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Pregnancy and Reproductive Risk Factors for Cardiovascular Disease in Women

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Abstract

Beyond conventional risk factors for cardiovascular disease, women face an additional burden of sex-specific risk factors. Key stages of a woman's reproductive history may influence or reveal short- and long-term cardiometabolic and cardiovascular trajectories. Early and late menarche, polycystic ovary syndrome, infertility, adverse pregnancy outcomes (e.g., hypertensive disorders of pregnancy, gestational diabetes, preterm delivery, and intrauterine growth restriction), and absence of breastfeeding are all associated with increased future cardiovascular disease risk. The menopause transition additionally represents a period of accelerated cardiovascular disease risk, with timing (e.g., premature menopause), mechanism, and symptoms of menopause, as well as treatment of menopause symptoms, each contributing to this risk. Differences in conventional cardiovascular disease risk factors appear to explain some, but not all, of the observed associations between reproductive history and later-life cardiovascular disease; further research is needed to elucidate hormonal effects and unique sex-specific disease mechanisms. A history of reproductive risk factors represents an opportunity for comprehensive risk factor screening, refinement of cardiovascular disease risk assessment, and implementation of primordial and primary prevention to optimize long-term cardiometabolic health in women.

Keywords

Cardiovascular Disease; Pregnancy; Risk Factors; Women; Sex; Gender

Introduction

Cardiovascular disease (CVD) is the leading cause of death in women and men in the U.S. and worldwide.[1] Women and men share conventional CVD risk factors, albeit with important sex differences,[2, 3] but mounting evidence has identified unique sex-specific risk factors related to reproductive and pregnancy history in women. These sex-specific risk factors are increasingly recognized in cardiovascular and obstetrical society guidelines, with premature age of menopause and adverse pregnancy outcomes (APOs) in particular now codified as risk-enhancing factors for atherosclerotic CVD (ASCVD).[4–7]

In this review, we summarize the current evidence for associations and mechanistic links between a woman's reproductive history and CVD risk, spanning menarche to menopause, infertility, and pregnancy (Figure 1). We review how reproductive history might be further incorporated in clinical practice and highlight important unanswered questions and directions for future research.

Age of Menarche and CVD Risk

Menarche is the onset of the first menstrual period and often considered the central event of female puberty. The average age of menarche is approximately 12 years in the U.S. Early menarche is typically defined as occurring before age 12 years, but some researchers have defined it as occurring before 10-11 years of age. While genetic factors play a role, potentially modifiable factors such as lower birthweight, increased weight fluctuation during childhood, and especially higher childhood body mass index (BMI) may increase the

likelihood of early menarche.[8] In parallel with rising rates of obesity in children, the mean age of menarche in the U.S. has decreased over the past 20 years from 12.1 to 11.9 years.[9] Black and Hispanic women are disproportionately likely to undergo early menarche.[10]

Early menarche is associated with future obesity and metabolic syndrome in adulthood. Whether this is independent of pre-menarchal and adolescent BMI values is unclear. In the U.K. EPIC-Norfolk study of 15,807 women, history of early menarche was associated with greater odds of having hypertension, diabetes, obesity (BMI ≥30 kg/m^2), and central obesity (waist circumference ≥80 cm) later in life.[11] Other studies have linked early menarche with greater risk of future metabolic syndrome and its individual components, including dyslipidemia and hypertension.[12]

Early menarche has been associated with a 15-30% higher risk of future CVD[11, 13, 14] independent of sociodemographic factors.[11, 14] Data further suggest the relationship between age of menarche and future CVD may be U-shaped, with increased risk also noted for late menarche (after age 17).[13–15] The association of early menarche with future CVD may be stronger in higher-risk women. Among women with suspected ischemia undergoing coronary angiography in the Women's Ischemic Syndrome Evaluation study (mean baseline age 58 years), a history of menarche ≤10 years of age was associated with >4-fold risk of a subsequent major adverse cardiovascular event over 6-year follow-up (hazard ratio [HR] 4.53, 95% CI 2.13-9.63) in adjusted analysis; menarche ≥15 years of age was also associated with CVD risk (HR 2.58, 95% CI 1.28-5.21).[15]

Mechanisms linking early menarche to increased CVD risk later in life are incompletely understood. Given the strong association between elevated childhood BMI and early menarche, early menarche may reflect genetic or lifestyle factors, including excess calorie consumption and reduced physical activity. Higher leptin levels, which are associated with increased adiposity, are associated with earlier onset of menarche.[16] This suggests dysregulation of adipokines during puberty may reflect negative metabolic influence that increases a woman's CVD risk later in life.[16] Early vs. normal or late menarche is associated with unfavorable levels of insulin, glucose, blood pressure (BP), and body fat among adolescent girls.[17]

Polycystic Ovary Syndrome and CVD Risk

Polycystic ovary syndrome (PCOS), which affects 5-13% of women, is characterized by amenorrhea or oligomenorrhea, hyperandrogenism and its associated clinical features (e.g., hirsutism, acne), and polycystic ovaries.[18] PCOS is associated with an adverse cardiometabolic profile. Women with PCOS have a higher prevalence of elevated BMI, dyslipidemia, hypertension, and insulin resistance and deficiencies in insulin secretion[19] compared with similarly-aged women without PCOS.[18, 20] The most common lipid abnormalities noted in PCOS are elevated low-density lipoprotein cholesterol (LDL-C), elevated triglycerides, and decreased high-density lipoprotein cholesterol (HDL-C) levels.[21] Among women with PCOS, insulin resistance is seen in approximately two-thirds,[22] and 7.5-10% have established type 2 diabetes (T2D).[23] Women with PCOS have a higher risk of developing T2D independent of BMI.[24] In addition, a recent meta-analysis

confirmed an association between PCOS and incident hypertension (pooled RR 1.70, 95% CI 1.43-2.07), although risk attributable to PCOS was greater among women of reproductive vs. post-menopausal age.[25] PCOS has also been associated with higher levels of inflammatory markers such as C-reactive protein (CRP) as well as thrombotic markers such as homocysteine.[26, 27]

Women with PCOS have greater carotid intima-media thickness (CIMT) and coronary artery calcium (CAC), even after adjusting or matching for BMI vs. women without PCOS.[28–30] The relationship between PCOS and clinical CVD is well established, but data are conflicting regarding whether excess cardiovascular risk conferred by PCOS is independent of other conventional risk factors. Some studies,[31, 32] but not all,[33, 34] have reported increased CVD risk among women with PCOS after accounting for adiposity. A recent meta-analysis found that PCOS was associated with a 30% higher risk of overall CVD (OR 1.30, 95% CI 1.09-1.56), including both coronary heart disease (CHD, OR 1.44, 95% CI 1.13-1.84) and stroke (OR 1.36, 95% CI 1.09-1.70).[35] A recent Danish registry found 19% increased risk of incident CVD (adjusted HR 1.19, 95% CI 1.07-1.33) for women with PCOS, but this association was not seen in women after age 50 years.[36] Women with PCOS are also approximately 3-fold more likely to develop APOs, including gestational diabetes mellitus (GDM) and preeclampsia, which in turn predict increased CVD risk.[37]

Contraception and CVD Risk

Multiple effective contraceptive options are available, including long-acting reversible contraception (LARC, levonorgestrel-releasing and copper intrauterine devices [IUDs] and subdermal implants), injectable depot medroxyprogesterone acetate, combined oral contraceptive pills (OCPs) that contain a combination of estrogen and progestins, progestin-only pills, the transdermal contraceptive patch ("the patch"), and the vaginal ring (NuvaRing) (Figure 2). Of these, LARCs are preferred given high efficacy and safety, especially in women with established CVD or high CVD risk, where avoidance of unplanned pregnancy is key.[38, 39] As copper IUDs are associated with increased menstrual bleeding, hormonal IUDs may be preferred in women taking antiplatelet therapy or anticoagulation.[39]

OCPs are the most prescribed contraceptive method in the U.S. and are used by approximately 25% of women of reproductive age. Safety concerns that arise from their use are largely related to estrogen content.[38, 39] The metabolism of the synthetic estrogens can cause blood pressure to rise, and normotensive women taking OCPs can have up to a 7-8 mmHg increase in BP.[40] Within the first year of use, risk of venous thromboembolism (VTE) is increased among OCP users (3-9/10,000 woman-years) compared with nonusers (1-5/10,000 woman-years).[41] Similar to elevations in BP, this increased VTE risk is attributed to the synthetic estrogens within the pills. Progestins in OCPs have evolved over time to reduce, but not erase, this VTE risk. The risk of myocardial infarction (MI) or ischemic stroke also appears to be higher in women using OCPs, especially those formulations with higher levels (≥50 μg) of estrogen.[42] The hormonal makeup of these pills has evolved, with newer generations of OCPs containing less synthetic ethinyl estradiol

(≤30 μg) than older generation pills, reducing the CVD risk associated with newer pills; older data may therefore overestimate contemporary OCP-associated risks.

Cardiovascular risk factors should be considered when prescribing OCPs. Women with uncontrolled hypertension (BP ≥160/100 mmHg) should not use OCPs, and they are also not recommended in women with systolic BP 140-159 mmHg and diastolic BP 90-99 mmHg or in women over the age of 35 years with controlled hypertension. Smoking is a relative contraindication with OCPs given that concurrent use is associated with a 10-fold increased risk of MI and 3-fold increased risk of stroke.[43] OCPs are not recommended in women at increased risk of VTE, which includes but is not limited to women in the early postpartum period, ≥35 years old who use tobacco, and those with thrombophilia.[39] The *U.S. Medical Eligibility Criteria for Contraceptive Use*, in addition, cautions against the use of OCPs in other groups of women, including women with a history of ischemic heart disease, migraine with aura, or complicated valvular heart disease or certain congenital heart disease conditions.[38] LARCs and progestin-only options are recommended for these patients.[38, 39] Although barrier methods are safe from a cardiovascular perspective, use of barrier methods in isolation is discouraged given their poor efficacy. An update to the U.S. Medical Eligibility Criteria is expected in 2022.

Infertility, Fertility Treatment, and CVD Risk

High-quality data on the relationship between infertility (defined by the World Health Organization as inability to achieve pregnancy after ≥12 months of unprotected intercourse), fertility treatment, and cardiovascular risk are limited. Women with infertility, even prior to conception, have a higher prevalence of cardiovascular risk factors,[44–46] suggesting that shared risk factors may underlie both infertility and CVD. Higher rates of diabetes and chronic hypertension[45] and obesity[46] are seen in both women with infertility and CVD as well as shared comorbidities, e.g., PCOS as discussed above.

Use of assisted reproductive technology (ART) itself is also associated with increased CVD risk, although causality is unclear. High-quality studies to clarify these relationships are challenging due partly to marked disparities in access to ART and variability in ART practice patterns. ART use is associated with significantly higher rates of APOs such as hypertensive disorders of pregnancy (HDP) and GDM,[44] conditions which in turn are associated with increased future CVD. A systematic review of 47 studies showed that *in-vitro* fertilization in particular is associated with HDPs.[47] Data regarding the longer-term associations of ART use with long-term cardiovascular health, however, are both limited and mixed.[44, 48] One cohort study of >6,000 women found no increased risk after successful ART, suggesting ART itself may not be a causal risk factor.[44] Further research is needed to clarify whether ART is a marker for subclinical risk at the time of fertility treatment or whether it contributes causally to CVD risk.

Pregnancy

Hypertensive Disorders of Pregnancy and CVD Risk

HDPs include pre-pregnancy chronic hypertension, gestational hypertension, preeclampsia/eclampsia, and preeclampsia superimposed on chronic hypertension.[49] Preeclampsia is a pregnancy-specific hypertensive disorder and multisystemic syndrome of inflammation, oxidative and endoplasm reticulum stress, and angiogenic dysfunction.[50] Early preeclampsia pathophysiology includes abnormal trophoblast invasion of the endometrium, which leads to incomplete spiral artery remodeling and, ultimately, placental ischemia, although researchers and clinicians suspect that the diverse presentations of preeclampsia likely reflect a spectrum of pathophysiology.[51] Our understanding of preeclampsia subtypes, at present, is rather crude and based largely on timing of onset during pregnancy (early vs. late), presence of severe features, or association with intrauterine growth restriction (IUGR). Each of these features may have different long-term implications.

Association of HDPs with CVD: HDPs are significant sex-specific risk factors for both short- and long-term maternal CVD. During the peripartum period, the odds of stroke,[52] MI,[52] cardiomyopathy[52, 53] and spontaneous coronary artery dissection (SCAD)[54] are significantly increased for women with vs. without a history of HDP. It is also well recognized that such CVD risk extends well into later life.[55–57] Meta-analyses and subsequent large prospective cohort studies have established a two-fold risk of CVD among women with a history of gestational hypertension[55, 57] or preeclampsia[55–57]; research suggests the risk is especially high following preeclampsia with severe features,[57] onset prior to 34 weeks' gestation,[8] term preeclampsia with small-for-gestational age (SGA) infant, or recurrent HDP in >1 pregnancy.[58]

HDPs are associated with future development of chronic hypertension and diverse cardiovascular conditions (Table 1). Furthermore, women with a history of HDPs tend to have earlier-onset CVD, suggesting that HDPs are associated with accelerated cardiovascular aging.[59, 60] Hypertension, diabetes and hyperlipidemia are diagnosed up to 10 years earlier and sub-clinical markers of vascular damage are significantly more prevalent among women with a history of HDP compared to women without.[61–64] Earlier-onset valvular heart disease has also been demonstrated.[62] Beyond the cardiovascular system, women with HDPs have been found to have >2-fold risk of death due to infectious, respiratory, and nervous system disease.[65]

Mechanistic links to CVD: HDPs and vascular disease share common mechanisms which may lead to both the development of preeclampsia and CVD during a woman's life course (Figure 3). The development of HDP in pregnancy has been termed a "failed stress test" that identifies women at higher risk of CVD later in life. Alternatively, or in addition, preeclampsia may causally induce long-term metabolic and vascular abnormalities that increase overall risk for CVD later in life. The extent of vascular dysfunction during pregnancy likely depends on a woman's genetic predisposition and interactions with pre-existing cardiovascular risk factors. Research demonstrates that the association between HDPs and future vascular disease persists but is attenuated when adjusted for pre-pregnancy

CVD risk factors.[56, 77] Causal mediation analyses further suggest that only approximately two-thirds of HDP-associated CVD risk is mediated via traditional CVD risk factors, chiefly development of chronic hypertension.[55, 62] Pathways to specific CVD outcomes likely vary across different HDP phenotypes. It has been postulated that accelerated cellular senescence may represent one mechanism of accelerated cardiovascular aging in women with HDPs.[80, 81]

There appears to be a strong genetic contribution to preeclampsia risk. Women whose first degree relatives had preeclampsia have a 2-3.5-fold risk of developing preeclampsia.[82, 83] Recent data demonstrate that women with HDPs have elevated polygenic risk of hypertension and obesity (Table 2), implying that HDPs signify latent genetic cardiometabolic risk.[84–86] In addition, the fetal *FLT1* gene, whose product (soluble fms-like tyrosine kinase receptor 1) is a causal preeclampsia biomarker, has been associated with development of maternal preeclampsia.[86]

Gestational Diabetes and CVD Risk

GDM results when pancreatic beta-cells incompletely respond to the physiologic and placental-mediated insulin resistance that characterizes pregnancy.[87] Approximately one third of women who develop GDM will develop T2D in the future, corresponding to a 7-fold greater risk compared to women without GDM.[88] International diabetes associations recommend glucose screening starting within the first 1-6 months postpartum and lifelong screening every one to three years in women who develop GDM.[89–91] In women who develop GDM, subclinical risk factors (e.g., suboptimal glycemic control, dyslipidemia, CRP, adiponectin) may be evident prior to pregnancy and early in the first trimester.[92]

Women who develop GDM have a 2-fold risk of CAC at midlife independent of progression to prediabetes or T2D[93] and 1.5- to 2-fold risk of cardiovascular events[94]; CVD event risk appears greater if there is progression to T2D.[94,82] Similar to the relationship between impaired gestational glucose tolerance and risk of subsequent T2D, there appears to be a dose-dependent relationship between degree of glucose impairment during pregnancy and risk of subsequent CVD.[95] These relationships have been consistently demonstrated across databases, countries, and ethnic groups.[95]

Preterm Delivery and CVD Risk

The association between preterm delivery (PTD) and future maternal CVD risk is well established.[96, 97] The underlying mechanisms, however, remain unclear. PTD is broadly defined as a live birth prior to 37 weeks gestation and further delineated based on gestational age (late preterm [34-36 weeks], moderately preterm [32-36 weeks], and very preterm [<32 weeks]). In the U.S., Black women experience the highest rate of PTD at 29% higher than the national average (Figure 4) and have nearly 3-fold risk of delivering a very preterm baby (3.1% vs 1.2% in White women).[98]

Whether PTD occurs spontaneously or due to medical necessity influences its relationship with future CVD risk.[99] Compared with spontaneous term delivery, medically indicated PTD is associated with a higher risk of cardiovascular mortality (HR 3.7) than spontaneous PTD (HR 1.7).[100] Women who experience medically indicated moderate-to-very-preterm

delivery due to HDPs appear to be the highest risk group. Preeclampsia, however, only explains ~25% of the association between PTD and CVD.[101] Although spontaneous and medically indicated PTD share many ASCVD risk factors, the most notable difference is in vascular function. The augmentation index, which indirectly measures smooth muscle vascular function, appears to be reduced in women with spontaneous PTD vs. medically indicated PTD. These findings have been reproduced in both the early antepartum as well as the early postpartum phase.[102, 103]

Infant Birth Weight, Fetal Growth, and CVD

Infant birth weight has been independently associated with maternal CVD risk. In the Women's Health Initiative (WHI), delivery of a low-birth-weight infant was independently associated with increased maternal ASCVD risk after adjustment for conventional risk factors and other APOs (adjusted OR 1.25).[104] Infant birth weight has also been shown to predict maternal life span.[105]

Many studies have examined the association SGA and IUGR, i.e., SGA associated with pathologic growth restriction, with CVD.[106] Fetal growth has been correlated with subclinical markers of CVD including arterial stiffness and endothelial dysfunction.[107, 108] Bonamy et al. observed a multiplicative interaction between gestational age and birth weight, with a 3-fold maternal CVD risk in women with preterm and SGA infants even after accounting for socioeconomic factors, smoking, and pregnancy-related complications.[109] Growth restriction at term is also associated with increased risk of maternal CVD,[110] and, to a lesser extent, with paternal CVD.[105] This suggests that environmental and behavioral risk factors may influence both parents and infants.

Most cases of IUGR are thought to result from uteroplacental insufficiency due to poor implantation of the spiral arteries and subsequent increased placental vascular resistance, which has similarities to the early pathophysiology of preeclampsia. Preexisting hypertension and increasing maternal age have also been associated with growth restriction and may result from endothelial dysfunction that affects placental implantation. Low levels of insulin-like growth factor 1 are found in pregnancies complicated by IUGR and are also associated with increased risk of CVD suggesting a potential shared mechanism.[111] Further research is needed to understand the complex interplay between environmental, behavioral and maternal vascular health and the association between birth weight, fetal growth, and CVD risk.

Other Adverse Pregnancy Outcomes and CVD Risk

Placental abruption has been associated with cardiovascular risk factors and CVD.[112, 113] In a retrospective Dutch study, abruption was strongly associated with other concomitant APOs as well as with higher BMI, total cholesterol, and fasting blood glucose in women with isolated abruption without other APOs.[112] A large retrospective cohort study similarly found a 1.7-fold risk of CVD (aHR 1.7, 95% CI 1.3-2.2) in women with placental abruption or infarction.[113] Pregnancies with large-for-gestational age fetuses are also associated with increased CVD risk, likely mediated by associations with elevated BMI and diabetes.[114, 115]

Though there are numerous shared risk factors between miscarriage and CVD, including obesity and cigarette smoking, data show that miscarriage is independently associated with future CHD and MI after adjustment for conventional risk factors.[116, 117] Greater number of miscarriages appears to associate with progressively higher CVD risk,[117, 118] with one cohort study observing a >3-fold CVD risk associated with ≥3 miscarriages (HR 3.18, 95% CI 1.76-5.78).[118] Mechanisms linking miscarriage to CVD remain unclear, although shared vascular, genetic, immunologic factors have been proposed.[119]

Breastfeeding and CVD Risk Reduction

Maternal breastfeeding is associated with a lower risk of later-life cardiometabolic and CVD independent of socioeconomic and lifestyle factors. A recent meta-analysis indicated that achieving ≥1 year of cumulative lactation was associated with 13% lower risk of chronic hypertension,[120] with a dose-responsive relationship between duration of lactation and degree of risk reduction.[121] An even stronger dose-dependent protective association has been observed between lactation and incident T2D.[120, 122] Notably, associations were not explained by postpartum weight differences by breastfeeding status.[121, 122]

Similar associations have been observed for subclinical atherosclerosis and clinical CVD events.[35] In the Study of Women's Health Across the Nation (SWAN) Heart Study, women who did not breastfeed had elevated risks of aortic calcification (aOR 3.85, 95% CI 1.47-10.00) and CAC (aOR 2.78, 95% CI 1.05-7.14) compared to women who breastfed each child for ≥3 months, even after adjustment for demographic and lifestyle factors.[123] In the Nurses' Health Study, women with ≥2 years of cumulative breastfeeding vs. no breastfeeding had 23% (95% CI 6-38%) lower adjusted risk of CHD events.[124] A recent analysis observed similar findings for cardiovascular hospitalization and mortality.[125]

A smaller number of studies have examined lactation and cardiometabolic risk factors specifically in women with APOs with mixed findings. In a study of 622 women with various APOs seen 6 months postpartum at a dedicated postpartum transitional clinic in Ontario, Canada, increased lactation duration was associated with higher HDL-C and lower fasting glucose, triglycerides, BMI, and risk of metabolic syndrome after adjustment for demographic factors and pre-pregnancy confounders.[126] Finally, in CARDIA, longer duration of lactation was associated with lower risk of incident metabolic syndrome, with greater protection observed in women with vs. without GDM.[127]

Gestation is associated with accumulation of maternal visceral fat and insulin resistance.[128] Given the observed associations of lactation with cardiometabolic traits human and animal studies, lactation has been hypothesized to reset maternal metabolism postpartum. Specific protective mechanisms, however, are incompletely understood. A recent analysis found that lactation duration was inversely associated with computed tomography imaging-derived measurements of pericardial adipose tissue and visceral adipose tissue volumes assessed at age 50, and that longitudinal weight changes mediated only ~20% of this relationship.[129] Mouse studies suggest lactation-related hormones may preserve pancreatic beta cell function.[130]

Parity and CVD Risk

Most large cohort studies suggest a J-shaped relationship between parity and CVD, in which the highest risk is among nulliparous and grand multiparous (≥5 births) women.[131] The Atherosclerosis Risk in Communities Study found that a history of ≥5 live births was associated with CHD risk and hospitalization for MI, independent of breastfeeding history.[132] These studies also found that having a prior pregnancy and no live birth was associated with greater CHD and heart failure risk. Parikh et al., in the largest study to date of 1.3 million Swedish women, observed a J-shaped association between parity and CVD with a nadir of CVD risk in women with 2 births, HR 1.09 (95% CI 1.03-1.15) for women with 1 birth, and HR 1.47 (95% CI 1.37-1.57) in women with ≥5 births.[133]

Parity may be a proxy for socioeconomic and behavioral factors.[134] In the British Women's Heart and Health Study and British Regional Heart Study, a J-shaped association has been observed between number of children and CHD in both sexes, with the lowest prevalence among those with 2 children, suggesting a role of social and lifestyle factors. For those with ≥2 children, each additional child increased the age-adjusted odds of CHD by 30% in women vs. 12% for men, however, suggesting the possibility of additional biological effects in women.

Several putative biological mechanisms have also been proposed to explain this relationship. Repeated pregnancies may result in multiple exposures to the metabolic changes of pregnancy, including insulin resistance, impaired lipid metabolism, weight gain, inflammation, and oxidative stress that result in enduring vascular changes.[135] Further research is needed to fully understand the biological and/or social mechanisms responsible for these associations.

Menopause

The Menopausal Transition and CVD Risk

Menopause is a critical reproductive aging event signifying the end of fertility. The menopause transition (MT) is a complex phase marked by dynamic changes in hormonal and menstrual bleeding patterns as well as multiple physiological and psychological symptoms.[136] A recent American Heart Association scientific statement identifies the MT as a uniquely impactful period of time associated with acceleration in CVD risk.[137] Longitudinal studies following women as they transition through menopause have contributed substantially to our understanding of how the MT is related to increased CVD risk in women.[138]

Lipids/lipoproteins: During the MT, women experience adverse changes in several lipids/lipoproteins measures that have been linked to a greater risk of CVD thereafter. Increases in total cholesterol, LDL-C, and apolipoprotein B levels occur from 1 year before to 1 year after menopause, independent of chronologic aging.[139] Menopause-related increases in LDL-C are independently associated with greater risk of carotid plaque in subsequent years.[140] The association between the MT and HDL-C is complex.[141] Recent longitudinal evaluation of multiple metrics of HDL[142] demonstrates significant increases in HDL-C over

the MT accompanied by changes in other HDL metrics (e.g., efflux capacity) consistent with a more atherogenic profile.[143, 144] Associations of HDL subclasses with early markers of atherosclerosis vary by menopause stage, with higher small HDL-P, lower large HDL-P, and smaller HDL size associated with greater risk of CAC or density in late peri-menopause than in the pre/early peri-menopause stage.[145] Notably, higher estradiol level during the 2 years post-menopause is associated with greater triglyceride content of HDL,[145] a feature that has been linked to greater CVD risk.[146] Thus, changes in HDL quality during the MT are affected by estradiol level and the timing relative to menopause. This could have clinical implications for timing of the initiation of menopausal hormone therapy (HT) and calls for a re-evaluation of the inclusion of HDL-C in risk prediction[147] for midlife women in future studies.

Weight gain and body composition: Women at midlife experience increases in their body weight, apparently unrelated to the MT itself.[148] However, the MT influences where women store body fat. Most recently, using data from SWAN, a nonlinear increase in abdominal visceral adipose tissue was reported with acceleration starting at 2 years before menopause. This acceleration was independent of age, lifestyle factors and overall adiposity. Importantly, the study also showed that the reported menopause-related acceleration in visceral abdominal fat was related to a significant increase in internal CIMT independent of traditional risk factors and overall adiposity.[149] During this period women also accumulate cardiovascular fat[150] which has been associated with increased CVD risk.[151,152]

Vascular health measures: The MT is associated with adverse vascular remodeling (changes in CIMT and adventitial diameter).[138, 153] The MT is also linked to functional metrics of the vasculature.[154–156] Endothelial function may begin to decline during perimenopause.[154] Moreover, arterial stiffness, measured by carotid femoral pulse wave velocity, accelerates within 1 year of menopause independent of other risk factors.[156] Whether changes in vascular health metrics during the MT predict later CVD is currently unknown.

Premature/Early Age of Menopause and CVD Risk

Women experience menopause at a median age of 50.0 years (interquartile range: 48.0-53.0 years).[157] However, 7.3% of women experience menopause between the ages of 40-45 (early menopause) and 1.9% before the age of 40 (premature menopause).[157] Black women experience early menopause more frequently than White or Hispanic women.[158] In addition to reproductive aging, age at menopause is increasingly recognized as a marker of somatic aging and general health.[159] Earlier age of menopause is consistently associated with greater risks of CHD, heart failure, CVD mortality, and/or all-cause mortality.[160–162] Among 144,260 postmenopausal women (40-69 years old at enrollment in 2006-2010) from the UK Biobank followed through 2016, compared with women who experienced menopause after age 40, women with premature natural menopause (<40 years) had a 1.36-fold increase in risk (95% CI 1.19-1.56) for a broad CVD composite outcome independent of traditional risk factors and use of menopausal HT.[160] Similarly, meta-analysis of 32 observational studies including 310,329 women showed a higher risk of overall (RR 1.50, 95% CI: 1.28-1.76) and

fatal (RR 1.11, 95% CI: 1.03-1.20) CHD associated with age of menopause onset <45 vs. ≥45 years after adjustment for conventional CVD risk factors.[163]

The association of premature menopause and CVD risk may be bidirectional. Data from the Framingham Heart Study showed that worse cardiovascular risk factor profile before menopause is associated with earlier menopause, independent of factors known to impact menopause timing.[164] Additionally, a first CVD event before age 35 is associated with 2-fold risk of early menopause.[165]

Exact mechanisms linking age of menopause with CVD risk are unclear. Recent research analyzing data from 11,495 postmenopausal women (aged 40-70) from the UK Biobank with whole exome sequences and 8,111 (aged 50-79) from the WHI with whole genome sequences assessed clonal hematopoiesis of indeterminate potential (CHIP), the age-related expansion of hematopoietic cells with leukemogenic mutation without detectable malignancy, as a potential mechanistic link between premature/early menopause and CVD.[166] CHIP has been linked to accelerated atherosclerosis.[167] Adjusting for potential confounders, premature menopause was independently associated with CHIP; this association was only evident in natural premature menopause but not in surgical premature menopause, supporting the notion that CHIP may predate premature menopause or that both conditions may share upstream risk factors. These findings suggest that history of premature menopause may help identify individuals for CHIP screening and surveillance to guide targeted CVD prevention.

Spontaneous vs. Surgical Menopause and CVD Risk

Menopause can occur as spontaneously or as the result of medications (e.g., chemotherapy) or surgery. Both the mechanism and timing of menopause affect the cardiovascular system differently. Surgical menopause is defined as bilateral salpingo-oophorectomy (BSO), which results in the abrupt loss of endogenous ovarian hormones. Large observational studies suggest that BSO prior to the age of natural menopause is associated with an increased CVD risk and mortality.[168] In the abovementioned UK Biobank study, surgical premature menopause was associated with an 87% increased risk of composite CVD (HR 1.87, 95% CI 1.36-2.58) while natural premature menopause was associated with a 36% increased risk (HR 1.36, 95% CI 1.19-1.59); for CHD specifically, HRs were 2.52 (95% CI 1.48-4.29) and 1.39 (95% CI 1.06-1.82) for surgical and natural premature menopause, respectively.[160] Observational data from both the Nurses' Health Study and the Danish Nurses Cohort Study found that HT use was associated with attenuated CVD risk after surgical premature menopause.[169, 170]

Vasomotor Symptoms and CVD Risk

More than 70% of women report vasomotor symptoms (VMS) at some point during midlife. VMS, including hot flashes and night sweats, are the cardinal symptoms of the MT, though are not isolated to this transition period.[171, 172] There appears to be a dose-dependent relationship between frequency of VMS and CVD risk factors. Women with VMS have a worse overall cardiovascular risk profile.[173] Longitudinal data from the SWAN showed correlation between VMS presence and LDL-C, apolipoprotein B, triglycerides, HDL-C and

apolipoprotein A-1 levels, adjusting for CVD risk factors.[174] VMS are also linked to future hypertension,[175] insulin resistance,[174] and diabetes, independent of obesity.[176]

VMS are correlated with worse metrics of subclinical CVD including increased CIMT, endothelial dysfunction, and arterial calcification. Women with vs. without hot flashes have reduced flow-mediated dilation and greater aortic calcification, independent of CVD risk factors and estradiol.[177] Women who experience hot flashes also have higher CIMT than those without.[178] This relationship appears to be influenced by timing of symptoms, with women who experience VMS earlier in the MT having higher mean and maximal CIMT than those with consistently low frequency of VMS across the MT.[179]

VMS are associated with the development of clinical CVD events. A large meta-analysis reported a 28% increased risk of CVD after adjusting for traditional risk factors.[163] In SWAN, frequent and persistent VMS were associated with increased risk of later CVD events.[180] A prospective cohort study of 11,725 women (aged 45-50 at baseline) followed for 14 years reported 2-fold increased odds of CHD in women with frequent VMS relative to women without symptoms.[176] Other studies show that frequency of VMS is not the only marker of CVD risk. One study showed a stronger association between night sweats and CHD development than with hot flashes.[181] Severity of VMS is also associated with increased risk of CVD.[182]

Exogenous Hormone Therapy and CVD Risk

Prior to randomized controlled trials (RCTs), observational and animal models consistently reported a 40-50% reduction in CVD in women receiving HT compared to nonusers.[183, 184] The belief that HT prevents CVD dramatically changed, however, after unexpected results emerged from 2 large double-blind RCTs. The WHI (primary prevention trial) and the Heart and Estrogen/progestin Replacement Study (HERS, secondary prevention trial) of menopausal HT both concluded that there was no benefit of HT on CVD risk.[185, 186] Furthermore, the WHI study found increased CVD events in older women randomized to HT, while the HERS trial found increased CVD events during the first year of HT use compared to placebo.

Subsequent analyses of the WHI study identified that those receiving HT in the age group 50-59 years or within 10 years of entering menopause did not have excess CVD risk. A 2015 Cochrane review of RCT data also found less CHD in women who started HT less than 10 years after menopause (RR 0.52, 95% CI 0.29-0.96).[187] In a WHI substudy, women who were within 5 years of their final menstrual period also had significantly lower mean CAC when randomized to HT vs placebo after 7 years of follow up.[188] The "timing hypothesis" suggests there is a critical window in which the risks versus benefits of HT and CVD change, whereby women who start HT closer to the age of menopause may have a neutral or possibly reduction in risk of CVD, while women further from menopause (>10 years) and starting HT may have an increased risk of CVD.[189]

Two contemporary RCTs evaluated CIMT and CAC in healthy women who had recently entered menopause to study the timing hypothesis. The Kronos Early Estrogen Prevention Study randomized women within 3-years of their final menstrual period to oral conjugated

estrogen, transdermal estradiol patch, or placebo, with cyclic oral progesterone. After 4 years, there was no difference in CIMT between HT versus placebo groups.[190] The Early versus Late Intervention Trial with Estradiol compared oral estradiol with vaginal progesterone gel vs. placebo in women within six years (early cohort, median age 55.4 years) or >10 years since menopause (late cohort, median age 63.6 years). After 5 years, the early cohort of women randomized to oral estradiol had lower progression of subclinical atherosclerosis as measured by CIMT (p=0.008).[191] These results showed that using HT at the time of menopause did not increase subclinical atherosclerosis progression. While no direct comparison RCTs have examined the appropriate estrogen dose or method of delivery in HT, studies suggest that transdermal estradiols pose lower VTE and stroke risk than oral estrogens.[192, 193] Current HT position statements recommend starting HT in women with premature menopause and continuing through the average age of natural menopause.[194]

While the risks and benefits of exogenous HT on cardiovascular health have been extensively studied over the past 4 decades, current consensus is that HT is appropriate for treatment of VMS in women who are otherwise healthy, within 10 years of menopause, and under age 60 years. However, the decision to pursue HT should still take into consideration a woman's individual CVD risk through a shared decision-making model (Figure 5). Future studies should focus on HT dose, formulation, route of delivery, and duration of use with respect to CVD risk.

Incorporating Reproductive History in Clinical Practice

Sex-specific risk factors represent an important component of comprehensive CVD risk assessment in women. Women with PCOS, for instance, should be screened for glucose intolerance, dyslipidemia, and hypertension.[195, 196] As noted above, a history of premature menopause and APOs are now considered risk-enhancing factors to refine ASCVD risk assessment and guide statin prescription among women aged 40-75 years with borderline (5-<7.5%) or intermediate (7.5-<20%) calculated 10-year ASCVD risk using conventional risk calculators, e.g., the Pooled Cohort Equations.[4,5] Consensus statements recommend close monitoring for CVD risk factors in women during the first year postpartum following APOs.[197] Though guidelines recommend aspirin use for the prevention of preeclampsia in persons at risk,[198] data are unclear regarding the long-term benefit of aspirin use for cardiovascular prevention in women with a history of HDP.[198] A recent AHA statement on menopause and CVD recommends an aggressive prevention-based approach for women during the menopause transition to decrease the probability of a future CVD event.[137] For women whose CVD risk may be uncertain (e.g., borderline/intermediate calculated 10-year CVD risk), monitoring for subclinical development of CVD including CAC measurement can be considered to identify those who might benefit from preventive pharmacotherapies.[199, 200] Overall, a history of pregnancy-associated and other reproductive risk factors for CVD represent an opportunity for primordial and primary prevention.

Appropriate risk assessment and prevention of CVD in women remains a challenge.[201, 202] One study found that only 42% cardiologists felt "extremely well prepared" to assess cardiovascular risk in their female patients, and only 22% reported using guideline-directed prevention guidelines in treating female patients.[203] This is an especially important issue in

the U.S. given the considerable burden of CVD risk factors among women, with pronounced racial/ethnic disparities.[1, 204, 205]

Additional work is needed to better educate women about their risk of CVD such that they can become more active in their own care. Recent data show that only 45% of U.S. women recognize that CVD is the leading cause of death among women,[203] and fewer than half of Canadian women recognized common symptoms of and risk factors for CVD.[206] Minority women in particular continue to significantly underrecognize their risk of CVD.[203] Awareness of CVD risk factors and symptoms has been shown to improve patient engagement with healthful behaviors and medication adherence.[207, 208]

With many elements of cardiovascular health to be discussed in a time-limited clinical encounter, efficiently incorporating reproductive history in clinical practice can be challenging. Formal clinical tools have been developed to help with this integration. A toolkit recommended by the American College of Obstetrics and Gynecology provides an algorithm to help in screening and identifying women who may be at increased CVD risk based on pre-pregnancy or pregnancy history.[7, 209] Enhanced CVD risk factor screening can also be facilitated by standardized pre-visit patient questionnaires and patient note templates to prompt reflection on and discussion of risk factors.[202] Written educational materials about cardiovascular health may efficiently supplement clinical encounters.

Postpartum transitional clinics for women with APOs have emerged as a promising strategy for identifying women at elevated risk for CVD and facilitating the transition to longitudinal primary care.[210, 211] Many structural barriers exist to universal access to such clinics, however, including inconsistent access to healthcare insurance particularly among high-risk women, lack of social support for maternity leave, and logistical challenges to accessing medical appointments with a young infant. In addition, bundled payments for obstetrical care represent a potential financial disincentive for systems to introduce transitional clinics. Many patients are now turning to wearable consumer medical technologies, such as mobile phone applications ("apps") and remote BP monitoring, to become more actively engaged in their own care; these results can be integrated into clinic visits to help facilitate patient-centered lifestyle recommendations.[202, 212, 213] Reliance on wearables, however, risks exacerbating existing racial and socioeconomic disparities among those without access to these new technologies. Finally, all fellows-in-training should receive education regarding the importance of reproductive history-taking as part of their core educational curriculum,[214, 215] and women's cardiovascular health topics should be featured more prominently at professional society conferences such that all providers may feel better informed about the unique aspects of caring for women with CVD.

Unanswered Questions and Future Directions

Despite considerable advances in our understanding of sex-specific risk factors for CVD, many unanswered questions remain (Table 3). Ongoing research is needed to elucidate the pathophysiology of sex-specific CVD risk factors and their mechanistic links to later-life CVD to inform precision prevention strategies. Whether prevention strategies tailored to specific subsets of women can alter long-term cardiometabolic risk trajectories will be a critically important area of future clinical investigation. Including more women, and

in particular women of child-bearing age who may be either pregnant or breastfeeding, as well as women transitioning through menopause,[137] in clinical trials remains an important component of efforts to address these knowledge gaps, as does shifting the priorities of trial leaders, pharmaceutical companies, and regulatory bodies to recognize the value of this inclusion. Capturing reproductive history in clinical trials is critical to generate evidence about the effects of therapies on specific subpopulations of women. To date, incorporation of sex-specific risk factors to refine CVD risk assessment has not demonstrated clinically meaningful risk reclassification over the intermediate term in relatively low-risk populations.[216, 217] However, ongoing efforts to develop sex-specific risk calculators over longer time horizons (e.g. 30-year or lifetime risk) and in diverse populations remain important, as traditional risk models underestimate CVD risk in women with reproductive risk factors.[216] Increased clinician and patient awareness of sex-specific CVD risk factors and implementation of evidence-based prevention strategies are critical to improving the cardiovascular health of women.

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Abbreviations and Acronyms

APOs	Adverse pregnancy outcomes
ART	Assisted reproductive technology
ASCVD	Atherosclerotic cardiovascular disease
BSO	Bilateral salpingo-oophorectomy
BP	Blood pressure
BMI	Body mass index
CRP	C-reactive protein
CVD	Cardiovascular disease
CIMT	Carotid intima-media thickness
CHIP	Clonal hematopoiesis of indeterminate potential
CAC	Coronary artery calcium
CHD	Coronary heart disease
GDM	Gestational diabetes mellitus

HDL-C	High-density lipoprotein cholesterol
HT	Hormone therapy
HDPs	Hypertensive disorders of pregnancy
IUD	Intrauterine device
IUGR	Intrauterine growth restriction
LDL-C	Low-density lipoprotein cholesterol
MT	Menopause transition
MI	Myocardial infarction
OCPs	Oral contraceptive pills
PCOS	Polycystic ovary syndrome
PTD	Preterm delivery
SGA	Small-for-gestational age
SCAD	Spontaneous coronary artery dissection
SWAN	Study of Women Across the Nation
T2D	Type 2 diabetes
VMS	Vasomotor symptoms
VTE	Venous thromboembolism
WHI	Women's Health Initiative

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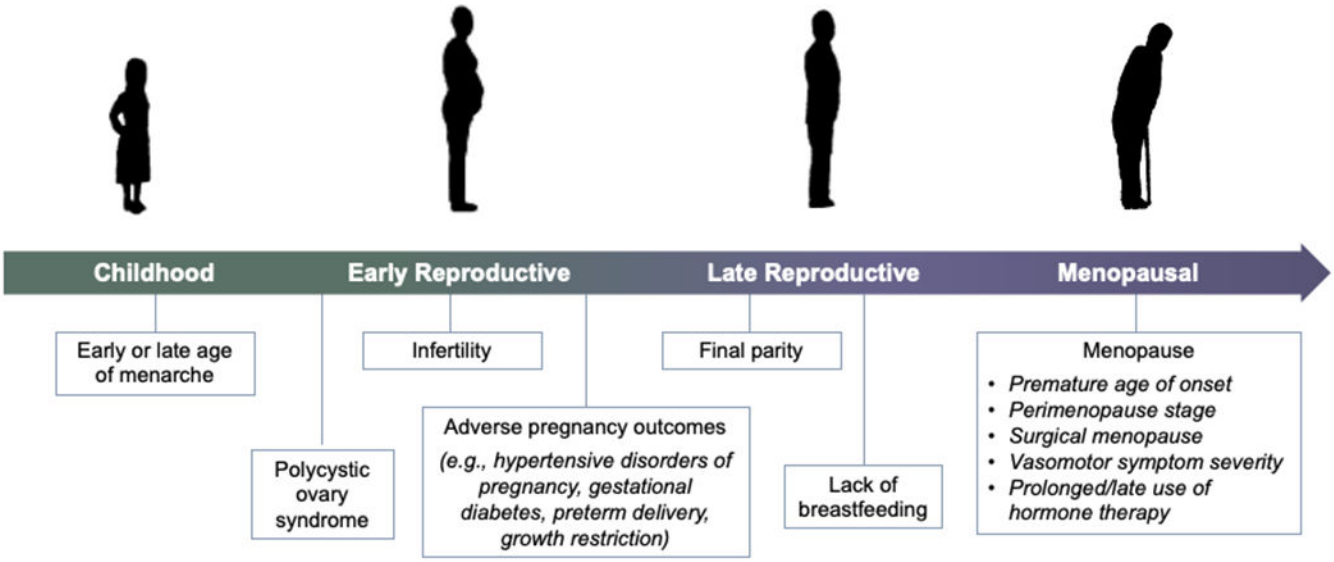
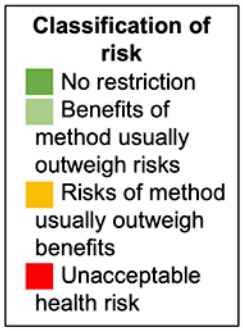


Figure 1. Key reproductive exposures associated with future risk of cardiovascular disease in women.

Key stages of a woman's reproductive history may influence or reveal short- and long-term cardiometabolic and cardiovascular trajectories. Early and late menarche, polycystic ovary syndrome, infertility, adverse pregnancy outcomes (e.g., hypertensive disorders of pregnancy, gestational diabetes, preterm delivery, and intrauterine growth restriction), and absence of breastfeeding may all be adversely associated with a woman's cardiovascular risk. In addition, the menopause transition represents a period of accelerated cardiovascular disease risk, with timing (e.g., premature menopause), mechanism, and symptoms of menopause, as well as treatment of menopause symptoms, each modifying these risks.



Method	Typical-use 1-year failure rate (%)	Multiple risk factors for ASCVD	Established ASCVD	Uncontrolled hypertension (SBP ≥160 or DBP ≥110 mmHg)	Complicated valvular heart disease	Known thrombogenic mutation
Copper IUD	Low (preferred) (<1%)					
Levonorgestrel IUD	Low (preferred) (<1%)					
Subdermal implant	Low (preferred) (<1%)					
Depot medroxy-progesterone acetate	Moderate (6-12%)					
Progestin-only pills	Moderate (6-12%)					
Combined oral contraceptive pill	Moderate (6-12%)					
Barrier methods	High (18-28%)					

Figure 2. Effectiveness and select cardiovascular considerations of commonly used contraceptive methods.

Contraceptive failures rates are from Lindley et al. (39). Complicated valvular heart disease refers to endocarditis and valvular lesions associated with atrial fibrillation or pulmonary hypertension. For additional cardiovascular considerations, refer to the *U.S. Medical Eligibility Criteria for Contraceptive Use* (38).

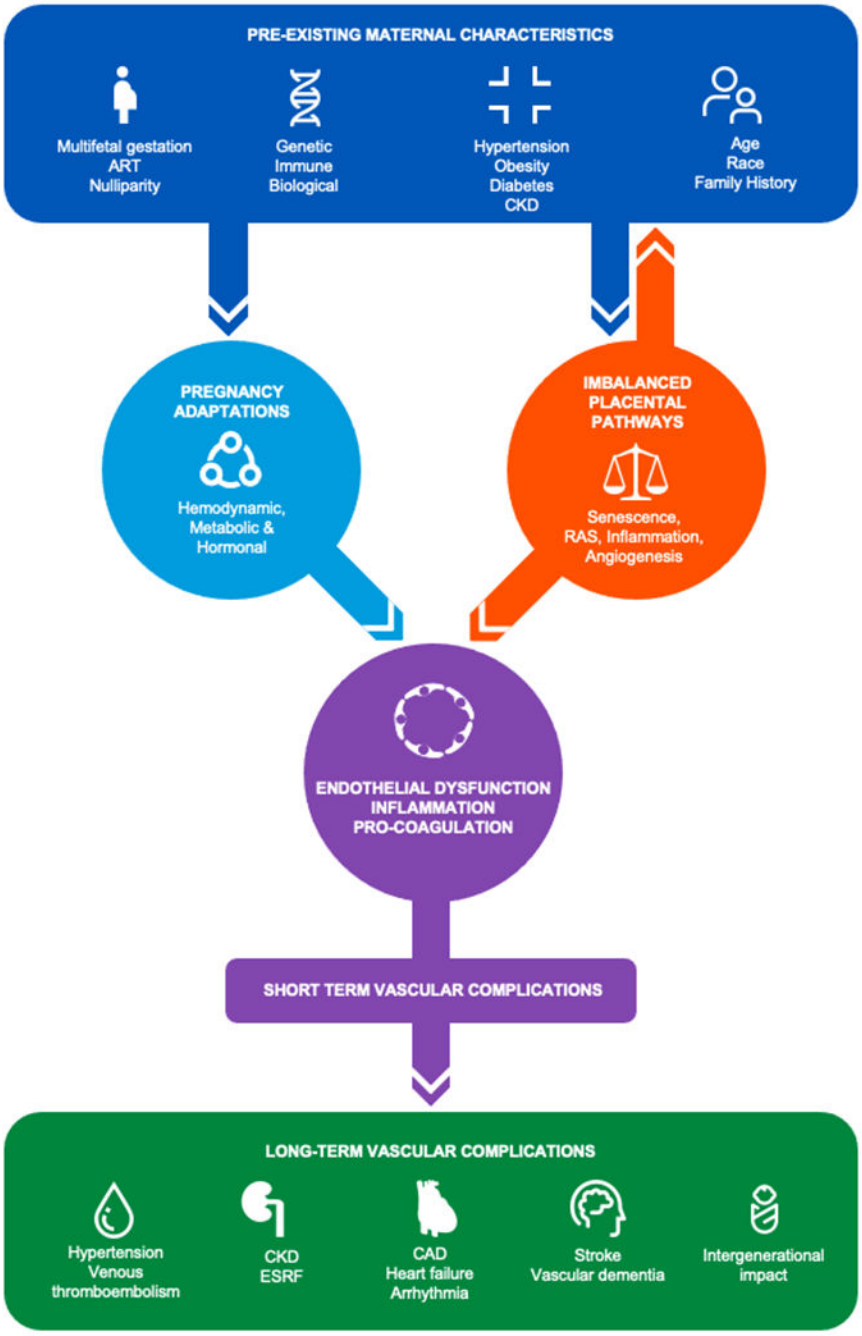


Figure 3. Putative mechanisms linking of hypertensive disorders of pregnancy to cardiovascular disease.

Hypertensive disorders of pregnancy are phenotypically heterogeneous, which likely reflects interactions between pre-existing maternal characteristics, genetics, and comorbidities (hypertension, obesity, diabetes, and chronic kidney disease), pregnancy-specific factors (nulliparity, multi-gestation and assisted reproduction), and an imbalance of placental biological pathways. Hypertensive disorders of pregnancy are linked to short-term vascular complications as well as earlier and increased risk of developing traditional cardiovascular disease risk factors and diverse cardiovascular conditions.

ART = assisted reproductive technology, CKD = chronic kidney disease, RAS = renin angiotensin system, ESRF = end stage renal failure, CAD = coronary artery disease

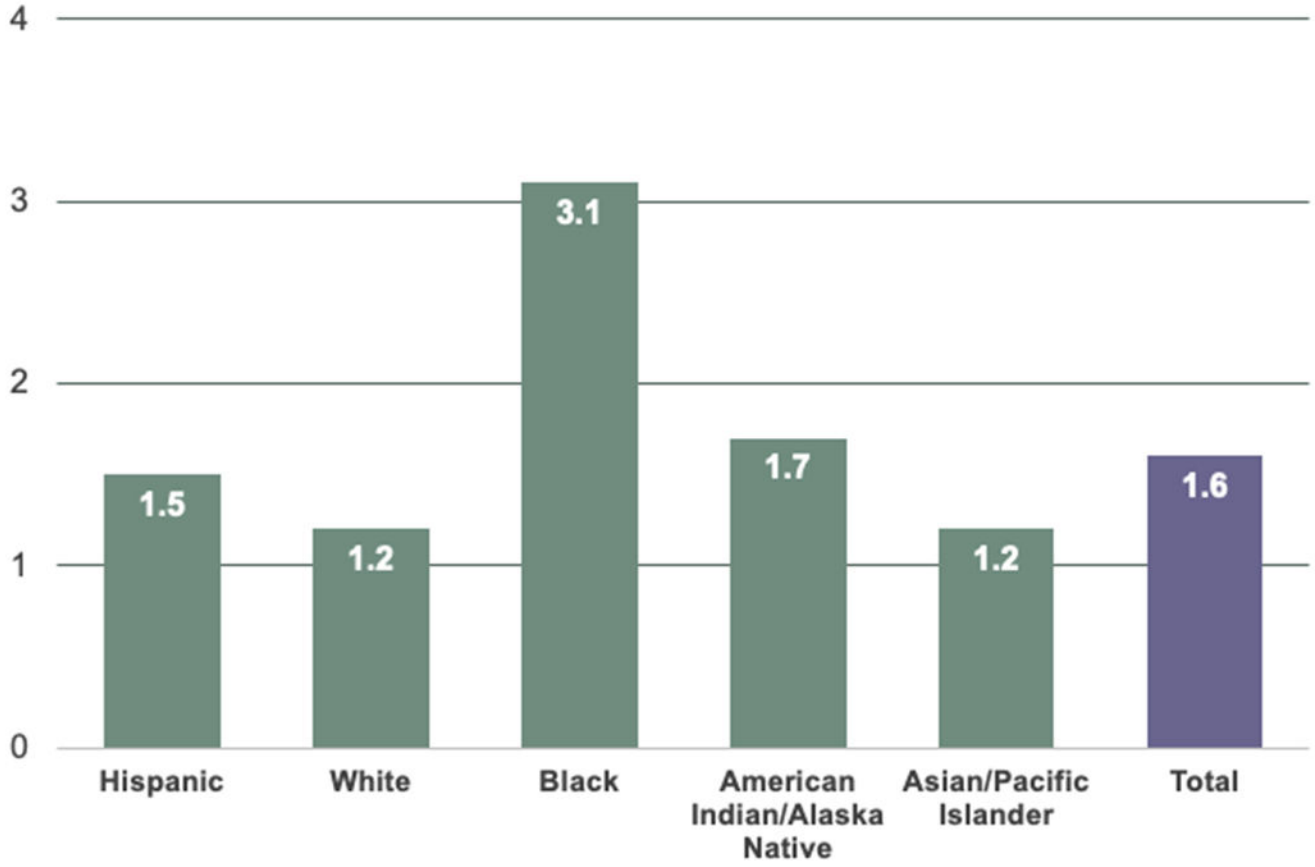


Figure 4. Rate of very preterm delivery (<32 weeks gestational), U.S. average between 2017-2019.
In the U.S., Black women experience the highest rate of preterm delivery at 29% higher than the national average.
All race categories exclude Hispanics. Very preterm is less than 32 weeks' gestation.
Data source: National Center for Health Statistics, final natality data.

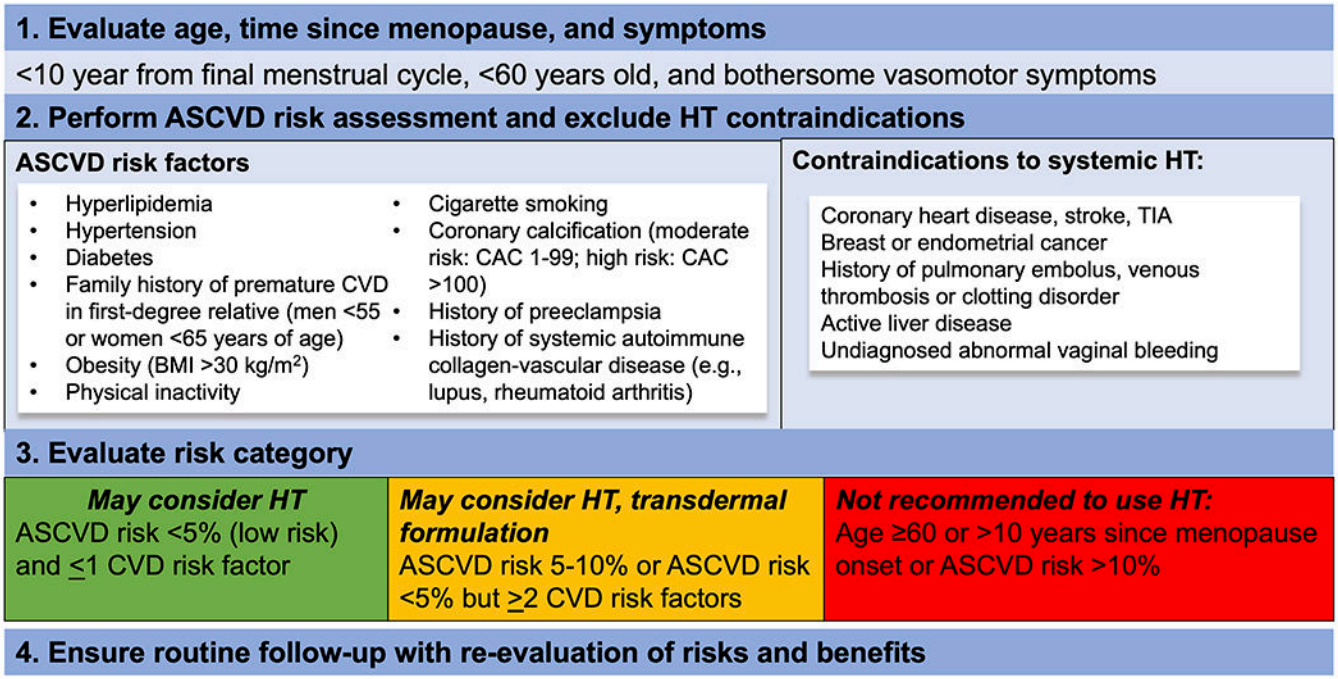


Figure 5. Contemporary approach to prescribing hormone therapy and hormone therapy risk assessment.

Hormone therapy is appropriate for treatment of vasomotor symptoms in women who are otherwise healthy at the time of menopause, within 10 years of menopause, and under age 60 years. However, the decision to prescribe hormone therapy should still consider a woman's individual cardiovascular disease risk factors and employ a shared decision-making approach.

Table 1.

Long-term cardiovascular risks associated with hypertensive disorders of pregnancy.

Maternal Outcome	Study Design	Events	Effect estimate (95% CI)
Hypertension (≥140/90 mm Hg)			
Hypertensive pregnancy disorder	Prospective cohort	566	aHR 2.3 (1.9-2.8)[66]
	Retrospective cohort	-	aHR 2.8 (2.5-3.1)[67]
Preeclampsia	Meta-analysis	-	OR 3.9 (3.1-5.0)[68]
	Meta-analysis	-	RR 3.1 (2.5-3.9)[69]
	Meta-analysis	-	RR 3.7 (2.7-5.1)[70]
	Prospective cohort	4,259	aHR 4.5 (4.3-4.6)[56]
	Prospective cohort	1,922	aHR 2.2 (2.1-2.3)[60]
Gestational hypertension	Prospective cohort	979	aHR 2.8 (2.6-3.0)[60]
Cardiovascular disease ‡			
Hypertensive pregnancy disorder	Prospective cohort	25,606	aHR 1.7 (1.6-1.8)[56]
	Prospective cohort	145	aHR 1.6 (1.3-1.9)[55]
	Prospective cohort	49	aHR 2.3 (2.0-2.7)[71]
Gestational hypertension	Meta-analysis	-	OR 1.7 (1.3-2.2)[57]
	Prospective cohort	54	aHR 1.4 (1.1-1.9)[55] *
Preeclampsia	Meta-analysis	-	OR 1.7 (2.5-3.0)[57]
	Prospective cohort	861	aHR 1.7 (1.6-1.8)[56]
	Prospective cohort	91	aHR 1.7 (1.3-2.1)[55]
Preeclampsia with severe features	Meta-analysis	-	OR 2.7 (2.5-3.0)[57]
Early onset preeclampsia †	Meta-analysis	-	OR 5.6 (1.5-21.4)[68]
	Retrospective cohort	-	aHR 4.9 (3.0-7.8)[72]
Coronary heart disease			
Hypertensive pregnancy disorder	Prospective cohort	1,954	aHR 1.8 (1.3-2.6)[62]
	Retrospective cohort	1,001	aHR 2.2 (2.0-2.3)[73, 74]
	Prospective cohort	102	aHR 1.7 (1.3-2.3)[66]
	Prospective cohort	54	aHR 1.9 (1.4-2.5)[55]
	Retrospective cohort	-	aHR 2.2 (2.0-3.8)[67]
Preeclampsia	Meta-analysis	-	RR 2.5 (1.4-4.4)[75]
	Prospective cohort	664	aHR 1.7 (1.5-1.8)[56]
	Prospective cohort	35	aHR 2.1 (1.5-3.0)[55]
All stroke			
Hypertensive pregnancy disorder	Retrospective cohort	273	aHR 1.9 (1.6-2.2)[74]
	Prospective cohort	262	aHR 1.8 (1.6-2.1)[56]

Maternal Outcome	Study Design	Events	Effect estimate (95% CI)
Preeclampsia	Prospective cohort	130	aHR 1.9 (1.3-2.6)[66]
	Retrospective cohort	-	aHR 1.9 (1.4-2.7)[67]
	Meta-analysis	-	RR 1.8 (1.3-2.6)[75]
	Prospective cohort	93	aHR 1.9 (1.5-2.4)[56]
	Prospective cohort	46	aHR 1.5 (1.1-2.1)[55]
Ischemic hemorrhage	Prospective cohort	123	aHR 1.7 (1.4-2.1)[56]
Intracerebral hemorrhage	Prospective cohort	43	aHR 1.7 (1.2-2.4)[56]
Subarachnoid hemorrhage	Prospective cohort	91	aHR 2.0 (1.6-2.5)[56]
Heart failure			
Hypertensive pregnancy disorder	Prospective cohort	1,300	aHR 1.7 (1.0-2.6)[62]
	Retrospective cohort	480	aHR 4.2 (3.7-4.8)[73]
	Prospective cohort	145	aHR 1.5 (1.3-1.9)[56]
	Retrospective cohort	66	aHR 1.8 (1.4-2.4)[76]
	Prospective cohort	55	aHR 2.7 (1.6-4.6)[66]
Preeclampsia	Meta-analysis	-	RR 4.2 (2.1-8.4)[75]
	Prospective cohort	67	aHR 2.1 (1.6-2.8)[56]
	Retrospective cohort	51	aHR 2.0 (1.5-2.7)[76]
	Prospective cohort	13	aHR 2.0 (1.1-3.7)[55]
Atrial Fibrillation			
Hypertensive pregnancy disorder	Prospective cohort	529	aHR 1.4 (1.1-1.6)[66]
Preeclampsia	Prospective cohort	86	aHR 1.7 (1.4-2.2)[56]
Vascular dementia			
Gestational hypertension	Retrospective cohort	654	aHR 3.0 (2.1-4.3)[77]
Preeclampsia	Retrospective cohort	654	aHR 2.4 (1.8-3.2)[77]
	Prospective cohort	14	aHR 2.2 (1.2-4.0)[78]
Chronic kidney disease			
Hypertensive pregnancy disorder	Prospective cohort	1,279	aHR 4.3 (3.8-4.8)[71]
Gestational hypertension	Meta-analysis	-	RR 1.5 (1.1-2.0)[79]
Preeclampsia	Meta-analysis	-	RR 2.3 (1.5-3.5)[79]
End stage kidney disease			
Gestational hypertension	Meta-analysis	-	RR 3.6 (2.3-5.7)[79]
Preeclampsia	Meta-analysis	-	RR 6.6 (2.7-14.8)[79]

*Chronic hypertension was included as a CVD endpoint in this study.

[†] Early preeclampsia = <34 weeks' gestation

[‡] Cardiovascular disease included ischemic or hypertensive heart disease, or stroke

Hypertensive disorder or pregnancy was a combined endpoint of chronic hypertension, gestational hypertension, preeclampsia, preeclampsia superimposed on chronic hypertension and eclampsia.

Different studies adjusted for different variables. Comparison groups were women who had normotensive pregnancies.

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = hazard ratio, OR = odds ratio, RR = risk ratio, a = adjusted.

Table 2.

Evidence for genetic associations of hypertensive disorders of pregnancy with chronic hypertension and obesity.

Study	Sample	Main findings: Blood pressure	Main findings: Body mass index
Honigberg et al. 2020[85]	2,772 cases with HDPs, 211,593 parous controls (UK Biobank)	● OR for HDPs per SD of systolic BP PRS: 1.22 (95% CI 1.17-1.27) ○ Gestational hypertension: 1.24 (95% CI 1.13-1.35) ○ Preeclampsia: 1.19 (95% CI 1.08-1.31) ● OR for HDPs per SD of diastolic BP PRS: 1.22 (95% CI 1.17-1.26) ● rs7692387-A (*GUCY1A3* intron variant) had disproportionately large protective effect against HDPs in comparison with BP effect	● OR for HDPs per SD of BMI PRS: 1.06 (95% CI 1.02-1.10) ● BP and BMI PRS independent and additive when jointly modeled
Steinthorsdottir et al. 2020[86]	5,181 cases with preeclampsia, 61,426 parous controls (3 European and 2 Central Asian cohorts) 1,532 cases with gestational hypertension, 50,943 parous controls (Icelandic cohort)	● OR for preeclampsia per SD of hypertension PRS: 1.26 (95% CI 1.22-1.31) ● OR for gestational hypertension per SD of hypertension PRS: 1.48 (95% CI 1.04-1.57)	● OR for preeclampsia per SD of BMI PRS: 1.07 (95% CI 1.02-1.13) ○ After further adjustment for hypertension PRS: 1.04 (95% CI 0.99-1.09) ● OR for gestational hypertension per SD of BMI PRS: 1.12 (95% CI 1.06-1.17) ○ After further adjustment for hypertension PRS: 1.06 (95% CI 1.01-1.12)
Gray et al. 2021[84]	498 cases with preeclampsia, 1,864 parous controls (5 U.S. sites; all with European ancestry)	● OR for preeclampsia per diastolic BP risk allele: 1.11 (95% CI 1.01-1.21) ○ Early-onset (<34 w) preeclampsia: 1.30 (95% CI 1.08-1.56)	● OR for preeclampsia per BMI risk allele: 1.10 (95% CI 1.00-1.20)

HDPs = hypertensive disorders of pregnancy; OR = odds ratio; SD = standard deviation; CI = confidence interval; BP = blood pressure; PRS = polygenic risk score; BMI = body mass index

Table 3.

Unanswered questions and key areas for future research on sex-specific cardiovascular disease risk factors in women.

Menarche and fertility

- Do unique hormonal or epigenetic mechanisms link early and late menarche and polycystic ovary syndrome with future CVD risk?
- Are assisted reproductive technologies causally linked to CVD or simply a signal for underlying infertility and associated shared risk factors with CVD?

Pregnancy and adverse pregnancy outcomes

- What are the shared and unique pathophysiologic pathways underlying the various adverse pregnancy outcomes? How do long-term cardiometabolic implications differ across different adverse pregnancy outcomes and their subtypes?
- What are the key novel mechanisms and pathways linking adverse pregnancy outcomes with later-life CVD risk?
- Are associations between parity and CVD risk driven by socio-behavioral or biological effects (or both)?
- What is the protective mechanism of breastfeeding against CVD, and can this be leveraged therapeutically?

Menopause

- Do cardiometabolic changes during the menopause transition independently predict future CVD?
- What are the mechanisms linking premature age of menopause and vasomotor symptoms with CVD?
- What are the relationships among clonal hematopoiesis of indeterminate potential, premature menopause, and CVD?
- Is there a role for exogenous estradiol in cardiometabolic and lipid profile improvement in subsets of postmenopausal women?

Overarching questions for future research

- Can reproductive history prompt targeted cardiometabolic risk-reduction approaches for primordial and primary prevention?
- Can mechanistic insights into reproductive exposures yield novel preventive strategies and therapeutics?
- How do associations between reproductive history and CVD differ across racial/ethnic groups?
- Can sex-specific cardiovascular risk prediction models effectively incorporate reproductive history to refine risk prediction?
- How can we better educate clinicians about the role of reproductive history in CVD risk?

CVD = cardiovascular disease