Reproductive milestones across the lifespan and cardiovascular disease risk in women

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death for women across the developed and developing world. Beyond traditional cardiovascular risk factors, a number of reproductive milestones have been recognized. The goal of this White Paper, issued by the International Menopause Society in conjunction with World Menopause Day 2023, is to highlight female reproductive milestones in terms of potential cardiovascular risk and to review recommendations for minimizing that risk. The primary milestones discussed relate to menstrual cyclicity, adverse pregnancy outcomes, breast cancer treatments, and menopause. Each of these categories has a number of permutations that have been shown in observational studies to be associated with increased cardiovascular risks. In current clinical care, recognition of these reproductive milestones has been encouraged so patients can be informed and motivated to engage in primary prevention of cardiovascular disease early in their life course rather than retrospectively later in life. Options for specifically targeted care with specialist teams are designed to enhance success with risk identification, screening and possible detection of CVD, and optimally, primary or secondary prevention of CVD. Promoting cardiovascular health of women has far reaching effects for themselves, their families, and their progeny. It's time to make women's cardiovascular health a priority.

Introduction

In spite of advances in diagnosis and treatment, cardiovascular disease (CVD) remains the number one cause of death in women throughout the developed and developing world. According to the World Heart Federation (WHF), CVD, including heart disease and stroke, is the most common non-communicable disease globally, responsible for nearly 20.5 million deaths, of which more than three-quarters occur in low- and middle-income countries[1]. Cardiovascular disease is responsible for 35% of deaths in women each year – more than 13 times the rate of breast cancer and greater than all cancers combined[2].

In 2021, the *Lancet* Women and Cardiovascular Disease Commission set the task of reducing the global burden of CVD in women by 2030[3]. This international team emphasized that 'cardiovascular disease remains understudied, under-recognized, underdiagnosed, and undertreated.' One of their goals was to ignite global awareness of sex-related and gender-related disparities in CVD[3]. In the following year, the American Heart Association (AHA) issued a call

to action to increase awareness of CVD in women[4]. A primary concern of both groups was that the favorable decline in CVD mortality observed during the past four decades –including coronary heart disease (CHD) and stroke – was decelerating[3,4].

Need for increasing awareness

Perception of risk, the primary factor associated with compliance with CVD preventive recommendations[5,6], has declined among women. In 2019, versus a decade earlier, women were 74% *less* likely to identify heart disease as a leading cause of death[7], and twice as likely (16.5% versus 7.9%) to identify breast cancer versus heart disease as the leading cause[7].

Risk factors for CVD in women can be divided into three categories: well-established risk factors, under-recognized risk factors, and sex-specific risk factors[3]. The well-established are most familiar as targets of medical therapies and lifestyle modifications. They include medical conditions – hypertension, dyslipidemia, and diabetes – along with lifestyle related issues – obesity, unhealthy diet, sedentary lifestyle, and smoking or tobacco use. Hypertension is 'the leading global risk factor for CVD and is the most substantial and neglected health burden in women'[3]. Women have a higher risk of acute myocardial infarction (AMI) associated with hypertension, dyslipidemia, and diabetes than men[3]. Obesity is the most important modifiable risk factor for hypertension and makes a substantial contribution to mortality in women. Under-rated factors include psychosocial risk factors (depression and anxiety); abuse and intimate partner violence (inducing chronic stress); socioeconomic and cultural status, race and poverty; poor health literacy; and environmental risk factors (air pollution). Sex-specific risk factors have come under the spotlight in recent years. They include premature menopause, gestational diabetes, hypertensive disorders of pregnancy, preterm delivery, polycystic ovary syndrome, and systemic inflammatory and autoimmune disorders[3].

The presentation of acute coronary syndromes can differ between men and women, although most present with typical chest pain or chest discomfort[8]. Presenting symptoms in women might include atypical chest pain, dyspnea, weakness, fatigue and indigestion[8]. In a recent survey, fewer women recognized these classic symptoms – chest pain, numbness, jaw pain, or chest tightness – as common signs of myocardial ischemia and heart attack[7]. Denial of symptom recognition and delay seeking and receiving care contribute to the persistence of disparities[4].

Care disparities (vs. men) that existed in the 1990s, persist today. Among patients with acute coronary syndrome (ACS), women < age 65 were less likely to achieve door-to-balloon times within the 90-minute target[4]. Women with the same clinical history as men were less likely to be referred for cardiac-catheterization[4]. Among patients with MI with obstructive coronary arteries, mortality was higher for women, especially at younger ages[4]. Finally, in-hospital mortality was higher in women after revascularization procedures[4]. Among patients presenting with ischemic stroke, women were less likely to be transported to the hospital by emergency services, less likely to receive imaging within the 25-minute target, and less likely to receive tissue-type plasminogen activator with the 2-hour target[4].

In spite of this evidence of need, nearly 20% of postgraduate medical trainees reported no or minimal training in sex-based medical concepts. Clinical education must emphasize risk factors specific or predominantly occurring in women. Interdisciplinary collaboration between medical specialists is necessary. Research, community engagement, and advocacy for public policy and legislative interventions are needed. Awareness campaigns must accentuate the wide-ranging benefits of prevention and lifetime cardiovascular health optimization[4]. These are ambitious and challenging undertakings, and are recognized globally[3].

Sex-specific risk factors in women

When considered in terms of women's life span, the onset of heart attack and stroke historically occurs at ages ≥ 70. The decades before, however, can be considered a 'window' of opportunity for unique risk factor identification and intervention[9]. Over the past 5 years, interest in sex differences in CVD has escalated, with identification of an evolving number of sex-specific factors to aid in recognition and assessment of women's CVD risk (Table 1)[10-17]. Genetic links between cardiometabolic disorders and sex-specific risks have been established[18]. Integrating women-specific risk factors into quantitative risk assessment across the life span is necessary[4].

Along with traditional risk factors, the WHF recognizes high blood pressure or diabetes during pregnancy and menopause as CVD risk factors[2]. A history of preeclampsia and premature menopause (age < 40) have been formally recognized by the AHA and American College of Cardiology (ACC) as risk-enhancing factors[19], but sex-specific risks have yet to be incorporated into any formal risk assessment calculators.

The goal of this White Paper, issued by the International Menopause Society (IMS) in conjunction with World Menopause Day 2023, is to highlight female reproductive milestones in terms of potential cardiovascular risk and to review recommendations for minimizing the risk of CVD in women. While recognizing that traditionally the IMS White Paper emphasizes issues specific to the menopause transition and postmenopause, the focus of this White Paper was selected because of compelling, emerging evidence that the cardiovascular health of women at midlife and beyond reflects reproductive events over their lifespan. A number of reproductive milestones are discussed including those related to the menstrual cycle, adverse pregnancy outcomes, breast cancer treatments, and menopause.

Menstrual cyclicity

In 2006, the American College of Obstetrics and Gynecology (ACOG) issued a Committee Opinion titled "Menstruation in Girls and Adolescents: Using the Menstrual Cycle as a Vital Sign," [20]. The essence was that, once girls begin menstruating, clinicians should ask at every visit the patient's first day of her last menstrual period and the bleeding pattern. By including an evaluation of the menstrual cycle as a 'vital sign', the importance of menstruation in overall health is reinforced. Identification of abnormal menstrual patterns in adolescence may improve early identification of potential adult health concerns. Menstrual cycle characteristics related to cardiovascular risk include premature, late, or irregular menarche, polycystic ovarian syndrome, and functional hypothalamic amenorrhea. Risks of hormone-based contraception are considered[11].

Early menarche

Virtually all discussions of sex-specific risk factors for CVD include early or premature menarche, defined by some as < age 12 and by others as ≤ age 10[10-15,17]. In the Nurses' Health Study, the multivariable-adjusted CV risk for early menarche ≤ age 10 was 1.22 (1.09–1.36)[21]. In an umbrella review of 33 studies, the hazard ratio (HR) for composite cardiovascular disease was 1.15 (95% confidence interval (CI) 1.02–1.28)[22] (Table 2). Premature menarche is associated with development of the metabolic syndrome and increases in body mass index (BMI) and visceral adiposity[15].

Menstrual cycle irregularity

Menstrual cycle irregularity across the reproductive lifespan was shown in the Nurses' Health Study to be associated with premature mortality (< age 70)[23]. In over 24 years of follow-up, 79,505 premenopausal women without CVD, cancer, or diabetes mellitus reported length and regularity of menstrual cycles. Outcomes included all-cause and cause-specific premature (≤ age 70) mortality. Those whose cycle was always irregular or absent were at increased risk for premature death (< age 70) due to CVD and cancer. With menstrual irregularity or absence reported at ages 14–17, in multivariate models the risk of premature death was increased (relative risk (RR) 1.22; $p = 0.006$); for menstrual irregularity at ages 18–22, the risk was further increased (RR 1.39; $p = 0.004$); and for menstrual irregularity at ages 29–46, the highest risk of premature death occurred (RR 1.50; $p = 0.001$)[23]. Significantly increased risk of premature mortality persisted after adjusting for BMI, physical activity, lifestyle factors, and excluding women with hirsutism and clear signs of polycystic ovarian syndrome (PCOS)[23].

Polycystic ovarian syndrome

The potential for cardiovascular risk in women with PCOS reflects the frequent development of the metabolic syndrome and its components (hyperandrogenism, obesity, insulin resistance, dyslipidemia, and hypertension) with evidence of subclinical and clinical CVD[24]. In a meta-analysis of cohort studies, the odds ratio for ischemic heart disease was 2.77 (95% confidence interval (CI) 2.12–3.61)[25]. However, a 2021 National Heart, Lung and Blood Institute (NHLBI) workshop found that evidence for independent associations between PCOS and CVD was inconclusive[26]. In contrast, the 2023 International Guideline for Management of PCOS recommends that PCOS should be included as a CVD risk factor in risk assessment tools, that women with PCOS should be considered at increased risk of CVD and potentially, of CV mortality, and they should be assessed for CVD risk factors. Preventive strategies should be prioritized[27].

Functional hypothalamic amenorrhea

Whether functional hypothalamic amenorrhea (FHA), a spectrum of clinical disorders – extreme caloric deprivation (anorexia nervosa), excessive energy expenditure (the athletic triad), or stress-induced amenorrhea – is associated with increased CVD risk is uncertain[28,29]. Primate models of stress-induced amenorrhea demonstrated abnormal coronary vasomotion and premature

atherosclerosis[30]. The Women's Ischemia Syndrome Evaluation (WISE) reported endothelial dysfunction in women with FHA[31]. More study is needed to confirm long-term CVD risk.

Hormone-based contraception

The early association of oral contraceptives (OCs) with increased short-term CVD risks (thrombosis, stroke, and ischemic heart disease) reflected higher doses of ethinylestradiol than those currently prescribed (< 35 μg and often, < 20 μg)[15]. In a recent analysis from the UK Biobank, increased stroke risk (HR 2.49; 95% CI 1.44–4.30) was observed primarily during the first year of use[32]. Recommendations to avoid OCs include women who smoke and are > age 35 years, or who have uncontrolled hypertension or thrombophilia[15]. Women with migraine have increased risk of stroke with OCs; those with dyslipidemia have elevated risks of MI and stroke[22]. Women with a history of high blood pressure in pregnancy who then used combined OCs (COCs) had a higher risk for myocardial infarction and venous thromboembolism (VTE) than COC users who did not share that history[33]. For women with CVD or high baseline CVD risk, long-acting reversible contraceptive options and progestin-only choices are preferable[14]. Progestins may have independent effects on vascular health[34]. Risk of thrombosis appears to be lower with norgestrel- or levonorgestrel-containing OCs compared with those containing desogestrel or gestodene; risk may be higher yet with drospirenone[35]. The question of whether COCs confer long-term CVD risks or possible benefits merits additional study[36].

Infertility

In a prospective cohort study of the Nurses' Health Study II (n = 103,729), 27.6% of participants reported infertility[37]. Those with a history of infertility had a greater risk of CHD (HR 1.13; 95% CI 1.01–1.26), particularly with an earlier age of infertility (≤ 25 years) (HR 1.26; 95% CI 1.09–1.46). Causes of infertility were predominantly ovulatory disorders (HR 1.28; 95% CI 1.05–1.55) or endometriosis (HR 1.42; 95% CI 1.09–1.85). Whether women had PCOS or compromised ovarian reserve was not specified, neither were drugs for ovulation induction or presence of inflammation. In a prospective follow-up of the Women's Health Initiative (WHI), a history of infertility at baseline was associated with an increased risk of heart failure, specifically, with preserved ejection fraction (HR 1.27; p = 0.002)[38]. This occurred independently of traditional cardiovascular risk factors. Of note, peripartum cardiovascular complications (preeclampsia, heart

failure, arrhythmias, stroke, pulmonary edema and venous thromboembolism) have been reported when conception was achieved through assisted reproductive technology[39].

Adverse pregnancy outcomes

In 2018, ACOG and the AHA leadership promoted collaboration in risk identification and reduction of CVD in women[40]. Adverse pregnancy outcomes (APOs) – preeclampsia, gestational diabetes, small for gestational age, low birth weight, growth retardation, and preterm delivery – are more common in women with pre-pregnancy risk factors – hypertension, glucose intolerance, hyperlipidemia, and obesity. All APOs portend future CVD[41].

An umbrella review examined the association between reproductive factors in young women and subsequent CVD[22]. The review included 24 meta-analyses and eight systematic reviews with median patient follow-up of 8–10 years, and evaluated the association of fertility-related factors and adverse pregnancy outcomes with future CVD events (composite CV outcomes, ischemic heart disease, peripheral artery disease, stroke, and heart failure). Women with recurrent preeclampsia experienced the highest risk – a 3-fold rise in congestive heart failure. Preeclampsia was associated with a 2-fold greater risk of composite CV outcomes, including ischemic heart disease and stroke. Gestational hypertension, placental abruption, and recurrent miscarriage were associated with 1.5–1.9-fold increased risks. Early menarche, preterm birth, and PCOS increased risks < 1.5-fold.

In another analysis, a hypertensive disorder of first pregnancy was associated with a significant increased risk of CVD (CHD or stroke) (HR 1.6)[42]. When distinguished as preeclampsia vs. gestational hypertension, preeclampsia was associated with a 2.2-fold increased risk of CHD, whereas gestational hypertension was associated with a 1.6-fold increased risk of stroke[42]. The potential physiologic mechanisms linking hypertensive disorders of pregnancy with CVD include endothelial dysfunction and inflammation[14]. A Mendelian randomization analysis found that any hypertensive disorder of pregnancy was associated with CHD and ischemic stroke[43].

To further appreciate the extent of risks during pregnancy, the intergenerational life cycle has recently been spotlighted, calling attention to the interpregnancy effects of the mother's experience upon the fetus[44]. A review of Danish national health registers revealed that those born to mothers with hypertensive disorders of pregnancy had an increased risk for diabetes[45].

History of adverse pregnancy outcomes poses a special challenge. In recognition of the need for collaboration between cardiologists and obstetricians to promote risk identification and reduction of CVD[40], an emphasis on pre-pregnancy counselling, monitoring during pregnancy, mindful planning of delivery, and prolonged postpartum follow-up with appropriate multidisciplinary care has been proposed[44,46-49]. In the US, where maternal mortality rates are amongst the highest of developed countries, some academic centers have established cardio-obstetrics units to facilitate these goals[46], a measure endorsed by the Lancet Commission[3].

Breast cancer

Breast cancer and CVD share risk factors: age, diet, family history, alcohol intake, hormone replacement, obesity/overweight, physical activity, and tobacco use[50]. Although breast cancer is not a reproductive milestone, *per se*, treatment often disrupts reproductive function and compromises ovarian hormone production. The field of Cardio-oncology has emerged as clinical awareness of the far-reaching cardiovascular implications of cancer itself and cancer treatments has advanced. In a cohort from the Surveillance, Epidemiology, and End Results cancer registry that included women with definitive treatment for localized breast cancer and who were alive 5 years after their initial diagnosis, the cumulative incidence of non-breast cancer mortality was almost seven times higher than the cumulative incidence of breast cancer mortality. CVD was the most common cause, affecting 30%[51].

When viewed from the perspective of cancer treatments – chemotherapy, radiation therapy, and endocrine therapy – each affects CV risk differently. Chemotherapy contributes to induced ovarian failure, while agents such as anthracyclines and trastuzumab directly contribute to CV injury, increasing the risk of congestive heart failure[50]. Radiation therapy (RT) of the chest wall increases ischemic heart disease, valvular and pericardial injury, and cardiomyopathy[11,50,52,53]. In the Women's Environmental Cancer and Radiation Epidemiology (WECARE) study of young women (< age 55) with breast cancer, left-sided RT was associated with a significant 2.5-fold increase in CVD events in comparison with right-sided RT[54]. In another study, heart failure and atrial fibrillation/flutter were common within a decade following irradiation[55].

In a 5-year study from the UK comparing CV event rates after initiating endocrine therapy (aromatase inhibitors (AIs) versus tamoxifen), the rate of myocardial infarction or stroke was similar between treatments, whereas the rate of heart failure was significantly increased by 86%

and CV mortality by 50% with AIs vs. tamoxifen[52]. In a separate analysis, thrombotic events dominated CV risks with selective estrogen receptor modulator therapies whereas, with AIs, metabolic syndrome, hypertension, and dyslipidemia were prevalent, and CV event rates increased[56].

In summary, for women undergoing treatment for breast cancer, screening and identification of CVD risk factors and promotion of healthy lifestyle behaviors are priorities. For women with a history of treated breast cancer, these measures should be continued. Referral for cardiac evaluation could be appropriate for monitoring of cardiac function depending upon the specific treatments, symptom development, and clinical presentation, a measure endorsed by the Lancet Commission[3,50,53].

Menopause

As opposed to the reproductive milestones detailed above which are experienced by some, menopause is a universal event for reproductively competent persons born with ovaries who live long enough. The menopause transition can be considered a portal to the second half of life, and as such, provides an opportunity to reassess lifestyle, recognize ongoing and potential health concerns, and encourage a proactive approach to future well-being, particularly cardiovascular well-being[57]. The complexities of cardiometabolic changes during the menopause transition have recently been addressed[13,16,58]. Four key aspects with potential for affecting CVD risk include cardiometabolic health changes, symptoms of menopause, the reproductive lifespan, and menopausal hormone therapy.

Cardiometabolic health changes

Increased prevalence of the metabolic syndrome occurs during the menopause transition, accompanied by increased subclinical atherosclerosis[16,58]. Clinically, weight gain (due to aging) and redistribution of fat as abdominal obesity (due to menopause) occurs while visceral adipose tissue also increases[58]. Increased insulin resistance, deterioration of the lipid profile (increases in low density lipoprotein and triglycerides), and alterations in skeletal muscle composition and metabolism may also contribute to the adverse cardiometabolic profile associated with the menopause transition[16,58].

Vasomotor symptoms

Among the myriad symptoms of the menopause transition, cardiovascular risk is associated with vasomotor symptoms (VMS), sleep disturbances, and depression. Prospective longitudinal evidence from the Study of Women Across the Nation (SWAN) first revealed varying patterns of VMS across the menopause transition[59]. Early onset of VMS, whether persisting or declining after menopause, was associated with increased carotid intima-medial thickness[59]. The association of unfavorable CVD risks with early-onset VMS in premenopausal women has been corroborated[60]. Women with VMS have been shown to have poorer endothelial function, increased aortic calcification, increased coronary artery calcification (CAC), higher carotid IMT and carotid plaque, acute reduction of cardiac vagal control, more prevalent with overweight or obesity, and early-onset VMS (aged 40–53)[61]. Associations between VMS and CVD risk have been reported across multiple cohorts including SWAN, WISE, Healthy Woman Study, MsHeart[61], and the International Collaboration for a Life Course Approach to Women's Reproductive Health and Chronic Disease Events Consortium[62]. Early-occurring VMS are among the strongest predictors of subclinical CVD of many covariates assessed – stronger than CVD risk factors and sex steroid hormone levels[61]. The SWAN investigators have also identified a nearly 2-fold greater risk of clinical CVD events in women reporting frequent VMS of two decades duration[63]. VMS may be emerging as a novel, female-specific CVD risk factor[63]. Associations with VMS include a history of hypertensive disorders of pregnancy and gestational diabetes mellitus[64,65]. It is unknown whether treatment of VMS will reduce CVD risk.

Reproductive lifespan

The reproductive lifespan extends from menarche to menopause with an approximate duration of 40 years. For women who experience menopause < age 40, with a reproductive lifespan of < 30 years duration, CVD risk increases[11]. An analysis of pooled data from 15 observational studies across five countries including 301,438 women identified increased CVD risk in women with menopause < age 40[66]. The event rate was 4.1/1000 person-years; HR 1.55 (95% CI 1.38–1.73), consistent with estimates from other studies[22,67,68]. Shortened reproductive lifespan has been associated with increased risks of ischemic heart disease[21], congestive heart failure[69], and diabetes[70]. Whether these associations reflect shared origins (genetic, lifestyle, environmental

risks) leading to premature aging or are simply attributable to premature estrogen deficiency is a subject of active investigation and debate[71-73].

Menopausal hormone therapy

During the 1980s, scores of observational studies reported benefits of estrogen therapy on cardiovascular risk factors, surrogate markers of CV risk, and clinical CVD outcomes[74]. The Postmenopausal Estrogen and Progestin Intervention (PEPI) trial reported that the effects of conjugated equine estrogen (CEE) and medroxyprogesterone acetate (MPA) or micronized progesterone (MP) on CVD risk factors ranged from neutral to beneficial[75]. Subsequent randomized controlled trials of hormone therapy enrolled women ages 50–79 to evaluate secondary (e.g. Heart and Estrogen Progestin Replacement Study, HERS)[76] and primary (e.g. Women's Health Initiative, WHI)[77,78] prevention of CVD with disappointing results. In the WHI, risks (heart attack, stroke, venous thromboses and breast cancer) exceeded preventive benefits (fracture and colon cancer reduction)[78]. When the CEE-alone trial results were compared to those of the combined therapy (CEE plus MPA) trial, divergent outcomes for cardiovascular and breast cancer events were revealed (more events with combined therapy; fewer with CEE alone)[78]. Further analyses revealed mortality benefit for younger women taking CEE alone[79,80]. A recent umbrella review which assessed 60 systematic reviews, 102 meta-analyses of randomized controlled trials and 38 meta-analyses of observational studies, reported benefit for CVD mortality with estrogen-only therapy, but adverse effects of MHT on stroke and CVD incidence[81].

Stratified analyses of the WHI outcomes by decade of age and years since menopause provided a more clinically relevant assessment of risks and benefits[77,78]. Given that younger women (ages 50–59) are more likely to present with bothersome VMS, it was reassuring that risks were lower than in women ≥ age 60)[78]. Most expert groups recommend a stepwise evaluation to assess appropriateness and safety of women who are considering hormone therapy for symptom relief[57,82-85]. This includes review of contraindications, standardized risk assessment of CVD and breast cancer, and confirmation of uterine status. For women willing to consider hormone therapy, absence of contraindications and low baseline risks of CVD and breast cancer allow the full spectrum of hormone therapy options. For those with intermediate CVD risk, transdermal estradiol therapies and micronized progesterone, if required for uterine protection, are preferred.

Transdermal estradiol preparations have less effect on clotting factors, blood pressure, triglycerides, C-reactive protein, and sex hormone binding globulin, and, at lower doses, are preferable for women with VTE risk, hypertension, hypertriglyceridemia, obesity, metabolic syndrome, diabetes, and history of gallbladder disease[57]. Whereas, for those at high CVD risk, a non-hormonal option for VMS symptom relief should be considered. Oral micronized progesterone seems to have little or no adverse effects on lipids[75]. Several observational studies (ESTHER, E3N, Million Women Study) have evaluated risk of thrombosis and found that risk was higher with MPA than other progestins[86-88]. Micronized progesterone and pregnane derivatives are considered to be neutral regarding thrombosis[86].

Cardiovascular disease risks and benefits of menopausal hormone therapy

What is the current thinking about CVD risk when initiating hormone therapy? If < age 60 or within 10 years of menopause onset, the benefit–risk ratio is favorable for treatment of symptoms and reduction of bone loss and fractures. If age > 60 or more than 10 years since menopause onset, greater absolute risks of heart attack, stroke, thrombosis, and dementia have been reported[85]. What is the current thinking about CVD benefit with hormone therapy? This question continues to generate controversy.

The timing hypothesis revisited

In response to negative outcomes of both primary and secondary CHD prevention trials that enrolled subjects on average at least a decade older than the usual age of menopause, the timing hypothesis, initially proposed by Thomas Clarkson in response to findings in his primate studies, has been revisited[89]. His data originally suggested that estrogen therapy could prevent CHD if initiated close in time to menopause in young women with healthy vasculature at baseline. In the WHI, some findings were consistent with the timing hypothesis. Women ages 50–59 who received estrogen alone for 7.2 years showed a significant reduction in MI, CAC at study end, and reduced revascularization rates[78]. The Danish Osteoporosis Prevention Study (DOPS) was designed to evaluate the effects of hormone therapy on bone health in perimenopausal and recently postmenopausal women. An open-label trial with a number of methodological criticisms, DOPS reported that the prespecified CV safety outcome – a composite of death or hospitalization for MI or heart failure – was reduced at the end of 10 years of therapy in women assigned to hormone

therapy[90]. In further efforts to confirm the timing hypothesis, two randomized placebo-controlled trials were initiated using the surrogate CVD endpoints of CAC and carotid intimal thickness. The Kronos Early Estrogen Prevention Study (KEEPS) evaluated two estrogen preparations, a lower dose of conjugated equine estrogens than used in the WHI and transdermal estradiol at a dose similar to CEE 0.625 mg, both cycled with oral micronized progesterone. At study end, progression of atherosclerosis did not differ in the hormone therapy groups versus placebo[91]. The Early versus Late Postmenopausal Treatment with Estradiol (ELITE) trial evaluated oral estradiol with vaginal progesterone in women < 6 years and > 10 years since menopause. After 5 years of follow-up, carotid intima-media thickness had not progressed to the same degree in the women who started estrogen < 6 years since menopause; CAC was similar between treatment groups[92].

The inconsistencies in trial outcomes could reflect differences in ages of subjects, baseline health, estrogen dose, preparation, mode of administration or concurrent progestogen exposure, and have dissuaded some from recommending estrogen for CHD prevention[3,57,85] while others[13,82] allow that early use of estrogen therapy could provide vascular benefit. Similarities in the trials that provided evidence in support of the timing hypothesis include administering oral estrogen preparations in doses equivalent to or greater than CEE 0.625 mg with little to no progestogen exposure, for durations ≥ 5 years, to younger women (< age 60), close in time to menopause (≤ 6 years)[74]. Based upon these findings, some groups – including the IMS – refer to the possibility of primary prevention even though HT is not approved for this indication[82].

Duration of therapy

Questions arise regarding continuing hormone therapy as women age or restarting hormone therapy if VMS recur after discontinuation[93]. Unfortunately, a paucity of evidence-based guidance regarding the safety of stopping and restarting, or continuing therapy for prolonged periods for women who initiated hormone therapy at the time of menopause for VMS symptom relief challenges the ability to make firm recommendations. Clinical consensus statements allow for continuing MHT in healthy women ≥ age 65 without contraindications following an annual discussion of anticipated risks and benefits and re-evaluation of individual health status[57,82-85]. Commonsense measures include reducing the dose and considering transdermal versus oral estrogen preparations[93]. If new health considerations alter the safety profile, changing to a non-hormonal therapy for symptom relief may be the most prudent approach[93].

Considerations for early menopause or premature ovarian insufficiency

Although 18 years of follow-up of the WHI revealed no increase in mortality for any age group[75], mortality benefit was suggested for women with early menopause due to bilateral salpingo-oophorectomy (BSO). With CEE-alone (after hysterectomy) and BSO at age 50–59, mortality was reduced by 32%; and for those with BSO < age 45, mortality was reduced by 40%[80]. For women with premature ovarian insufficiency (POI) or early menopause, universal recommendations include – in the absence of contraindications or elevated CVD or breast cancer risks – starting hormone therapy promptly following diagnosis and continuing until the anticipated age of natural menopause when the advisability of continuing can be reassessed[57,83,85,94-99].

Most studies have detected an association of POI with cardiovascular disease risk in midlife[22,68,100,101]. In the Canadian Longitudinal Study on Aging, women with POI had a higher 10-year Framingham Risk Score than those with natural menopause at the anticipated age, comparable to those with surgical menopause[102]. Most, but not all, support the finding of elevated CVD risk in women with POI[103]. A Mendelian randomization study that found increased risks of CVD (atrial fibrillation, coronary artery disease, heart failure, and stroke) with earlier age at first birth, number of live births, and earlier age at menarche, found no association with age at menopause[104]. These reports are provocative and underscore the need for more research to establish CVD risk and confirm practice recommendations.

Primary prevention of cardiovascular disease

Within the past 5 years, updated recommendations for primary prevention of CVD in women accentuate screening for sex-specific risk factors[11,105,106]. Adopting a life course perspective, with attention to women's reproductive milestones as outlined in this IMS White Paper, will be beneficial for clinicians now. In the future, sex-specific risks will hopefully be incorporated into standardized CVD risk calculators. Close monitoring and early modification of recognized cardiometabolic factors are key strategies that will at least partly mitigate increased cardiovascular risk conferred by these reproductive factors.

From the standpoint of lifestyle (exercise, diet, weight control, and smoking cessation), recommendations for prevention are universal. In addition to these measures, the WHF, which has as its mission to address all nations/ethnicities, also recommends avoiding alcohol and stress. From

the standpoint of evaluation and management of blood pressure, blood glucose, and blood cholesterol, the WHF recommendations are the same as those in the US and other developed nations.

One accepted strategy consists of encouraging five health behaviors (eat better, be more physically active, quit tobacco, get healthy sleep, and manage weight) along with recommendations to control three risk factors: blood lipids, blood glucose, and blood pressure)[107]. The concept of 'Ideal Cardiovascular Health' includes achieving all these targets[107]. In the US, however, the prevalence of ideal CV health is <1%. The number of persons with ≥ 5 metrics at ideal levels declines with age: for adolescents, at puberty, 45%; at 20–39 years, the peak childbearing years, just 32%, at 40–59 years, the menopause transition, only 11%, and by ≥ 60 years, when manifestations of CVD present, just 4% reach this target[107]. The benefits of striving for ideal CV health are well established. In addition to markedly lowering risk of CVD events and mortality, evidence supports a reduction in the risks of cancer, dementia, end-stage renal disease, and chronic obstructive pulmonary disease. One could anticipate better cognitive function and quality of life, a longer health span, and lower health care costs[107].

From a global perspective, compelling challenges remain to achieve CVD prevention for all. Psychological, racial, ethnic, socioeconomic, geographical, and environmental conditions that lead to disparities in access to medical care, health-promoting resources, and cardiovascular wellbeing must be addressed[3]. The Lancet Commission has provided an overview of specific conditions to be considered in select global geographic areas when identifying and implementing prevention strategies[3]. Clinician awareness of racial and ethnic differences in cardiovascular risk factors and preventive therapies in their home country is an essential step for effective care[108].

Final bottom-line recommendations from the Lancet Commission include:

(1) Close the knowledge gap with appropriately powered clinical trials and health-surveillance systems;

(2) Enhance awareness of cardiovascular disease in women through education;

(3) Target well established, sex-specific, and under-recognized risk factors through screening, detection, and early intervention; and

(4) Strengthen health-care systems and engage health-care professionals.

KEY POINTS

- A growing number of reproductive milestones are associated with increased risks for cardiovascular disease in women.
- Development of a checklist of reproductive milestones that are associated with increased CVD risk would assist practitioners to elicit relevant history from their patients, heighten surveillance for traditional CVD risks, and recommend appropriate preventive measures.
- Adoption of sex-specific milestones as CVD risks included in formal risk calculators would increase general awareness and validate their importance.
- Instituting preventive measures early when the reproductive milestone is initially identified would be anticipated to improve CVD outcomes.
- Reinforcing preventive measures at every clinical visit will enhance awareness of CVD in women and encourage preventive efforts

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Table 1. Reproductive factors contributing to cardiovascular disease risk in women**.**

Menstrual cycle
Menstrual cyclicity/irregularity
Early menarche
Polycystic ovarian syndrome
Functional hypothalamic amenorrhea
Hormone-based contraception
Infertility/fertility treatment
Adverse pregnancy outcomes
Preeclampsia
Gestational hypertension
Gestational diabetes
Miscarriage
Stillbirth
Placental abruption
Preterm birth
Low birth weight
Small for gestational age
Final parity (< 1 or ≥ 5)
Breast cancer
Chemotherapy
Radiation therapy
Endocrine therapy
Menopause
Metabolic syndrome
Vasomotor symptoms
Shortened reproductive lifespan
Early menopause and premature ovarian insufficiency
Menopausal hormone therapy

Table 2. Reproductive milestones and cardiovascular disease risk in women.

Risk increase	Composite cardiovascular outcome	Ischemic heart disease	Stroke	Heart failure
3-fold	–	–	–	Recurrent preeclampsia
2-fold	Preeclampsia, still birth, preterm birth	Preeclampsia, recurrent preeclampsia, preterm birth, gestational diabetes	COCs, preeclampsia, recurrent preeclampsia	
1.5–1.9-fold	Gestational hypertension, placental abruption, POI, gestational diabetes	COCs, early menopause POI, recurrent miscarriage	COCs, recurrent preeclampsia, preterm birth, gestational diabetes	
< 1.5-fold	Early menarche, PCOS, early menopause	Miscarriage, PCOS, preterm birth, menopausal symptoms	PCOS	
Reduced	Longer breast feeding			

COCs, combined oral contraceptives; POI, premature ovarian insufficiency; PCOS, polycystic ovarian syndrome

Data taken from Okoth K, et al. *BMJ* 2020 Oct 7, Table 1, Summary Findings and text[22]