Major Adverse Cardiac Events in Postmenopausal Females with Acute Coronary Syndromes

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Abstract:
More women die of cardiovascular diseases than from any other illness. Evaluation of coronary artery disease (CAD) among postmenopausal women has been neglected, since it is been considered to be rare.

Keywords: Menopause, cardiovascular, CAD.

Introduction:

Menopause is defined as the permanent cessation of menstruation. The diagnosis is made retrospectively after menstruation is absent for 12 months. Most women enter menopause between the ages of 49 and 52 years ***(1)***.

Menopause before the age of 40 years is defined as premature menopause. It represents a primary ovarian failure where there is a depletion of ovarian follicles, the primary source of estrogen. The majority of symptoms are due to estrogen deficiency***(2)***.

Menopause is a significant event that all women experience in their lifetime, and they spend one-third of their life in the postmenopausal stage. This brings in significant physiological changes and symptoms that are frequently referred to as postmenopausal syndrome. These symptoms adversely affect the quality of life ***(3)***.

Stages of reproductive aging

Reproductive aging includes 7 stages: 5 before and 2 after the final menstrual period not all women will experience each of these 7 stages. Moreover, the duration of each of these stages varies between women, and each stage is characterized by variable changes in the menstruation pattern, hormonal levels, and menopause-related symptomatology, underscoring the complexity of studying the MT and its potential for health-related sequelae ***(4)***.

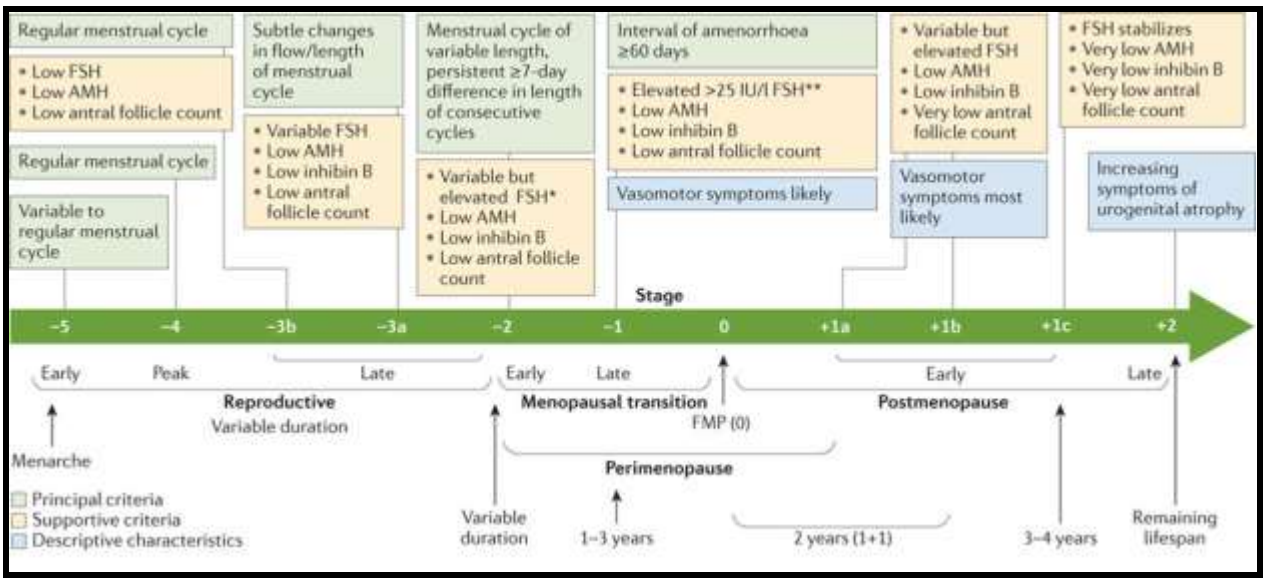

Figure 1: The Stages of Reproductive Aging ***(5)*.**

Epidemiology of IHD in women

The view of CAD as a "man's disease" is gradually dissipating as its recognition as a major cause of morbidity and mortality amongst women continues to grow. Among Americans aged 20 years or older, 16.5 million have CAD (6.3% US adults) ***(6)***.

The prevalence among men is 7.4% and 5.3% in women ***(7)***. As women age, the incidence of all initial coronary events including myocardial infarction (MI), angina pectoris, unstable coronary syndromes and coronary deaths) increases and eventually approaches that of men by age 60 ***(8, 9)***.

Women develop coronary heart disease (CHD) several years later than men, with a notable increase in CHD risk during midlife, a period coincident with the menopause transition (MT). This observation led to the hypothesis that the MT contributes to the increase in this risk***(5)***.

There is a lag time period of about 10 years in the incidence of all coronary events in women behind men which increases to about 20 years for critical events such as MI and sudden death ***(7, 10)***. Notably, the incidence of total coronary events triples in women over age 65 compared to younger women ***(11)***.

There is evidence of a racial disparity as black women aged 45–64 within the Atherosclerosis Risk in Communities (ARIC) study were significantly more likely than their white counterparts to experience CVD death as a first event ***(12)***.

Discouragingly, recent statistics indicate that although the overall CVD mortality is decreasing for both men and women, it is accelerating in younger women, especially those in mid-life ***(13, 14)***.

Effects of menopause on metabolic parameters

For more than 50 years, estrogen has been considered cardioprotective. The first suggestions arose from sex differences in clinical presentation of myocardial

symptoms and events; angina and infarction appear about a decade earlier in men than in women ***(15)***.

Oestrogen deficiency has profound metabolic and vascular effects. It is associated with adverse changes in lipids and lipoproteins. There is an increase in total and LDL cholesterol, together with apolipoprotein B, an increase in triglycerides, and a decrease in HDL cholesterol and apolipoprotein A1 ***(16)***.

Levels of lipoprotein (a), an independent coronary risk factor, also increase. There may be increased oxidation of LDL particles which encourages atheroma formation ***(17)***.

Glucose and insulin metabolism also changes at the menopause. Whilst there is no immediate change in circulating glucose and insulin concentrations, this masks a decrease in pancreatic insulin secretion with a simultaneous decrease in insulin clearance ***(18, 19)***.

Following the menopause, there is a steady decrease in insulin sensitivity so that postmenopausal women become increasingly insulin resistant. There is often an increase in fat mass, but more importantly, there is a redistribution of body fat with a relative increase in central fat ***(20)***.

This results in further abnormalities of lipids, lipoproteins, glucose, and insulin metabolism due to increased fatty acid fluxes into the portal vein. It is possible that there are increases in blood pressure associated with the menopause although it is difficult to separate menopausal effects from those of ageing, but there is an increased incidence of hypertension in postmenopausal women ***(1)***. There is also an impairment of vascular endothelial function ***(21)***. All of these changes encourage the development of atheroma ***(17)***.

Risk factors of CVD in menopause

(I) BMI and adiposity

More than 42% of US women 40 to 59 years of age have a BMI ≥30 kg/m2 ***(22)***. The age-adjusted prevalence of obesity is higher among middle-aged women (40–59 years of age, 42.1%) than younger women (20–39 years of age, 34.4%) ***(23)***.

In postmenopausal women with a BMI ≥40 kg/m2, a waist circumference of 115.5 to 122 and >122 cm, compared with ≤108.4 cm, was associated with higher total mortality and incidence of both CHD and heart failure ***(24)***. Moreover, postmenopausal women who had normal BMI with higher central adiposity (defined as waist circumference ≥88 cm) were at higher risk of mortality than those with normal BMI and no central adiposity ***(25)***.

(II) Sedentary life style

Evidence demonstrates a strong inverse dose-response association between amount of physical activity and cardiovascular mortality ***(26)***. Current recommendations encourage women to engage in ≥150 min/wk of moderate-intensity aerobic (or 75 min/wk of vigorous) physical activity ***(5)***.

A systematic review found that the association between sedentary behavior and all-cause mortality and CVD mortality was nonlinear. Specifically, the risk for all-cause and CVD mortality risk increased more rapidly with >8 h/d of sedentary behavior***(27)***.

(III) Cigarette smoking

Women who smoke die ≈11 years earlier than women who have never smoked ***(28)***. A meta-analysis of prospective cohort studies suggests that the relative risk of CHD from smoking 1 cigarette per day is higher in women than in men ***(29)***. Compared with women who never smoked, women who smoke have an increased risk of CHD and stroke incidence, as well as mortality from CHD and all causes ***(30)***.

(IV) Blood pressure

Hypertension remains the most prominent modifiable CVD risk factor that increases with age among women ***(31, 32)***. Pooled data from 124 prospective cohort studies that included 1.2 million individuals, of whom 44% were women, found that, after controlling for comorbidities, every 10–mm Hg increase in SBP was associated with a 15% increased risk of CVD for both men and women ***(33)***.

(V) Diabetes mellitus

Diabetes is a stronger risk factor for CVD mortality in women than in men ***(34, 35)***, and some evidence suggests a link between menopause and higher risk of type 2 diabetes ***(20)***. In a pooled analysis of >850 000 participants with diabetes, the risk of CVD was 44% greater in women compared with men ***(36)***.

Menopause related symptomatology

As women traverse the MT, they may experience multiple symptoms such as hot flashes and night sweats (ie, vasomotor symptoms), mood changes (eg, depression and anxiety), and sleep and cognitive disturbances, as well as genitourinary and sexual function changes. Links between many of these symptoms and CVD risk have been found ***(37, 38)***.

(I) Vasomotor symptoms

Vasomotor symptoms are the most common menopause-related symptoms (≈80% of midlife women) that affect a woman's quality of life and may require medical treatment. Vasomotor symptoms can last for 10 years, with a longer duration among women whose symptoms begin early in the MT ***(39)***.

The timing and frequency of vasomotor symptoms vary over the MT, with 4 patterns having been identified: (1) early onset of vasomotor symptoms 11 years before FMP with a later decline, (2) onset near the FMP with a later decline, (3) persistently high frequency, and (4) persistently low frequency ***(40)***.

The cause of vasomotor symptoms seems to be multifactorial, with reproductive hormones playing an integral role. Other factors found to be related to a higher occurrence and severity of vasomotor symptoms include obesity before menopause, cigarette smoking, higher levels of anxiety and depression, lower level of education, and premenopausal symptoms. Data on physical activity, diet, and alcohol consumption and their associations with vasomotor symptoms occurrence are not consistent ***(39)***.

Vasomotor symptoms reported at midlife have been linked to an adverse lipid profile, insulin resistance, and greater risk for incident hypertension ***(41)***. A cross-sectional SWAN analysis reported that

women with hot flashes had reduced flow-mediated dilation and greater aortic calcification, independently of CVD risk factors and estradiol, compared with women reporting no hot flashes ***(42)***.

(II) Sleep disturbance

Sleep disturbance is a common complaint during the MT. Women report poorer sleep during the perimenopause stage than the late reproductive age, with the severity of sleep-disordered breathing increasing as women transition from premenopause to postmenopause, independently of chronological aging or changes in body habitus ***(43)***.

Vasomotor symptoms, hormonal changes, comorbid conditions, obesity, and psychosocial factors have been linked to increased sleep disturbances during the MT***(40)***.

Cross-sectional studies of women at different stages of the MT showed significant associations of objective measures of poorer sleep quality with greater risk of metabolic syndrome ***(44)*** and both carotid plaque and cIMT ***(45)***. Self-reported poor sleep quality has been independently linked to a greater risk of aortic calcification in midlife women ***(46)*** and to higher arterial stiffness in perimenopausal, but not premenopausal, women ***(47)***.

(III) Depression and anxiety

Well-designed longitudinal studies of clinical depression reported 2- to 5-fold higher risk for major depressive episodes during perimenopause compared with late premenopause. Moreover, midlife women are more likely to experience anxiety symptoms over the MT, which peak during late perimenopause. Both depression and anxiety symptoms tend to decline after menopause ***(38, 40)***.

Depressive symptoms during the MT also have been strongly linked to increased CVD risk ***(48, 19)***. In healthy women 46 to 59 years of age in the SWAN Heart Study followed up for 5 years, having ≥3 versus no episodes of depression was significantly associated with elevated coronary artery calcification scores***(50)***.

Cardiovascular mortality

Although there has been a decline in overall cardiovascular mortality in men and women from 2000 to 2014, the leading cause of death among women remains CAD ***(7)***. Despite advances in diagnostic and medical therapies, increased public awareness efforts and improved access to care, greater than 250,000 women in the US still die annually from CHD-related deaths fivefold higher than women with breast cancer ***(51, 52)***.

Women are more likely to die after their first MI whereas men have four times more coronary events than women ***(6)***. There is an even greater disparity among middle-aged black women as they have a 2.5 times higher mortality from CAD than similarly-aged white women ***(53)***.

The vast majority of studies have reported higher mortality rates for women compared with men after an acute MI, but this trend may be explained by age, higher prevalence of cardiac risk factors, poorer clinical presentation and treatment

differences ***(54)***. There is also evidence suggesting worse mortality rates in younger women following an acute MI ***(55, 56)***.

Hormonal replacement therapy and cardiovascular outcomes

Oestrogen induces vasodilatation by stimulating nitric oxide production and by reducing the release of the potent vasoconstrictor, endothelin-1. It also inhibits calcium channels and activates BKCa channels ***(57)***. Oestrogen reduces angiotensin-converting enzyme activity and is usually associated with small decreases in blood pressure. The addition of drospirenone, a progestogen with antimineralocorticoid effects, results in a further decrease in blood pressure ***(58)***.

Oestrogen has a dose-dependent effect on matrix metalloproteinases which are involved with vascular remodelling ***(59)***. Thus high-dose oestrogen could potentially destabilise atheromatous plaques but at lower doses oestrogen may normalise the remodelling processes and potentially reduce atheroma formation ***(17)***.

Many observational studies have shown that postmenopausal HRT use is associated with a 40–50% reduction in cardiovascular outcomes, primarily CHD events. There is also good evidence that HRT use is associated with reduced CHD mortality ***(17)***. In a study of over 90,000 women, those initiating HRT below age 60 years showed a significant reduction in CHD death, whereas in those initiating HRT above age 60 years, the reduction was non-significant ***(60)***.

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