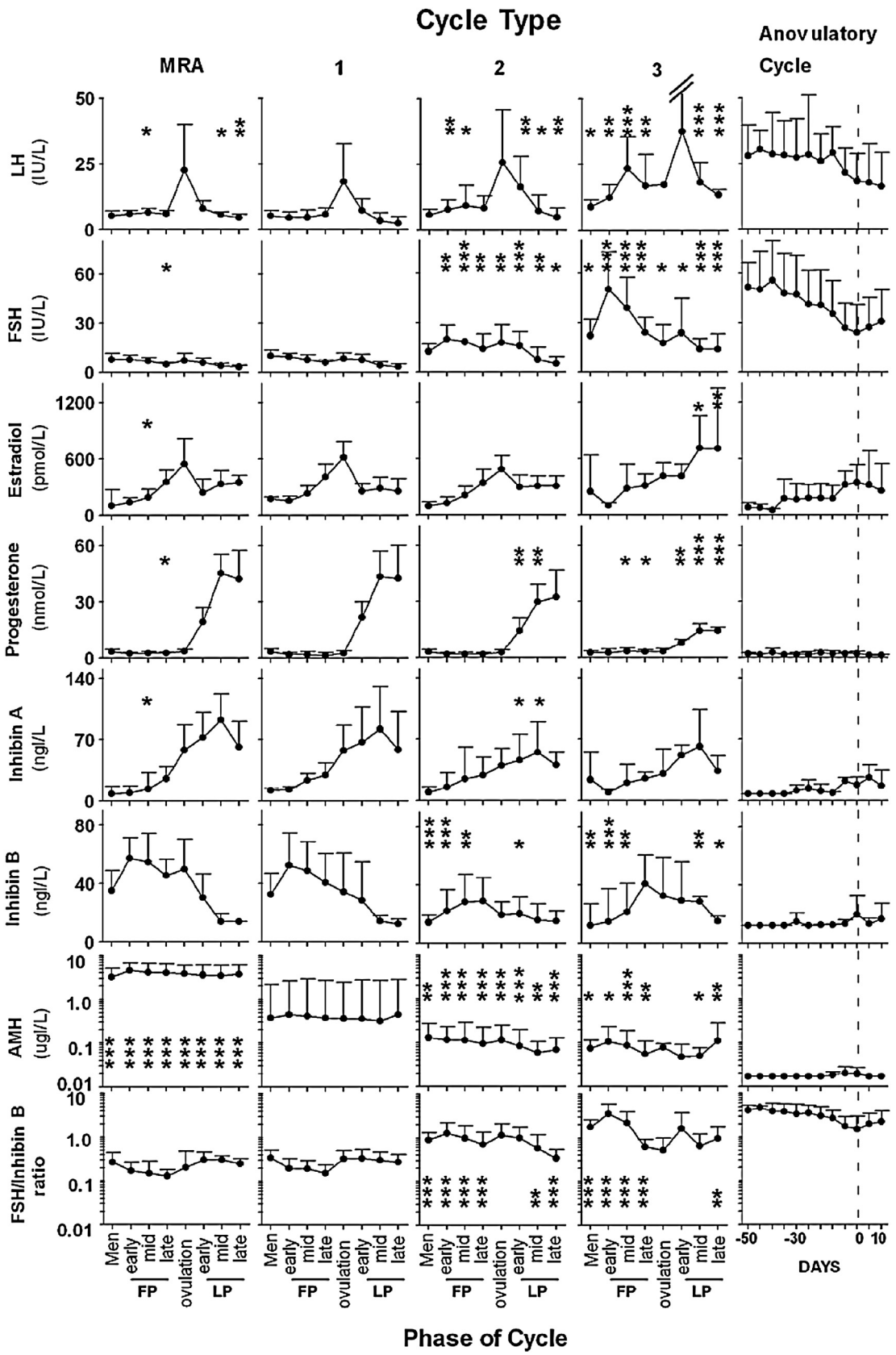

Fig. 3. Serum hormones profiles in all cycles according to the MRA group, cycle types 1, 2, and 3 and anovulatory cycles. (All comparisons are made with cycle type 1 group.) Mean ± SD $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. AMH, antimüllerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; MRA, mid-reproductive age; FP, follicular phase; LP, luteal phase; Men, menstruation.

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low AMH levels play in the disruption of ovulatory function in the perimenopause remains unclear, but given its close association with the NGF pool and primordial follicle recruitment [88] and the complexity of underlying follicle wave activity, it is likely to be very important.

6. Abnormal menstrual bleeding

Menstrual bleeding symptoms are challenging to study but extensive subjective data was collected in the Seattle Women's Midlife Health and the SWAN studies. In the Seattle study [89], the most common subjective menstrual cycle changes prior to the menopause transition were flow-related and included a lighter menstrual flow (32%), a heavier menstrual flow (29%), a shorter duration of flow (24%) and a longer duration of flow (20%). Only 14% reported cycle irregularity as the initial change, and only 11% reported the initial change was an increase in cycle length [90]. When compared to perimenopausal women with no menstrual complaints, subjective reports of 'heavy flow' in perimenopausal women were associated with higher levels of estradiol during the follicular phase [91–93], luteal phase [94,95], or when taken randomly throughout the menstrual cycle [96]. Although an analysis of subjective reports and endocrine data in the SWAN study did not reveal a direct relationship between hormone levels and menstrual flow, they confirmed the findings from a smaller quantitative study on menstrual blood loss in perimenopause [95] that menstrual blood loss (MBL) was greater following ovulatory cycles than anovulatory cycles [78]. It has been proposed that the increase in MBL reported in the late perimenopause in particular, is likely to be a result of ovulatory cycles that follow a prolonged interval of anovulation, where unopposed estradiol contributes to abnormal proliferative changes in the endometrium. Erratic and elevated levels of estradiol associated with variable ovulatory cycle length and elongated anovulatory cycles in the perimenopause may also contribute [6]. Such changes would also be expected to increase the risk of endometrial carcinoma [97].

7. Bone and cardiovascular health in the perimenopause

Findings from prospective examinations of bone mineral density (BMD) across the menopausal transition demonstrate an early and accelerated rate of bone loss, particularly in the lumbar spine, with the greatest reduction in BMD occurring in the year before the final menstrual period and the first 2 years after the final menstrual period [98]. In the SWAN, bone loss was found to accelerate dramatically from the early to late perimenopause and postmenopause, with annual bone losses of 1.8–2.3% in the lumbar spine and 1.0–1.4% in the hip (Finkelstein, Brockwell et al., 2008). Similar rates of accelerated bone loss were reported in a longitudinal French [99] study and in the Melbourne Women's Midlife Health Project (MWMH) [100]. In the MWMH project, the estimated average annual rate of bone loss around the time of the final menstrual period was 2.5% in the lumbar spine and 1.7% in the femoral neck. Significantly, the SWAN data confirmed that ethnic differences in BMD could be almost completely eliminated by controlling for weight (except spinal BMD in Caucasian women). Although body weight was not an independent predictor of the rate of bone loss, compared with women in the highest tertile of body weight, rate of bone loss was 35–55% greater among women in the lowest tertile of body weight [101]. Rates of bone loss were greatest among Chinese and Japanese women, intermediate among Caucasian women, and lowest among African- American women. However, like the baseline differences in BMD, these variations were largely accounted for by differences in body weight rather than race/ethnicity. The SWAN has therefore helped to reinforce the finding that Caucasian race is a risk factor for bone loss, and that adjusting for body weight is critical in the determination of peak bone mass as well as a woman's risk of bone loss during the menopausal transition [101].

There is compelling data to suggest that the perimenopausal bone loss is associated with high levels of FSH rather than falling levels of estradiol [102–104]. FSH appears to have direct effects on bone, in part by enhancing receptor activator of the nuclear factor kB ligand (RANKL) stimulated osteoclast development and activity [105,106]. In a cross-sectional study, FSH was significantly correlated with bone resorption among perimenopausal women, but serum inhibin A levels seem to predict bone resorption levels better than did FSH [107]. The role of the inhibins in bone remains unclear, however both inhibin A and inhibin B appear to inhibit osteoblastogenesis and osteoclastogenesis and also to suppress osteoblast and osteoclast development [108]. The role of progesterone in bone loss and maintenance remains unclear. There was no association found between measures of luteal function (urinary PdG assays) and BMD in premenopausal and early perimenopausal women in the SWAN [109], however, further studies are needed to examine the specific impact of changes in ovulatory function in midlife women. Although there appears to be an association between vasomotor symptoms and bone loss, the reasons remain unclear. Sustained elevations in serum cortisol and epinephrine [110] from the stress of hot flushes and loss of sleep have been hypothesized as being important [111].

Important longitudinal data on coronary heart disease (CHD) from the SWAN, the Healthy Women Study, the Melbourne Midlife Health Project, the Fels Longitudinal study and the Taiwan Chin-Shan Community Cardiovascular Cohort has revealed that adverse changes in the lipid profile (increased LDL and triglycerides) occur between early perimenopause and the early postmenopause and that premenopausal lipid levels can predict the extent of subclinical vascular disease 14–20 years later [98]. The perimenopause itself does not appear to have an influence on the development of insulin resistance or diabetes (when controlled for BMI), but data from the SWAN suggests that the perimenopause is associated with development of the metabolic syndrome (abdominal obesity, dyslipidemia, impaired glucose tolerance, and hypertension) [112] and therefore most likely represents a window of risk for the development CHD. Similarly, although there does not seem to be a strong relationship between the perimenopause and development of hypertension, the increased incidence of hypertension at midlife and beyond emphasizes the importance of closely monitoring blood pressure in these age groups and lowering blood pressure to optimal levels to minimize future risk of CHD [113–115]. Perhaps yet another contribution to increased risk of CHD at menopause is the decline in endothelial function that appears to occur around the time of the final menstrual period [116–118]. Data from the SWAN suggests that the presence of vasomotor symptoms may be an important marker for adverse vascular changes [119] and they include endothelial dysfunction, decreased flow mediated dilation and high levels of aortic calcification [120–122]. Studies on the link between vasomotor symptoms and CHD risk are continuing.

8. Management strategies

The decision to begin hormonal therapies during the perimenopause will be determined by presence of symptoms including sleep disturbance, vasomotor symptoms and abnormal uterine bleeding. General management and prevention measures on the other hand should be universal and include a blood pressure measurement, thyroid function, Vitamin D level, fasting lipid profile and a general CHD risk assessment. Heading off the increased risk of CHD during this time in reproductive life is a very important consideration and adopting a "sooner the better" approach for instigating

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an optimal diet and active lifestyle is more likely to reduce risk than delayed intervention [115]. There is evidence from observational studies (but not from RCT's) that suggests that estrogen containing therapies have the potential to reduce the risk of CHD when started in the late perimenopause or early menopause and when combined with preventative measures [123,124]. In a recent report of the Danish study (DOPS), there was a 50% reduction in mortality, heart failure or acute myocardial after 10 years of randomized hormone therapy when begun early after menopause [125]. The apparent benefits in this study were not offset by any increase in risk of cancer, venous thromboembolism or stroke [125].

When vasomotor symptoms are a feature, especially when associated with the late perimenopause and oligomenorrheoa (indicating low estrogen levels), hormone therapy can play its most beneficial role. In women with a uterus, provided that there are no significant contra-indications, low dose oral contraceptives (OC) are particularly useful because they can eliminate the fluctuations in hypothalamo-pituitary-ovarian function. If the OC is contraindicated in these women, a sequential regimen of hormone replacement therapy may be useful as long as it is acknowledged that adequate contraception will not be provided. Transdermal estradiol is often the preferred delivery option in the presence of cardiovascular risk factors such as obesity, hypertension, cigarette smoking or risk of venous thromboembolism, and doses for adequate symptom relief can be prescribed. When uterine protection is needed, at least 10–15 days of a progestin every 28 days is required [126].

Approaches to abnormal uterine bleeding (AUB) especially heavy menstrual blood loss include simple non-steroidal anti-inflammatory agents, 21 day (in 28 day cycle) cyclical progestin or progesterone therapy, the oral contraceptive pill (OCP), endometrial ablation, progestin-releasing intrauterine devices (IUS) and hysterectomy. Supplemental luteal phase progestin or progesterone therapy has not been shown to be effective in the doses studied, however cyclic progestin or progesterone therapy for 21 days has [127]. Oral contraceptive agents reduce bleeding, allow cyclical bleeding (if taken on a cyclical basis), improve vasomotor symptoms, reduce bone loss, and reduce the risk of uterine and ovarian malignancy [128]. Although often considered by expert consensus to be a first-line treatment of AUB in healthy, non smoking perimenopausal women, there is a lack of trial data to generally recommend their use in AUB [129]. A major drawback with their use is the increased risk of adverse side effects such thromboembolism and other symptoms in older women [128]. Progestin-releasing intrauterine devices provide effective relief from menorrhagia, dysmenorrhea and contraception and can reduce heavy bleeding by 80–97% [130]. They are comparable to endometrial ablation [131,132], in terms of controlling the bleeding rates at 6 months to 2 years [133,134] and have cost-efficacy advantages [134–136]. In one Finnish study however, around 42% women initially treated with an IUS for heavy bleeding eventually had a hysterectomy after 5 years [137].

There are currently no established guidelines pertaining to the treatment and prevention of osteoporosis in perimenopausal women, but for those with established osteoporosis, pathological fractures or a high fracture risk selection of therapy should be considered individually [102]. The most accepted treatment in women under 60 years is hormone therapy, as it is rare to encounter a markedly increased risk of fracture before this age. In general bisphosphonates should be reserved until after the age of 60–65. While raloxifene, a selective estrogen receptor modulator is not an option in premenopausal and perimenopausal women, it may be an option for the younger early postmenopausal women with osteoporosis, although its efficacy in preventing non-vertebral and hip fractures is uncertain [126]. Other considerations such as maintenance of adequate dietary, supplemental calcium, vitamin D intake, weight bearing or resistance exercises and attention to modifiable risk factors and osteoporosis screening (if high risk) are important [102].

9. Conclusions

The STRAW and STRAW + 10 are internationally recognized female reproductive staging systems. They provide a consistent classification system for use in the clinical and research setting. The recently updated STRAW + 10 contains new subdivisions within stage −3 (late reproductive age) and stage +1 (postmenopause) and incorporates FSH and other biomarkers as supportive criteria. The characteristic features of reproductive aging outlined in the STRAW system occur as primordial follicle numbers fall to a critically low level (<1000) and key endocrine changes in the components of the hypothalamus-pituitary-ovarian feed-back system occur. These endocrine changes disrupt the normal cyclical ovarian hormone secretion and ovulatory patterns and result in a complex transition from predominantly normal ovulatory cycles, to predominantly abnormal ovulatory or anovulatory cycles before the final menstrual period. Detailed ultrasonographic show the changes in ovulatory function with reproductive aging largely determine the hormonal changes, menstrual cycle patterns and symptomatology that occur as the FMP draw closer. While the early perimenopause is characterized by disturbances in the timing and regulation of ovulation and menstrual bleeding, the late perimenopause is characterized by anovulation and oligomenorrheoa. When vasomotor symptoms are a clinical feature, especially when associated with oligomenorrheoa (indicating low estrogen levels), hormone therapy can play its most beneficial role.

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