Cardiovascular disease (CVD) remains the leading cause of death for women. Adverse pregnancy outcomes, including hypertensive disorders of pregnancy, gestational diabetes mellitus, preterm delivery, and low birth weight—affecting up to 30% of pregnant women—increase the risk of CVD. Early menarche and polycystic ovary syndrome are implicated. Premature and early menopause and significant vasomotor symptoms are all associated. Including reproductive risk assessment is critical when determining CVD risk and implementing evidence-based prevention strategies.

Cardiovascular disease (CVD) is the leading cause of death in women. Growing evidence demonstrates that reproductive risk factors portend a higher risk of CVD in women, leading to the inclusion of premature age of menopause and adverse pregnancy outcomes (APOs) in recent guidelines as risk-enhancing factors for atherosclerotic CVD (ASCVD).

Age of menarche and cardiovascular disease risk. Early menarche, occurring before age 10 years, is associated with a higher risk of an adverse cardiometabolic profile, including metabolic syndrome, obesity, dyslipidemia, and hypertension. The relationship between the age of menarche and future CVD may be U-shaped, with increased risk because of both early and late menarche (after age 17 y).

Polycystic ovary syndrome and cardiovascular disease risk. Polycystic ovary syndrome affects 5% to 13% of women and is characterized by polycystic ovaries, amenorrhea or oligomenorrhea, hyperandrogenism, hirsutism, and acne. It is associated with a higher prevalence of metabolic syndrome, obesity, dyslipidemia, hypertension, diabetes, relative insulin deficiency, and insulin resistance. There is an association with a 30% increased risk of CVD, including both coronary heart disease and stroke.

Contraception and cardiovascular disease risk. Safety concerns of oral contraceptive pills are largely related to estrogen, which has been associated with higher blood pressure and increased risk of venous thromboembolism, leading to a greater risk of myocardial infarction and ischemic stroke (estrogen dose ≥50 µg). Newer-generation oral contraceptive pills contain less synthetic ethinyl estradiol (≤30 µg), and there is lower risk. Long-acting reversible contraception (LARC)
methods (levonorgestrel-releasing and copper intrauterine devices and subdermal implants) are not associated with greater risk.  

**Parity, lactation, and cardiovascular disease risk.** There is a J-shaped relationship between parity and the risk of CVD. The highest risk is in nulliparous and grand multiparous women (≥5 births), with less CVD risk in women with two births. There are long-term cardioprotective effects of lactation and a positive association with a longer duration of lactation. Women who breastfeed have lower rates of diabetes, hypertension, and obesity. Breastfeeding also has been shown to benefit women with pregnancies complicated by APOs.

**Adverse pregnancy outcomes and cardiovascular disease risk.** Adverse pregnancy outcomes complicate up to 30% of pregnancies in some series and include hypertensive disorders of pregnancy (HDP), gestational diabetes mellitus (GDM), preterm delivery, and low birth weight. The American College of Cardiology and the American Heart Association (ACC/AHA) guidelines refer to APOs as risk-enhancing factors when CVD risk is formalized in CVD risk estimation.  

**Hypertensive disorders of pregnancy.** These include prepregnancy chronic hypertension, gestational hypertension, and preeclampsia/eclampsia. Incidence is 5% to 10% of all pregnancies. The effects of HDP extend beyond the peripartum period. A growing body of literature supports HDP as an independent risk factor for CVD later in life. Preeclampsia is associated with significantly greater odds of diabetes, metabolic syndrome, and central obesity—each is an independent risk factor for premature coronary artery calcification after controlling for a greater prevalence of these traditional cardiovascular risk factors. Hypertensive disorders of pregnancy are independently associated with future CVD after adjustment not only of established cardiovascular risk factors but also other APOs. Hypertensive disorders of pregnancy are associated with 2-fold higher odds of CVD, including coronary artery disease, peripheral vascular disease, and stroke. The risk of CVD outcomes is linked to the severity of HDP. Gestational hypertension is lower, followed by preeclampsia, and the highest risk for those with severe and/or preterm preeclampsia. It remains unknown the extent to which HDP and excess CVD risk is the result of shared cardiovascular risk factors and pathophysiologic pathways versus direct vascular damage.

**Gestational diabetes mellitus.** Gestational diabetes mellitus occurs in 2% to 10% of all pregnancies. It increases the risk of future diabetes by 7-fold and that of CVD by 2-fold. The risk of cardiovascular events in women with a history of GDM seems to be independent of the development of diabetes. Moreover, even impaired glucose tolerance in pregnancy without GDM is associated with greater midlife CVD.

**Preterm delivery.** Preterm delivery is defined by occurrence between 20 and 37 weeks’ gestation. Duration of pregnancy is inversely related to future maternal CVD risk. Women who have had an extremely preterm delivery have the highest risk. There is a 1.61-fold higher risk for hemorrhagic and ischemic stroke, a 2.47-fold risk for ischemic heart disease, a 1.73-fold risk for all-cause mortality, and a 1.79-fold risk for CV mortality 10 years after delivery. Stronger associations are found when preterm delivery occurs in combination with other APOs.
Infant birth weight. There is a strong correlation between low birth weight and the development of coronary artery disease, diabetes, and hypertension. Low birth weight is also independently associated with ASCVD after adjustment for known risk factors and other APOs.

Menopause transition. The menopause transition (MT) is marked by dynamic changes in hormones, menstrual bleeding patterns, and physiological and psychological symptoms, when there is an acceleration in CVD risk. During the MT, women experience adverse changes in several lipid/lipoprotein measures that have been linked to a greater risk of CVD. Menopause-related acceleration in visceral abdominal fat accumulation is related to a significant increase in internal carotid intima-media thickness— independent of traditional risk factors and overall adiposity. The MT is associated with arterial stiffness, as measured by carotid-femoral pulse wave velocity, independent of other CVD risk factors.

Premature/Early menopause. Early menopause (40-45 y) and premature menopause (<40 y) occur in about 7% and 3% of women, respectively. There is a greater risk of CHD, heart failure, CVD mortality, and/or all-cause mortality independent of conventional CVD risk factors. Large studies like the Nurses’ Health Study and the Danish Nurses Cohort Study have reported that hormone therapy (HT) attenuates the CVD risk because of premature menopause. Hormone therapy position statements recommend starting HT in women with premature menopause and continuing through the average age of natural menopause.

Vasomotor symptoms. Having frequent and persistent vasomotor symptoms (VMS) is associated with a higher risk of CVD events later in life, as is having severe VMS. A large meta-analysis reported a 28% increased risk of CVD after adjusting for traditional risk factors. It remains unknown whether treatment of VMS (with HT or non-HT regimens) ameliorates the increased risk for women with severe VMS.

Pearl. Increased awareness of reproductive risk factors to be included in CVD risk assessment will lead to improving the CV health of women by using evidence-based CVD risk-reduction prevention strategies. Further research is needed to better understand the links between reproductive risk factors and CVD later in life.

References


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This *Practice Pearl*, developed by the author, provides practical information on current controversial topics of clinical interest. It is not an official position of The Menopause Society. Clinicians must always take into consideration the individual patient along with any new data published since the publication of this *Pearl*. The *Practice Pearl* series is led by Editor Dr. Ekta Kapoor. All *Practice Pearls* receive four independent reviews.

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