Mechanisms and biomarkers of menopausal transition


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Abstract

Transition from perimenopause to menopause is often marked by mood swings, hormonal fluctuations and other biological symptoms such as sleep disturbances, hot flashes and changes in menstrual cycles. Symptoms typically begin during mid to late 40's and can last for 4-5 years. This period can greatly impact quality of life in women; affecting emotional, physical, social well-being and is linked to increased risk of diseases like cardiovascular conditions, diabetes, osteoporosis and obesity. Perimenopause progresses through two main phases namely; irregular menstrual cycles and amenorrhea culminating into menopause. The global prevalence of perimenopausal symptoms varies across regions with vasomotor symptoms of hot flashes and night sweats being more common in certain populations based on ethnicities and geographical locations. The mechanisms behind these symptoms including hormonal fluctuations and their effects on brain and cardiovascular health are complex. Estrogen withdrawal is associated with mood disorders and cognitive changes. Management strategies including hormone replacement therapy (HRT), cognitive behavioural therapy (CBT) and lifestyle modifications are essential in mitigating symptoms and improving overall health in menopausal women. A holistic approach involving proper nutrition, medications, exercise and psychological self-care play crucial role in enhancing well-being during perimenopausal to menopausal transition in women.

Keywords: Perimenopause, menopause, vasomotor symptoms, estrogen, women health

1. Introduction

The last phase of women's reproductive cycle is known as perimenopause which can also be termed as a 'transitional phase'; approaching from reproductive towards the non-reproductive stage. This phase is often marked with varied alterations in the body of women that can be evident as physical or biological changes. Mood swings associated with hormonal changes are the most common visible features during this phase (1). Although menopausal transition or perimenopause often shows decrease in fertility; pregnancy is still possible during perimenopause (2,3). The symptoms of menopause begins during mid or in the late 40's and lasts for about 4-5 years till the stage of menopause occurs. These symptoms greatly affect social, physical, personal and work life having a profound influence on quality of life in perimenopausal and menopausal women. Also during menopausal transition, women experience considerable changes in their bodies which often is the contributing factor to developing a range of diseases like diabetes, cardiovascular diseases, endocrine disorders, obesity, osteoporosis to mention a few (4). There are two phases of menopausal transition wherein the first phase includes irregularity in menstrual cycle or amenorrhoea for at least 3 months. Here, there will be decreased number of ovarian follicles with increase in follicle stimulating hormone (FSH) and this phase is also called as perimenopause. The last phase where complete absence of menses is observed for 12 months is the menopause. These phases are part of natural ageing process in every women's life and therefore management approaches should control the discomfort caused during this transition rather than focussing on the phases (5,6). This topic will thereby cover the overall difficult symptoms, mechanisms, risk factors and managing the transition of perimenopause to menopause.

2. Global prevalence of perimenopause and its symptoms

Perimenopause, an important turning point is frequently accompanied with vasoconstriction and changes in urogenital systems which can significantly impact women's mental health along with physical well-being. The World Health Organization (WHO) predicts that by 2030, there will be more than 1.2 billion menopausal women globally (7,8).According to epidemiological studies, there are significant differences in the symptoms based on the ethnicities and differing geographical regions. Vasomotor symptoms (VMS) such as night sweats/ hot flashes, insomnia and headaches are more prevalent in US-based women accounting for 50-82% as per SWAN (Study of Women's Health across the Nation) (9). However, the prevalence is lower in Northern American (36-50%) and Asian (22-63%) women (10). Another Indian study found that the prevalence of depression was at 40.0%, almost equivalent to Brazil's prevalence of 36.8% while it was lesser among Chinese women (25.99%) (11-13). The general symptoms associated among perimenopausal women's include disturbances in central nervous system (vasomotor, anxiety, depression, sleep disruption, cognitive ability, migraine), musculoskeletal (osteoporosis), urogenital (vaginal dryness, vulva itching or burning, recurrent lower urinary tract infections) weight and metabolic changes (obesity), decreased sexual activity, skin, mucosal and hair damage (1).

3. Potential mechanisms behind cardiovascular and cognitive changes during menopausal transition

Ovaries produce female sex hormone estradiol, a lipophilic steroid that can cross the blood-brain barrier to regulate homeostatic functioning and intrinsic behaviour in females (14). There are three subtypes of oestrogen receptors (ER) which include ER-α, ER-β and G-protein coupled ER. ER-α and β are widely distributed in brain and regulate mood, motor skills, cognition and neuroprotective ability. However during the aging process or menopausal transition, the estrogen levels decrease thereby contributing towards unfavourable neurological outcomes (15,16). Also, hot flashes observed in perimenopausal women is a VMS linked to increased glucose supply to the brain (17,18). Menopause is caused by steady decline of antral follicles in the ovaries leading to reduced production of inhibin B which is a contributing factor for increased levels of FSH during perimenopausal stage (19). Low levels of allopregnanolone (ALLO) have also been linked to mood disorders during menopausal transition phase although the exact mechanism is not well established (20). Estrogen withdrawal also disrupts serotonin system and MAO-A (monoamine oxidase) activity increases during the menopausal transition. Estrogens also have a favourable effect on the norepinephrine and dopamine pathways, which may explain why young women with schizophrenia have a better overall prognosis than men. Finally, while kisspeptin and neurokinin B have been shown to alter both the GnRH (gonadotropin releasing hormone), pulse and thermoregulation; little is known about kisspeptin's role in mood management during the menopausal transition (Figure 1) (21). Endogenous estrogen exposure throughout the reproductive years protects women from cardiovascular diseases, which is lost approximately ten years following menopause. Women with vasomotor symptoms during menopause appear to have a worsened cardiometabolic profile. However, menopausal transition trajectory varies from woman to woman; suggesting that range of clinical and biochemical indicators indicate personal mode of transition that may serve as predictors of future cardiometabolic risk (22).

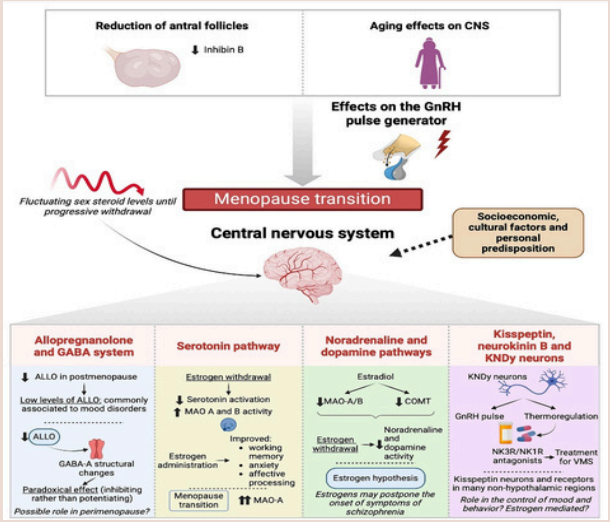

Figure 1. Neuroendocrine changes contributing to mood swings in women's during menopausal transition phase (21).

4. Biomarkers for menopausal transition

Despite the advocacy of World Health Organization's (WHO) for menopause care as part of universal health coverage; menopausal management remains inadequate even in developed nations. One major challenge is the difficulty in diagnosing menopausal status with many women experiencing delays and requiring multiple medical visits. Timely diagnosis is essential for managing menopause and preventing chronic diseases; highlighting the need for objective diagnostic methods. Ferritin and transferrin have emerged as promising biomarkers due to their cost-effectiveness and accessibility, potentially aiding in earlier detection and more effective health measures. Their relevance extends beyond menopause, as iron-related biomarkers have been linked to cardiometabolic conditions, underscoring the urgency of integrating such tools into menopausal healthcare strategies (23). Menopause marks permanent cessation of menstruation due to loss of ovarian follicular activity, typically occurring in women between their late 40's and early 50's, though individual variations exist. This transition is characterized by declining fertility and hormonal changes that contribute to climacteric symptoms. Key hormones involved in this process include estradiol (E2), follicle-stimulating hormone (FSH), inhibin B and anti-Müllerian hormone (AMH). Among these, AMH and inhibin B levels decline significantly during early menopausal transition with AMH being a particularly reliable biomarker of ovarian functions. As women approach the late menopausal transition, AMH levels become undetectable in many individuals, whereas FSH levels increase steadily, followed by a rapid rise in FSH and decline in E2 around the final menstrual period. Understanding these hormonal fluctuations is crucial for assessing reproductive aging and guiding healthcare interventions (24). Alghanim et al. (2024); developed pipeline to integrate multiomics data for classifying menopause status in female breast cancer, aiming to identify biomarkers that reflect molecular changes in breast cancer tissues. Using gene expressions, copy number alteration (CAN) and DNA methylation data, classification models were tested with Random Forest achieving the highest area under the receiver operating characteristic curve (AUCROC) of 0.962 and Support Vector Machine with a Gaussian Radial Basis Function (SVM-RBF) demonstrating the best accuracy (89.53%). To address class imbalance, the Synthetic Minority Over-sampling Technique (SMOTE) was applied. The pathway analysis linked selected genes to cancer pathways, including the ErbB signaling pathway associated with menopausal syndrome. Survival analysis confirmed distinct differences between premenopausal and postmenopausal breast cancer patients. The key genes (RUNX1, PTEN, MAP3K1, and CDH1) were identified as critical in distinguishing the two groups, reinforcing their established links to breast cancer and menopause (25). Ovarian cancer has the highest fatality rate among gynaecological cancers, largely due to diagnostic delays caused by non-specific symptoms. Davenport et al. (2022) evaluated the accuracy of different diagnostic test combinations, including menopausal status, ultrasound scans (USS) and biomarkers like CA125 and HE4 in both premenopausal and postmenopausal women. Results of the study showed that traditional methods like the Risk of Malignancy Index (RMI) have poor sensitivity particularly in premenopausal women. Alternative models such as risk of ovarian malignancy algorithm (ROMA), LR2, and ADNEX demonstrated higher sensitivity though often at the cost of specificity. ADNEX showed highest sensitivity in postmenopausal women but with reduced specificity (26). Neuroimaging studies reveal significant changes in brain structure, connectivity and metabolism across menopausal transition stages, distinct from chronological aging. While brain biomarkers stabilized post-menopause; gray matter volume (GMV) recovery and mitochondrial ATP production correlated with preserved cognitive functions, indicating adaptive compensatory processes. However, peri and postmenopausal women with APOE-4 genotype showed increased amyloid-β deposition, highlighting potential risk for Alzheimer's disease (27). Long term effects of untreated VMS is also been recognized as a biomarker for chronic diseases in menopausal women. Hence, managing chronic diseases in postmenopausal women begins with recognition that VMS may signal future health risks, emphasizing the need for proactive and effective management strategies (28).

5. Management of risk factors of menopausal transition

The management of menopausal symptoms requires holistic and effective approaches for overall well-being in women. VMS in women are most common and the possible risk of mental health disorders during menopausal transition impact mental well-being. Women with more negative attitudes toward menopause may have unhelpful cognitive appraisals of VMS. This may result into increased feelings of anxiety further amplifying these effects on mood and functioning. In contrast, positive coping tactics may reduce impact of VMS on mood swings. There are significant global variances in attitudes toward

menopause which may explain the disparity in associated symptoms between countries (29). Hence, cognitive behaviour therapy (CBT) has been shown to be useful for depression and anxiety as well as for sleep disturbances and vasomotor symptoms. The UK National Institute for Health and Care Excellence (NICE) recommendations expressly prescribe CBT for depression during menopause (30).

Hormone replacement therapy (HRT) is another approach to control the symptoms associated with menopause. HRT includes estrogen which may be with or without progestogen and occasionally testosterone for the relief of menopausal symptoms. However, there are various risk factors associated with HRT which include breast cancer and mortality. According to UK Committee on Safety of medicines, HRT should not be the first line of treatment for women older than 50 years suffering from osteoporosis (31). However, for treating VMS and genitourinary symptoms during menopausal transition, HRT is the first line of therapy while non-hormonal therapy including paroxetine and venlafaxine can also be effective (32). The study of Leitao *et al.* (2024) highlights the importance of healthy dietary habits and psychological self-care contributing towards weight management during menopausal transitions (33). Hence, proper nutrition, exercise or movement routines and stress reduction strategies can assist women towards maintaining best health throughout perimenopause. Ayurveda too offers management of these symptoms through Panchakarma, Rasayana, Yoga, Pranayama, and diet. Menopause is linked to Vata dosha which negatively affects various physiological systems and their functioning. Ayurvedic therapies including Rasayana herbs, Vata-balancing treatments etc. can help women navigate menopause smoothly and maintain positivity for overall well-being (34). Thulasi V. *et al*. (2022) evaluated the effects of *Guduchi satva*, an Ayurvedic Rasayana with *ksheera* in managing perimenopausal symptoms. Women aged 40–50 were given 1g *Guduchi satva* twice daily with 25 ml boiled milk for 30 days. Assessments at 0, 31, and 60 days showed significant reduction in symptoms with p-value <0.001, proving its effectiveness. This suggests that Ayurvedic management, particularly *Guduchi satva* can offer relief from perimenopausal symptoms naturally (35). Also, studies have revealed the benefits of dietary supplements such as flaxseeds, soy isoflavones, probiotics and nuts in improving metabolic health. Additionally, protein supplementation especially whey and milk-based proteins showed potential in supporting muscle and bone health and can be useful in menopausal transitions (36).

6. Conclusion

Perimenopause marks a significant transitional phase in woman's life, leading to menopause. This phase is characterized by various physical, biological, hormonal and emotional changes that can have a profound impact on quality of life in women. Symptoms like hot flashes, mood swings and sleep disturbances are common and can significantly affect daily functioning. Moreover, this transition can contribute to the development of health issues such as cardiovascular diseases, diabetes and osteoporosis. While the trajectory of the menopausal transition varies among women; understanding the clinical and biochemical indicators that predict future health risks is crucial. Effective management strategies include hormone replacement therapy (HRT), cognitive behavioural therapy (CBT), lifestyle modifications with alternative treatments like Ayurveda playing a crucial role in mitigating symptoms and reducing the risk of associated diseases. The experience of menopausal transition in each woman is unique and management approaches should be individualized. A holistic, multidimensional approach that incorporates medical, nutritional and psychological interventions is essential in supporting women through this critical stage of life for smooth transition, ultimately enhancing quality of life and long-term health outcomes.

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