MENOPAUSAL TRANSITION PERIOD: HORMONAL CHANGES, CLINICAL SYMPTOMS, DIAGNOSIS, AND MODERN MANAGEMENT APPROACHES

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SUMMARY

Background: The menopausal transition (MT) marks the end of a woman's reproductive years, characterized by hormonal changes, irregular menstrual cycles, and various symptoms impacting health and quality of life.

Objective: To understand the hormonal fluctuations during MT and the clinical implications for managing symptoms.

Method and Materials: The article synthesizes findings from various studies and consensus workshops, particularly the Stages of Reproductive Aging Workshop (STRAW), detailing hormonal changes and clinical presentations during early and late MT.

Results: MT involves erratic estradiol levels, decreased progesterone, and increased follicle-stimulating hormone (FSH), leading to irregular cycles, with notable events like luteal out-of-phase (LOOP) cycles. Symptoms often include abnormal uterine bleeding, hot flashes, sleep disturbances, and mood disorders. Hormonal therapies, including estrogen and selective serotonin reuptake inhibitors (SSRIs), are effective but should be administered cautiously due to associated risks.

Discussion: The hormonal chaos of MT complicates infertility and symptom management. Non-hormonal therapies and lifestyle modifications are beneficial but often less effective than hormone therapy.

Conclusion: A personalized approach to managing MT is crucial, integrating hormonal and non-hormonal strategies, lifestyle changes, and mental health support. Continuous research aims to optimize these interventions for better outcomes in women during MT.

Keywords: menopausal transition, perimenopause, hormonal changes, menstrual irregularity, anovulatory cycles, symptom management, hormone therapy, reproductive aging.

INTRODUCTION:

The menopausal transition (MT), which is also called the advanced reproductive age, represents the final years of a woman's reproductive life[1] and is associated with profound reproductive and hormonal changes,[28, 60] a decrease in the consistency of ovulation and changes in menstrual patterns.[58]

MT begins with the first onset of menstrual irregularity[28, 60] and with variations in menstrual cycle length and a monotropic rise in follicle-stimulating hormone (FSH), and ends with the final menstrual period, classically confirmed only when followed by 12 months of amenorrhea, thereby definished the final menstrual period (FMP).[1, 6, 28]

Perimenopause, which literally means "about or around the menopause," begins at the same time as the MT and ends one year after the final menstrual period.[1] The median age at the FMP is 51.4 years,[1, 6, 10] but chronological age cannot be substituted for reproductive age, as women reach menopause at different ages.[45]

MAIN BODY:

Perimenopause, instead of being merely a period of declining estrogen, is marked by three significant hormonal changes that can start in regularly menstruating women as early as their mid-thirties.: 1. Erratically higher estradiol levels, 2. Decreased progesterone levels (normally ovulatory, short luteal phase or anovulatory cycles), and 3. Disturbed ovarian-pituitary-hypothalamic feedback relationships.[52]

The stages of reproductive aging have been well described in two workshops, with the acronym **STRAW - Stages of Reproductive Aging Workshop (STRAW)**.[28-30, 60]

Based on the proceedings of a consensus conference, the STRAW report further classifies reproductive and post-reproductive life into seven stages, with the MT accounting for two of those stages: early and late.[1, 49]

In the early MT (stage –2), previously, regular menstrual cycles become more variable, and cycle length changes by seven days or more.[1] By the time Stage -2, the early transition, is attained, the ovarian follicle cohort has shrunk to a critical level, and, usually, a woman will note her first missed menstrual period.[28]

FSH is more consistently elevated by this time, and ovarian reserve measures, such as Inhibin B, AMH, or an ultrasound-measured antral follicle count, are now critically low. Because the follicle cohort is still relatively preserved at these early stages of the transition, the rise in FSH causes folliculogenesis to appear more rapidly, and the follicular phase of the menstrual cycle becomes shorter. Follicles grow more quickly but seem to ovulate at a smaller size. An increase in follicle growth during the luteal phase has also been noted, indicating that the dominant follicle for the subsequent cycle has developed significantly before menstruation.[28, 31] Recent data show that approximately a third of all perimenopausal cycles have a significant surge in estradiol occurring de novo during the luteal phase. These types of cycles, in which ovulation follows rapidly upon one another, with minimal follicular phase length, have been named **luteal out-of-phase or LOOP events**[31] and may explain a large proportion of symptoms and signs for symptomatic perimenopausal women.[52]

These types of cycles contribute further to the menstrual irregularity of perimenopause and are associated with hormone secretory patterns that deviate from midreproductive-aged women's hormone patterns. Specifically, lower luteal progesterone and higher FSH have been ob-

served, and erratic estrogen secretory patterns have been associated with the transition. Thus, some hormone changes may be related to altering menstrual patterns and increasing cycle irregularity, which can be profound and contribute to symptomatology.[28, 31]

If we look at LH levels, it is clear that perimenopausal women have a short follicular phase, missing about 5-7 days.

Many of the marked increases in ovulatory cycle E2 and cycle irregularities during the menopausal transition may be due to **LOOP events** and appear to be triggered by prolonged high follicular phase FSH levels.[60]

While older women have higher levels of Estradiol, Progesterone levels are low in this age group. And despite the high activity of estradiol, we don't have many follicles because of enough progesterone. At this time, the luteal phase is practically unchanged in duration, but the progesterone level is reduced, and the estradiol level is increased. Another fact that attracts attention to this age group is that despite the high numbers of estradiol, there is an increase in the level of FSH. This is the result of the reduction of AMH and Inhibin levels.

Another pattern of this period is the **LAG cycle,** which involves a short follicular phase with altered folliculogenesis, high estradiol, and low or reduced progesterone levels.

The number of anovulatory cycles increases when the cycle becomes irregular in women with previously regular cycles. Progesterone levels show that only a few cycles are ovulatory cycles, and the other cycles are not ovulatory in perimenopausal women. During these cycles, estradiol levels were steadily elevated, and when ovulation occurred, estradiol levels were back to their normal range.

In some cycles, the level of estradiol is increased, and the level of FSH decreases, which means that the feedback sensitivity is maintained to some extent during the aging process; however, this sensitivity is not stable and constant. During anovulatory cycles of perimenopause, progesterone levels are low, and estradiol and FSH levels are elevated.

The presence of LOOP and LAG cycles complicates infertility interventions

According to the new model, the balance between estrogen and progesterone, which implies the presence of high estrogen and low progesterone levels in perimenopausal women, may be caused by the development of multiple follicles without ovulation.

In perimenopausal women, atypical dominant follicles may be very large and grow to >26 mm in size. This is associated with higher estradiol levels and significantly lower progesterone levels.

Therefore, the hypothesis implies that the suppression of progesterone production occurs due to the high estradiol level produced by the atypical dominant follicle of the luteal phase. This is an entirely different model from what we have known so far.

Late MT (stage 1) is characterized by two or more missed menstrual periods, at least one intermenstrual interval of 60 days or more, and an FSH level greater than 40 IU/L.

Circulating estrogen is more likely to be low during anovulatory cycles, and the long periods of amenorrhea are accompanied by a sharp increase in the prevalence of typical menopausal symptoms. However, when a woman does have a menstrual cycle, it may be **ovulatory, anovulatory with relatively high estrogen levels, or anovulatory with low estrogen levels.** This stage is the speed bump of the menopausal transition.[28]

For the average woman, the menstrual milestone of the early transition (Stage -2) is age 47, the late transition (Stage -1) occurs at age 49, and the FMP at age 51. However, there is substantial variability in the onset of these milestones.[28]

Menopause is determined in retrospect after a year of amenorrhea. For women with at least one intermenstrual interval of 60 days or more, the median menopausal time is 2.6 to 3.3 years. Cigarette smoking may alter the ovarian aging process and advances the age of menopause by as much as 2 years.[1]

Endocrine changes for diagnosis of Menopausal Transition Period

Secretion of reproductive hormones during the MT fluctuates widely.[1]

The variations in circulating **FSH** levels with increasing age are most probably due to changes in ovarian physiology affecting the secretory pattern of the gonadotrope, and the ovary becomes increasingly resistant to stimulation by gonadotropins, probably due to the decreased number of follicles, which leads to a decline in the production of both estrogens and inhibins.[50] Early follicular phase FSH, taken between cycle days 2-5, is the most sensitive and convenient time in the cycle to perform its measurement.[49]

In perimenopausal women, **Estradiol** production fluctuates with FSH levels and can reach higher concentrations than those observed in young women under age 35.[1]

Progesterone levels during the early MT are lower than in women of mid-reproductive age and vary inversely with body mass index.[1] 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 frequent anovulatory cycles.[52]

Levels of **Androstenedione, Testosterone, and DHEA decline after menopause and menarche** but do not decline sharply after menopause because the theca cells continue to produce androgens.[1]

The prime mover in the feedback disruptions that result in the hormonal changes of perimenopause is now confirmed to be Inhibin B.[52,61] **Inhibin B** is a TGF-beta superfamily peptide that is produced by the granulosa cells of the growing follicle cohort - by antral and dominant follicles and directly suppresses the pituitary secretion of FSH.[49] As the follicle cohort shrinks, less Inhibin B is produced, leading to the well-characterized monotropic rise in FSH, a cardinal feature of the menopausal transition.[28]

Studies confirm the role of declining Inhibin B levels in allowing FSH to rise in the follicular phase. Elevated FSH, in turn, stimulates the second estradiol peak called LOOP during the luteal phase.[38]

Antimullerian hormone or Mullerian Inhibiting Substance - AMH/MIS are also tgf-beta superfamily peptides[49] secreted by the granulosa cells of small secondary and preantral follicles.[11] Levels parallel the number of remaining ovarian follicles measured by antral follicle counts (on transvaginal ultrasound).[52] They are not just produced by follicles in their terminal stages of growth but also by primary, secondary, and early antral follicles and, therefore, reflect more completely the follicle cohort.[49]

Antimullerian hormone (AMH) and Inhibin B have been used as peripheral serum markers of ovarian reserve. AMH is very effective in predicting the probability of a poor outcome with fertility therapy when it is low.[28] Theoretically, measuring AMH/MIS is the most effective way to measure a woman's progress toward menopause.

Some physicians use serum FSH levels early in the cycle (say cycle day 3) as a test for perimenopause. For an individual woman, however, FSH is neither sensitive nor specific.[52] There are hopes that the AMH will prove helpful in 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 and QBT.[52] Cycle lengths tend to shorten in older, regularly menstruating women, and the follicular phase becomes shorter. Shortened follicular phase lengths are associated with higher early-cycle serum estradiol levels and with higher urinary FSH levels in both follicular and late luteal phases.[52]

Relationships Between Cycle Characteristics and Clinical Correlations of Health in Midlife Women

Most women who are symptomatic during the MT present with frequent or excessive bleeding or with hot flashes and other symptoms of estrogen deficiency. [1]

Abnormal uterine bleeding (AUB) is expected during the MT, particularly once menses become irregular and unpredictable. Because the time interval surrounding menopause is characterized by relatively high acyclic estrogen levels[52] and relatively low progesterone production, women in the MT are at some increased risk for developing endometrial hyperplasia or carcinoma.[1,13]

SWAN findings suggest that unusually **heavy menstrual bleeding (HMB)** typically does not have a hormonal basis, and such patterns, especially when they are persistent, should be investigated for an underlying anatomical, gynecologic cause.[12, 49]

Recent epidemiological evidence indicates that **vasomotor symptoms or hot flushes** before or at the onset of the MT are common[16, 49], affecting 30-70% of premenopausal women (varies by race/ethnicity, BMI, smoking, anxiety, and depressed mood).[1, 16] They are likely to be mild in nature at these earlier stages of a woman's reproductive life.[32] Vasomotor symptoms cause a substantial amount of distress and reduction in health-related Quality of Life (HRQOL).[28, 33]

Lipid profiles and inflammatory markers in women with varying cycle lengths in SWAN, when controlled for body size, showed no difference except for triglycerides, which increased with increasing cycle length. Lower mean cycle estrone conjugates and pregnanediol glucuronide were associated with higher triglycerides, insulin, and inflammatory markers. In longitudinal SWAN studies, total perimenopause/early postmenopause and, falling E2 and rising FSH were independent of age, while HDL peaked in late perimenopause.[49]

Longitudinal studies have shown that hot flashes are associated with low exercise levels, smoking, high FSH and low estradiol levels,[1, 17] increasing body mass, ethnicity, socio-economic status, and a history of premenstrual dysphoric disorder (PMDD) or depression.[1,18]

Depressed mood disorders and increased anxiety also are increased during the MT. [1, 28] Community-based surveys indicate that perimenopausal women experience considerably higher levels of psychological distress and have an elevated risk of significant depression compared to both premenopausal and postmenopausal women.[1,19] **Major depression**, diagnosed using a Structured Clinical Interview for Diagnosis (**SCID**), was found to be more likely to occur in women during the late menopausal transition.[39, 40] Similarly, anxiety symptoms also appear to be more likely to be reported as women traverse menopause and may be linked to the onset of major depression.[28, 41]

Sleep disturbances are also widespread during the MT. Women begin to experience changes in their sleep patterns in their 40s, and these tend to worsen with entry into the menopausal transition.[28] Poor sleep is also related to aging and not only the menopausal transition period.[28, 34, 35] According to the **SWAN** data, difficulty sleeping was clearly associated with the perimenstrual phases of the cycle, with early perimenopausal women overall experiencing more poor sleep than women who had not yet experienced a break in their cycles.[28, 36] Overall, a 29% increase in the odds of reporting trouble sleeping was observed as women progressed from regular cycling into the early transition. Sleep quality was worse at the beginning and end of the menstrual cycle.[49] Women with metabolic syndrome experienced substantially less sleep efficiency by polysomnography.[28, 37]

Other common symptoms during the MT include **decreased libido, forgetfulness, vaginal dryness, dyspareunia, irritation, dysuria, and urinary incontinence.**[1,28]

The constellation of symptoms of vaginal dryness, irritation, and dysuria has been named **genitourinary syndrome of menopause (GSM)**.[38] The latter may be a more accurate reflection of the collective morbidity to the female genital tract caused by a lack of estrogen.[28]

Clinical Implications - Modern Management Approaches of Symptoms during the MT

Clinical strategies for addressing these issues typically include hormone therapy, which can be safely administered to most perimenopausal women for a short duration. Additionally, nonhormonal and behavioral therapeutic approaches can also be utilized.[28]

The most common strategies for managing perimenopausal hormonal chaos include: Continuous or cyclic oral contraceptives, use of standard HRT-replacement hormone therapy regimens, Estrogen only supplementation, TSEC - use of tissue-selective estrogen complex - bazedoxifene + conjugated estrogen, cyclic progestin-only therapy, GnRH agonist +HRT, Depo Medroxyprogesterone Acetate + estrogen (oral or non-oral), Progestin-containing IUD + estrogen (oral or non-oral), contraceptive patch, contraceptive ring and contraceptive injections or implants.

Long-term use of HT in older menopausal women has been associated with increased risks for venous thromboembolism, coronary events, stroke, and breast cancer.[1, 22] Although short-term treatment of symptomatic women during the MT likely poses significantly fewer risks, HT generally should be used in the lowest effective dose and for the shortest time required. Low-dose estrogen regimens (conjugated equine estrogens, 0.3 mg daily, or its equivalent) can achieve as much as a 75% reduction in vasomotor symptoms over 12 weeks, approaching the efficacy of standard-dose HT regimens. They may have fewer risks and side effects.[1, 23, 28] The decision to use HT should be made only after first carefully reviewing its risks and benefits for the individual.[1]

The relative safety of HT during the MT has not been thoroughly investigated. The results of one observational study have suggested that women who start HT near menopause had a decreased risk of coronary heart disease when taking estrogen alone (relative risk [RR] 1⁄4 0.66; 95% CI, 0.54– 0.80) or in combination with progestin (RR 1⁄4 0.72; 95% CI, 0.56–0.92) (24). A secondary analysis conducted by the investigators involved in the **Women's Health Initiative (WHI)** revealed that the risk for coronary heart disease was not significantly increased in women under age 60 years of age or within ten years of menopause.[25] Further studies to evaluate the safety and efficacy of HT during the MT and the early postmenopausal years are ongoing.[1]

When hormones are contraindicated or otherwise unacceptable to a patient, some other options are now on-label for treatment.[28]

Concerns about the risks of HT have increased interest in nonhormonal alternatives for treating symptoms in the MT. In some women, vasomotor symptoms during the MT can be reduced by wearing layered clothing, avoiding caffeine and alcohol, and keeping the ambient temperature a few degrees cooler. Herbal treatments such as black cohosh have been shown to have marginal or no benefit in placebo-controlled trials.[37, 45]

Neuroactive agents, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), alpha-adrenergic agents, and others, all have some efficacy in treating vasomotor symptoms.[1]

For vasomotor symptoms, paroxetine mesylate, a 7.5 mg long-acting salt of paroxetine, was recently approved by the FDA for this indication. For vaginal dryness, Ospemifene, 60 mg, a new selective estrogen receptor modulator (SERM), has also been FDA-approved. For adverse mood symptoms, the selective serotonin reuptake inhibitor (SSRI) class of drugs is a reasonable alternative for depression. Similarly, while there are no menopause-specific remedies for poor sleep, treatments ranging from behavioral modification for insomnia to melatonin receptor agonists may be tried. For women who have hot flashes that are bothersome only at night, Gabapentin in a small nightly dose of 100–300 mg may be highly effective.[28]

Both SSRIs and SNRIs may be effective, as norepinephrine and serotonin seem to play a role in the hypothalamic regulation of temperature homeostasis and are involved in the occurrence of hot flashes. Randomized placebo-controlled trials have shown that SSRIs (citalopram, sertraline, paroxetine) and SSNIs (venlafaxine) can help to reduce the severity and frequency of hot flushes.[1, 26, 27] Clonidine (an alpha-adrenergic agonist) and gabapentin also have some efficacy.[1, 26, 27] However, the effectiveness of neuroactive therapies does not equal that of HT.

Given that the onset of menopause cannot be predicted precisely, that women may ovulate up until their final menses, and that prescription drugs and alternative therapies may have potential adverse effects on pregnancy, clinicians should remain sensitive to the contraceptive needs of women during the MT.[1]

Nonpharmacologic or botanical remedies for menopausal symptoms have been largely ineffective in well-conducted clinical trials. These ineffective treatments include yoga,[42] omega-3 fatty acid supplementation,[43] and black cohosh.[28, 42-44]

Optimal hormonal management should slow the brain's aging process—estrogens maintain brain metabolism, synapses, mood, and cognition. Progestins increase irritability and decrease metabolism. The best product should suppress the endogenous function of the ovary, be the safest estrogen, be a safe and brain-neutral progestin, reduce the risks of developing withdrawal bleeding, and be in continuous mode.

Evidence-Based Additions:

Recent studies have highlighted several important considerations for managing MT:

Cardiovascular Health - HT has been associated with a reduced risk of coronary heart disease when started near menopause, particularly with estrogen alone.

Bone Health - HT can significantly reduce the risk of osteoporosis and fractures by maintaining bone density.

Mental Health - Cognitive-behavioral therapy (CBT) and mindfulness-based stress reduction (MBSR) have shown efficacy in managing mood disorders during MT.[1, 28, 35]

CONCLUSION:

The menopausal transition (MT) is a complex period characterized by significant hormonal changes and varied clinical symptoms. Effective management requires a personalized approach that may include hormonal and non-hormonal therapies, lifestyle modifications, and psychological support. The best product for managing the MT period should suppress the endogenous function of the ovary, be the safest estrogen, be a safe and brain-neutral progestin, reduce the risks of developing withdrawal bleeding, and be in continuous mode. Ongoing research refines these strategies to improve outcomes for women undergoing MT.

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