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PERIMENOPAUSE AND THE RISK OF CARDIOVASCULAR DISEASES

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Abstract

The perimenopause, which literally means "around the menopause". The term perimenopause should include the period immediately before the menopause (when the endocrinological, biological and clinical features of approaching menopause commence) and the 1 year after menopause (usually final menses by approximately 2 to 8 years). The term menopausal transition is used by the WHO to include only the portion of the perimenopause before the final menstrual period. It is heralded by the menopausal transition. A common initial marker is the onset of menstrual irregularity. The biology underlying the transition to menopause includes central neuroendocrine changes as well as changes within the ovary, the most striking of which is a profound decline in follicle numbers. Follicle-stimulating hormone (FSH) is an established indirect marker of follicular activity. Perimenopause begins in a woman's 40s, although it may start in her 30s. Subtle hormonal changes usually commence in a woman's 30s. Defining subsets of perimenopausal women by menstrual cycle patterns (menstrual cycle irregularity has been suggested as a risk factor for CVD) and hormonal profiles is a promising tool for identifying susceptibility to increased cardiovascular risks. This review provides the background for a novel approach to modelling the hormonal changes during the transition, the role of estrogen in the pathogenesis of atherosclerosis, altered lipid profiles and the risk of cardiovascular diseases.

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INTRODUCTION

The global burden of cardiovascular diseases (CVD) is rapidly increasing and CVD remains the leading cause of death among women [1]. For far too long, many believed that coronary artery disease (CAD) was primarily a "man's disease." With increased awareness of the fact that the leading cause of death in women is CAD, this notion is slowly eroding. CAD is a common cause of death or disability in men and women. The burden of CAD is high among women. However, it appears that the pathophysiology of CAD varies between women and men. On cardiovascular computed tomography, women have been shown to have smaller coronary artery diameters than men do [2]. Cardiovascular diseases have a major share in the incidence of non-communicable diseases [3]. Coronary artery disease (CAD)-which includes coronary atherosclerotic disease, myocardial infarction (MI), acute coronary syndrome, and angina-is the most prevalent form of cardiovascular disease and is the largest subset of this mortality [1]. Cardiovascular disease is responsible for more deaths in women each year. Women have different cardiac presentations than men and are more likely to be under diagnosed and undertreated for coronary artery disease [1,2].

Prevalence:

CVD is also one of the leading causes of deaths in India. It is the first among top 5 causes of deaths in Indian population. In 2000, there were an estimated 29.8 million people with CHD in India out of a total estimated population of 1.03 billion, or a nearly 3% overall prevalence [4].

CAD rates in India:

Since 1960, life expectancy in India has increased by 20 years to 61 years of age. From 1960 to 1995, the prevalence of CAD in adults increased from 3% to 10% in urban Indians and from 2% to 4% in rural Indians, with women having rates similar to men. Although the prevalence of CAD in rural India is half that of urban India, this is still two-fold higher than the overall CAD rates in the US and several-fold higher than in rural China. In 1990, there were 783 000 deaths due to CAD in India and this is projected to double by the year 2015, primarily due to affluence and urbanization [5].

Compared with the age group 34 to 44 years, CAD mortality among women increases 40-fold by the age of 80 years, when its incidence become identical in men and women. Women are about 10 years older than men at first manifestation of CAD, although they have a similar plaque burden [5]. This delay is thought to be due to the protective effects of estrogen that occur in the years before the menopause. As estrogen levels drop, often from the mid-40s onwards, the protective effect is lost and changes occur that lead to an increased risk for heart disease in the ensuing years [6].

The perimenopause:

The World Health Organization has defined the menopause as the cessation of menstruation resulting from loss of ovarian follicular activity (retrospectively defined as 1 year without flow), for which there is no other pathological or physiological cause [7].The word menopause literally means the cessation of menstrual cycles. It is derived from the Greek 'meno' (month) and 'pausis' (a pause, a cessation). The WHO formulates the most appropriate definition of the perimenopause. The term perimenopause should include the period immediately before the menopause (when the endocrinological, biological and clinical features of approaching menopause commence) and the 1 year after menopause (usually preceding final menses by approximately 2 to 8 years). The perimenopause, which literally means "around the menopause" [9].

Menopausal transition (MT):

The term menopausal transition is used by the WHO to include only the portion of the perimenopause before the final menstrual period

[8]. It is heralded by the menopausal transition. A common initial marker is the onset of menstrual irregularity. The biology underlying the transition to menopause includes central neuroendocrine changes as well as changes within the ovary, the most striking of which is a profound decline in follicle numbers. Follicle-stimulating hormone (FSH) is an established indirect marker of follicular activity [7].

The human menopause transition can be classified into three stages: early perimenopause (less predictable menses compared with premenopause), late perimenopause (characterized by cycle gaps of at least 3 months), and postmenopause (absence of menses for 12 consecutive months or more) [10]. Many clinicians regard the appearance of menstrual cycle irregularity in a previously regularly menstruating woman as confirmation of perimenopause. Menstrual cycle patterns, however, differ widely during perimenopause. Studies have shown that intermenstrual intervals often shorten significantly during perimenopause, and menstrual cycles may become irregular as well. Some women may skip several cycles and then return to regular cycles. Others may have irregular spotting or regular menstrual cycles until the onset of menopause [10].

The menopause transition represents a dynamic endocrine process that occurs at a different pace in each individual. Menstrual cycle irregularity heralds the beginning of early perimenopause and is defined as variable cycle length that differs from usual by more than 7 days. Evidence is emerging that not all irregular cycles are created equal. Women traversing menopause, the neuroendocrine underpinnings of the menopause transition involve insensitivity of the hypothalamus to estrogen, with loss of negative and positive estrogen feedback [11].

During perimenopause, ovarian estrogen production decreases, the pituitary gland increases follicle-stimulating hormone (FSH) production to stimulate the ovary to secrete estrogen [10]. Estrogen has many effects on the cardiovascular system, including favorable lipid profile, vasodilatation and inhibition of the development and progression of atherosclerotic lesions. While this overall cardiovascular profile of endogenous estrogen appears beneficial, one must not infer that estrogen deficiency is a CVD culprit without having sound epidemiologic evidence [11].

The menopause transition is associated with some changes in the lipid profile [3]. Increased LDL cholesterol and triglycerides and decline in HDL cholesterol were greater during perimenopause than postmenopause, whereas increase in blood pressure and fasting glucose levels were greater during post menopause [12]. Not only the increased levels of LDL-C, the composition of lipoprotein molecules changed as well. High-density lipoprotein cholesterol (HDL-C) particle size became smaller, indicating a prevalence of small HDLC with fewer cardiovascular protective properties than large HDL-C. LDL-C particle concentration also changed, with proportionally more small, dense LDL-C, which is most strongly associated with CVD risk. This finding suggests that the increase in coronary heart disease (CHD) in postmenopausal women may be partly due to accelerated increases in lipid levels and changes in their particle size and composition associated with the menopausal transition [13].

Increased levels of lipids and lipoproteins, blood pressure, glucose, insulin and sedentary life style as well as adiposity and smoking are well-established CVD risk factors. More recently, inflammatory and procoagulant states, as well as depression, have been recognized as risk factors for CVD in women [13].

Symptoms of Menopausal Transition:

More than 80% of women report physical and psychological symptoms with varying degrees of severity and life disruption. Few empirical studies, however, have examined the interrelated nature of symptoms associated with

the menopausal transition and early postmenopause and the effects of those symptom groups on quality of life. In some chronic diseases, symptoms may have greater impact when they co-occur in distinct clusters. This impact is referred to as "symptom experience" [14]. Anovulatory cycles and ovarian failure may be accompanied by a multiplicity of physical symptoms [14,15]. Estrogen deficiency causes vasomotor symptoms such as hot flashes and night sweats, sleep disturbances, vaginal dryness, urinary incontinence, and weight gain, are common physical conditions experienced by midlife women in the transition through menopause and early postmenopause. Psychological symptoms frequently associated with menopause include fatigue, irritability, and anxiety [15,16].

Vasomotor symptoms:

Vasomotor symptoms include hot flushes and night sweats. They occur in approximately 50-75% of women. These vasomotor symptoms can occur at any time, often disturbing sleep. This in turn can lead to insomnia, irritability, exhaustion and lack of concentration. The hot flash or flush is the most frequent perimenopausal vasomotor symptom, experienced by up to 85% of women [10,15]. Sleep disturbances of varying degrees of severity are frequently reported by perimenopausal women. Several common sleep patterns have been reported, including difficulty falling asleep, awakening in the middle of the night with trouble resuming sleep, and early morning awakening with an inability to resume sleep. Sleep disturbances can seriously affect quality of life, resulting in fatigue, irritability, and inability to concentrate [15,17].

As women make the transition from late perimenopause into early postmenopause, vulvo vaginal atrophy and urinary tract conditions may manifest. Both the female genital tract and the lower urinary system develop from the primitive urogenital sinus. Both are very sensitive to estrogen, with estrogen receptors present in lower genital tract and throughout the urinary tract, except from the bladder dome [10, 15]. In the genomic mechanism, steroids induce relatively long-term action on neurons by activating specific intracellular estrogen receptors (ERα and ERβ) that modulate gene transcription and protein synthesis. Thus, gonadal steroids modulate the synthesis, release and metabolism of many neuropeptides and neuroactive transmitters, and the expression of their receptors [18]. Moreover, sex steroids exert very rapid effects in the brain that cannot be attributed to genomic mechanisms. These rapid nongenomic effects of steroids modulate electrical excitability, synaptic functioning and morphological features [19]. Thereby, mood changes, sweating, anxiety, depression, insomnia and alterations of cognitive functions are some possible clinical consequences of the reduced regulatory effects exerted by gonadal and adrenal hormones on neurotransmitters and neuropeptides.

Hormonal changes during perimenopause:

The perimenopause is a time of markedly fluctuating hormone levels. Secretion of reproductive hormones during the MT previously was thought to decline progressively in a linear fashion, but hormone levels have since been shown to fluctuate widely. Studies in large cohorts of women have demonstrated that circulating FSH concentration rise progressively during the MT. The monotropic rise in FSH is attributed to a decrease in ovarian inhibin secretion rather than to a decrease in estradiol production [9].

In perimenopausal women, estradiol production fluctuates with FSH levels and can reach higher concentrations than those observed in young women under age 35 years. Estradiol levels generally do not decrease significantly until late in the MT. Despite continuing regular cyclic menstruation, progesterone levels during the early MT are lower than in women of mid-reproductive age and vary inversely with body mass index. Women in the late MT exhibit

impaired folliculogenesis and an increasing incidence of anovulation, compare to mid-reproductive-aged women. Testosterone levels do not vary appreciably during the MT [9].

Inhibin and activin are proteins produced by the granulosa cells, and plays an important role during menopausal transition. Inhibin A is secreted by the corpus luteum and inhibin B by the antral and dominant follicles. Consequently, inhibin A levels increase during luteal phase, and inhibin B concentrations rise during the follicular phase. Both inhibins inhibit pituitary FSH secretion. Activins are a related class of proteins that stimulate pituitary FSH release and drive from the combination of two inhibin β-subunits. The activin molecule is a homodimer composed of two covalently linked inhibin β-subunits, designated as activin A (βAβA) and activin B (βBβB). Antimullerian hormone (AMH) secreted by the granulosa cells of secondary and preantral follicles. Levels of AMH decrease markedly and progressively across the menopausal transition [20].

During the late reproductive stage, follicular phase inhibin B levels decrease as FSH concentrations rise [21]. As the menopausal transition progresses, luteal phase inhibin A levels also decline. Activin A concentrations also elevated in perimenopausal women. Whereas activins clearly play a local role in regulating pituitary FSH secretion, their ability to act as endocrine factors to influence the production of FSH has not been established. Thus, a decrease in secretion of inhibin A and inhibin B, corresponding increasing in activin production may favor increased FSH secretion in the absence of any decrease in estradiol production [22]. Estradiol levels usually remain in the normal range until follicular growth and development cease. However, estrogen levels have been reported to increase occasionally before menopause. Fluctuations of estrogen can become extreme during perimenopause, with occasional elevations to levels similar to those seen during early pregnancy, followed by prolonged low levels. In perimenopause, the increased secretion of FSH may precede overt decline in E2 levels as a sign of ovarian aging [10].

Mechanism of Atherosclerosis:

The initial injury that occurs in atherosclerosis is damage to the endothelial cells lining the blood vessels. Some of the factors leading to the injury include increased levels of oxidized low density lipoproteins (LDL-C) found in dyslipidemia, free radicals formed by cigarette smoking, possible infectious agents, and the shearing stress placed on endothelial cells due to hypertension. The endothelial cell wall injury triggers a cascade of events and the secretion of mediators that modulates the inflammatory response. The homeostatic properties of the surface of the endothelial cell become procoagulant allowing leukocytes and platelets to adhere. Nuclear factor kappa-B is released and initiates the transcription of cytokines involved in inflammation including tumor necrosis factor-α (TNF-α), chemokines such as monocyte chemoattractant protein-1 (MCP-1) and the vascular cell adhesion molecule-1 (VCAM-1). Monocyte chemoattractant protein-1 attracts circulating monocytes to the site of injury, and through binding to VCAM-1, monocytes adhere to the endothelial cell wall. The monocytes are then able to migrate across the endothelial barrier into the intima layer and differentiate into macrophages. They phagocytosize the increased amount of lipoproteins from the LDLs and transform into foam cells. The arterial wall begins to thicken as more LDLs are taken up by macrophages and an atheroma is formed. An atheroma is a core of lipids and necrotic cellular debris resulting from dying foam cells. The smooth muscle cells produce collagen which forms a fibrous cap over the atheroma. Eventually, the size of the atherosclerotic plague encroaches on the lumen of the blood vessel causing a reduction in blood flow. Plague develops most commonly in areas of increased

turbulence where direction of blood flow changes at branches and bifurcations. The continuous elaboration of the proteolytic enzyme, matrix metalloproteinases (MMP), by the macrophages under the fibrous cap initiates a breakdown of the collagen. As a result, the cap weakens and eventually ruptures. The atheroma and its thrombotic material is exposed and leads to the formation of a thrombus and ensuing emboli [23].

Estrogen alters the basic biology of atherosclerosis:

Estrogen is cardioprotective hormone. Estrogen production is one aspect of ovarian function that could explain the observed cardiovascular protection in women. For example, parenteral estrogen therapy markedly attenuates the development of atherosclerosis in female monkeys post-oophorectomy by directly modifying endothelial and vascular smooth muscle function. The healthy vascular endothelium provides a vasodilatory, anticoagulant, and antiadhesive surface for leukocytes and inhibits the proliferation of vascular smooth muscle cells [24]. For example, parenteral estrogen therapy markedly attenuates the development of atherosclerosis in female monkeys post-oophorectomy by directly modifying endothelial and vascular smooth muscle function. The impact of estrogen deficiency on the endothelium has been evaluated by observing endothelial function following estrogen replacement. Exogenous estrogen enhanced endothelium-dependent vasodilation in normo-cholesterolemic animals post-oophorectomy, as well as in monkeys with dietary atherosclerosis post-oophorectomy. Restoration of endothelial health is also expected to decrease atherogenesis. Estradiol administration corrects coronary endothelium-dependent vasodilation in postmenopausal women, but not in men, with atherosclerosis. This observation suggests that estrogen receptors play an important role in the observed improvement in vasodilation since these receptors are more abundant in women than in men. These findings indicate that estrogen has positive effects on the endothelium, effects that may be expected to decrease both the early and late manifestations of atherosclerosis. Estrogen could benefit women in the setting of an acute coronary event via other mechanisms. Estrogen modifies vascular repair after injury, for example, blunting neointima formation after balloon injury. These animal and human studies elucidate mechanisms whereby estrogen could modify fatal CVD, and in combination with observational data, have led to randomized trials of estrogen therapy to decrease fatal CVD in women [24].

Diagnosis of Menopausal Transition:

Diagnosis of the MT is based on clinical signs and symptoms. During perimenopause, oocytes undergo accelerated depletion, which leads to eventual cessation of ovulation and significant changes in serum and hormonal levels, especially estrogen. As ovarian estrogen production decreases, the pituitary gland increases follicle-stimulating hormone (FSH) production to stimulate the ovary to secrete estrogen. Menstrual cycle changes that occur in perimenopause are usually marked by elevated FSH levels and decreased levels of inhibin, whereas levels of estradiol and luteinizing hormone (LH) remain normal or may be elevated. However, FSH levels can fluctuate from month to month and from woman to woman during perimenopause, which limits their utility as a predictor [25,26].

Although hormonal changes occur during the MT, hormone measurements are not useful for predicting the stages of MT or the final menstrual period. However, FSH levels can vary significantly across cycles, and the utility of FSH levels for predicting menopause in individual women is therefore low [9]. Several hormonal systems manifest age-related changes that may or may not have their onset during the perimenopausal years. Conditions that are not related to perimenopause, such as obesity,

diabetes, thyroid disorders, or hypertension, often develop during midlife.

As a result, confirmation of perimenopause usually relies on the woman's medical history and the symptoms that she experiences (e.g., irregular menses, hot flashes), as well as ruling out other causes for those changes. However, the physical symptoms that occur and the pattern of menstrual cycles during perimenopause differ markedly from woman to woman. Thus, clinicians should not assume that irregular menstrual cyclesor bleeding indicates the onset of perimenopause without ruling out other causes, including local uterine pathology, pregnancy, and thyroid abnormalities [10].

CONCLUSION

However, we still need to integrate the endocrinology with symptoms and to be able to define the onset of perimenopause when cycles are irregular. Since perimenopause is largely unstudied. Hence, more research is needed in all areas concerning perimenopausal women. Perimenopausal woman's health and quality of life can be maintained and improved through preventive care, lifestyle modifications, early diagnosis of disease or increased risk for disease, and interventions when appropriate. Defining subsets of perimenopausal women by menstrual cycle patterns (menstrual cycle irregularity has been suggested as a risk factor for CVD) and hormonal profiles may be promising tool for identifying susceptibility to increased cardiovascular risks.

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