

Perimenopause: Review Article

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ABSTRACT

The perimenopause is the period that precedes the menopause and is a term used synonymously with “menopausal transition”. Stages -1 and -2 according of the STRAW+10 Staging System for Reproductive Aging in Women are included under it [1]. This is a crucial phase in the lives of women where they are juggling between peak stages of their career and taking care of family, both parents and children in most scenarios. This period is impeded by a wide range of perimenopausal symptoms like vasomotor, psychiatric, sleep, sexual, genitourinary, cognitive, and somatic symptoms [2]. This article reveals the impact of perimenopausal symptoms on the quality of life of women and the possible modalities of management.

Keywords: Perimenopause, Abnormal Uterine Bleeding, Vasomotor Symptoms, Obesity, Non-hormonal Therapy

Introduction

While menopause refers to the specific event of cessation of menopause, climacteric is the period of life starting from the decline in ovarian activity until after the end of ovarian function. Climacteric is defined as the period comprising of perimenopause, menopause and post-menopause [3].

Perimenopause corresponds to the stages -2 and -1 according to the STRAW+10 Criteria and marks the time when endocrinological, biological and clinical of menopause begin [1]. Early menopausal transition (Stage-2) is marked by increased variability in menstrual cycle length, defined as a persistent difference of 7 days or more in the length of consecutive cycles. Cycles in the early menopausal transition are also characterized by elevated but variable early follicular phase FSH levels and low AMH levels and AFC.

Late menopausal transition (Stage -1) is marked by the occurrence of amenorrhea of 60 days or longer. This increased variability in cycle length is accompanied by extreme fluctuations in hormonal levels and anovulation. In this stage, the levels of FSH are greater than 25 IU/L in a random blood draw.

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 occurs at age 51. However, there is substantial variability in the onset of these milestones [4]. Between 45 and 55 years of age, most women experience changes in roles, responsibilities, emotions and relationships accompanying ageing related changes.

Systemic Changes

□ Metabolic Changes

Estrogens are known to stimulate lipolysis and inhibit lipogenesis in visceral adipocytes via stimulation of the estrogen receptor alpha. Testosterone, on the other hand, favours fat disposition in the visceral area. Menopause is associated with a fall in estrogen levels and this lower estrogen concentration results in lowering of sex hormone-binding globulin (SHBG) which would lead to higher free testosterone concentrations [5]. This would consequently result in a preferential visceral adipose tissue accumulation, and thus induce insulin resistance and other components of the metabolic syndrome ie abdominal obesity, high blood pressure, impaired fasting glucose, high triglyceride levels, and low HDL cholesterol levels. Metabolic syndrome greatly raises the risk of developing grave comorbidities like diabetes, heart disease, stroke.

□ Vasomotor Symptoms

Hot flushes are the most common perimenopausal symptom which are usually described as a sudden feeling of intense warmth spreading through your chest, neck and face. Family members report a flushed appearance with red, blotchy skin. They are associated with palpitations and sweating, mostly on the upper body. This symptom though appears apparently benign theoretically, cause extreme distress and social anxiety in women affected by it and is responsible for other symptoms we discuss later like sleep disturbances and psychosocial symptoms.

The prevalence of hot flashes increases as a woman advances in her climacteric journey with the prevalence among women who had not begun the menopausal transition being 6% to 13%. As reproductive age advances, it increases progressively to ultimately be as high as 79% in women who had completed menopause [6].

Core body temperature is regulated by physiological processes that conserve and dissipate heat. Tight regulation between these is important for maintenance of optimal internal organ function. Disruption of this tightly controlled temperature circuit results in exaggerated heat-loss responses and presents as vasomotor symptoms. It had been a universal understanding that these symptoms were because of withdrawal of estrogens (especially estradiol) in perimenopause, but after multiple studies it was noted that the ambient serum estradiol levels were not relating to the occurrence and intensity of Hot flushes in perimenopausal women. The marker found to be more specific was raised FSH level [7].

Race, BMI, cigarette smoking, depressive symptoms, and alcohol intake were the other factors found to be responsible for vasomotor symptoms.

□ **Mood and Psychiatric Changes**

Overall Quality of life is comprised of physical and mental well being. In the SWAN cohort, prevalence of psychological distress (Centre for Epidemiologic Studies Depression Scale (CES-D) score ≥ 16 , Using a cut point of 16 to identify women with scores resembling those of patients with major depressive disorders) was 28.9% in the early menopausal transition, 25.6% in the late menopausal transition, and 22% in post menopause [8].

Major depressive episodes are defined by DSM V as having 5 or more symptoms (weight changes or change in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy or interest, feelings of worthlessness or guilt, decreased concentration, recurrent thoughts of death), one of which must include either depressed mood or loss of interest, causing significant distress or impairment in social, occupational, or other areas of functioning.

Depression is a burden on today's society with perimenopausal and post-menopausal women forming a major chunk of the population who go unnoticed by the healthcare system due to negligence and they end up spending a significant period of their lives with these psychosocial symptoms.

□ **Sleep Disturbances**

Trouble falling asleep, early awakening, and interrupted sleep are the most common sleep disturbances reported among peri menopausal women, which these symptoms significantly deteriorating their quality of life. Sleep disturbances are strongly associated with vasomotor and psychological symptoms along with stress and lifestyle factors.

Hot flashes, volatile mood, poor self-perceived health and quality of life, arthritis, metabolic syndrome and sleep apnoea associated with obesity are the contributing factors to sleep disturbances in this demographic.

Poor sleep prior to the transition is one of the predictive factors of worsening symptoms as the woman climbs up her reproductive age ladder. However, since sleep symptoms are also associated with aging in general in both men and women, it is not always clear whether such observations are directly related to menopause, estrogen withdrawal, or other hormone changes. Though, to the relief of these women, these symptoms tend to stabilize as a woman progresses to menopause.

□ **Sexual Concerns and Contraception**

Sexual dysfunction is a complex disorder, related to physiological and psychosocial factors. Decreased libido, responsiveness, and frequency of sex as well as a significant increase in dyspareunia are the sexual concerns in perimenopause. These stem from the psychological stresses of ageing, depression, vaginal dryness and strongly believing that interest in sexual activity declines with age. The overall reduction of estradiol is responsible for dyspareunia which worsens the agony.

As reported by Gracia CR et al. the fluctuating testosterone levels but not the testosterone, dehydroepiandrosterone sulfate (DHEAS), estradiol, or follicle stimulating hormone (FSH) levels measured over the study period were associated with reports of decreased libido [9].

Contraception in the perimenopausal period is a double-edged sword. While women in their late reproductive period still have the possibility of conception, this is the time when most of the pregnancies that occur are unwanted and also associated with high risk of pre-existing comorbidities, chromosomal aberrations and anomalies. This warrants the need for contraception. Reduction in Irregular menstruation, dysmenorrhea, heavy menstrual bleeding, ovarian cancer endometrial cancer and colorectal cancer are the added benefits if COCs are used.

But since these women are usually affected by comorbid conditions like Diabetes, hypertension, dyslipidemia, obesity and coronary artery disease, COCs should be used with caution as it is known to increase the risk of Venous thrombo embolism, MI, stroke and Breast cancer [10].

□ **Genitourinary Symptoms**

In the Melbourne Women's MidLife Health Project (MWMHP), symptoms of vaginal dryness were reported as bothersome by 3% of women in the reproductive stage, 4% of women in the early menopausal transition, 21% of women in the late menopausal transition, and 47% of women who are 3 years postmenopausal [11].

Urinary symptoms reported were incontinence, nocturia, increased frequency, recurrent urinary tract infections.

During perimenopause, estrogen levels reduce, causing structures around the pelvic organs to weaken. Bladder symptoms may be due to age-related autonomic denervation or decreased bladder muscle tone. Pelvic organ prolapse caused by parity and comorbidities such as diabetes, obesity, and depression, are associated with the prevalence of bladder symptoms. The vaginal mucosa releases glycogen which is fermented by the commensal bacteria lactobacilli to produce an acidic pH. This acts as a protective factor against pathogenic invasion. The reduced levels of estrogen during menopause lead to lower levels of Lactobacilli and an elevated pH. This makes the vagina and lower urinary tract more prone to infections.

□ **Skeletal Symptoms**

Perimenopause is characterized by an increased bone resorption, reduction in Bone Mineral Density and an increased fracture risk. Although dropping estrogen levels have been historically attributed to this bone loss, other factors are now under study.

Animal studies show FSH is required in order for bone loss to occur in states of estrogen deficiency. Gonadal peptides like inhibin A, inhibin B and activin have also been purported to contribute to changes in BMD as they suppress osteoblast and osteoclast development [11].

The skeletal symptoms can be bothersome to patients with constant fatigability, aches and pathological fractures hindering them from carrying out day-to-day activities.

Vitamin D and Calcium supplementation is therefore recommended in the post menopausal period and can also be extended into the period of perimenopause.

Evidence Based Management

Management of the complex period of perimenopause should comprise of 4 prongs.

- i) Detailed History, Examination and Investigation: Clinicians should approach these patients and their symptoms with appropriate knowledge on these multisystemic changes, having a strong index of suspicion of the symptoms of perimenopause.
- ii) Counselling: The ageing woman who is usually hesitant to approach medical care for her symptoms should be counselling with tender loving care about the symptoms of perimenopause and the upcoming journey of menopause. It is important to involve the family members in the process as their support and understanding on this matter can ease the stress on the perimenopausal lady.
- iii) Non Hormonal Therapy: Lifestyle modification, cessation of smoking, limited alcohol intake and strict management of comorbidities should be advised. Calcium, Iron, Vit D3 and antioxidant supplementation is suggested.
- iv) Hormonal Therapy: Combined estrogen-progesterone Hormone therapy are used when the recipient has an intact uterus. While they have proven benefits on most of the above perimenopausal symptoms like reduction in hot flushes, vaginal dryness, pathological fractures, adverse mood, recurrent UTIs and improvement in sleep patterns, they should be used with caution as they can increase the risks of Endometrial and breast cancer, dementia, gall stones, Venous thromboembolism, MI and stroke.

Along with systemic therapy, local application of estrogen also has benefit in cases of vaginal dryness, dyspareunia and recurrent UTIs.

Contraindications include a history of breast cancer, Congestive heart disease, previous venous thromboembolic episode, stroke, acute liver disease, unexplained vaginal bleeding, high risk endometrial cancer or Transient ischemic attack.

In patients presenting with fibroid, abnormal uterine bleeding or other endometrial pathology, Mirena (levonorgestrel releasing intrauterine system) can also be considered.

Conclusion

Perimenopausal woman needs treatment after detailed evaluation. Proper counselling is the anchor in the management and should be employed before starting out with any modality of management.

To improve Quality of life, hormonal or non-hormonal therapy should be initiated timely depending on the symptoms after ruling out the contraindicating factors.

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