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EDITORIAL COMMENT

Ischemic Heart Disease and Pregnancy

How Do They Interact?*

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Maternal mortality has been increasing in the United States, partly due to the increasing numbers of pregnant women at advanced maternal age, comorbid pre-existing conditions such as diabetes mellitus and hypertension, and the growing number of women with a congenital heart disease surviving to childbearing age.[1] Older age and higher comorbidities can increase the risk of adverse pregnancy outcomes (APOs). APOs include gestational diabetes mellitus, small for gestational age, preterm birth, and hypertensive disorders of pregnancy, which include gestational hypertension and preeclampsia. These APOs share common pathways and may be caused by placental dysfunction and oxidative stress. In addition, APOs and cardiovascular disease (CVD) share risk factors, including obesity, diabetes, renal disease, genetics, and pathophysiology. Not surprisingly, APOs are associated with a higher risk of future hypertension, ischemic heart disease, and stroke.[2]

Compared to women without APOs, women with APOs have a higher CVD risk factor burden, including higher levels of lipids, blood pressure, and body mass index several years post partum.[1] Whether women with APOs who develop coronary artery disease (CAD) have a higher risk of complications after treatment needs further investigation. In this issue of *JACC Advances*, Pehrson et al[3] examined the association between a history of preterm delivery and major adverse cardiovascular events (MACEs) after coronary stenting. They found that women with a history of preterm delivery had a higher risk of MACE and mortality. The study was based on a Swedish nationwide cohort of 5,766 women younger than 65 years who received their first coronary stent between 2006 and 2017 and who were followed up for a mean of 3.7 years. Overall, 16.7% had a preterm delivery, and 20.8% had a MACE following their first coronary stenting. Further subgroup analyses suggested that those with a history of early preterm delivery had a lower risk of MACE than those with late preterm delivery. The authors also note that the prevalence of preterm delivery before 2006 was declining in Sweden, about 6% in the 1980s compared to 5.5% in 2001.[4] This marked increase to 16.7% from 2006 to 2017 in the study by Pehrson et al[3] is alarming and needs further attention.

A study of this kind is difficult to do unless the database is comprehensive and collected over a long period of time as there may be a long period of time between pregnancy and developing severe atherosclerosis. Sweden's comprehensive national health insurance is ideal for such a study and thus resulted in very low rates of missing data. However, Sweden's population is ethnically homogeneous, and their results may not be applicable to all ethnic groups. Nonetheless, the results of this study should encourage more research studies to investigate the link between preterm delivery and future atherosclerotic complications.

Previous studies have shown that APOs can increase the risk of MACEs, but this study demonstrated that preterm birth can also increase MACEs after the treatment of the cardiovascular event, multiplying the consequences of having preterm birth. As the authors astutely highlighted, further studies are

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needed to understand the mechanisms of this associations to give us guidance on how to prevent these subsequent cardiovascular events.

Pregnancy is a dynamic process that challenges the cardiovascular system. While these changes are uncomplicated for most women, complications can occur in the mother and her baby. Approximately 10% of pregnant women in the United States experience preterm delivery.[5]

Preterm birth is a heterogeneous condition, and the pathogenesis is poorly understood. However, 1 critical event in preterm labor is the activation of the fetal adrenal glands' inflammatory response causing the elevation of fetal plasma interleukin-6 and cortisol production.[6] The cervical stroma experiences an influx of inflammatory cells leading to the release of cytokines and prostaglandins, stimulating cervical ripening and initiating birth. In the decade following a preterm delivery, this subgroup of women had higher levels of atherogenic lipids and carotid arterial wall thickening than women who delivered at term.[7] Additionally, studies have shown an inverse relationship of the duration of pregnancy gestation with insulin resistance, blood pressure, and low-grade inflammation.[8–10] The cardiometabolic dysregulation experienced during preterm birth has a common pathway with CVD, which may explain the link between the 2 pathologies.

At the opposite end of the gestational age is late-term or post-term birth. Post-term delivery has attracted far less attention than preterm delivery. Maternal risk factors associated with an increased risk of post-term delivery include obesity, lower socioeconomic status, ethnicity, and dietary factors.[11,12] Similar risk factors exist for the development of CVD. However, a study examining the correlation between late-term delivery and the future development of CAD has yet to be carried out.

It is now well known that APOs can identify women at elevated risk of CAD, usually earlier than traditional risk factors.[13] Preterm delivery is a risk factor on the list of APOs that should be screened for in assessing CV risk and may portend higher risk in women with adverse outcomes after percutaneous coronary intervention. Women with one or more pregnancy-related complications should have an early follow-up with a cardiologist. This assessment should include an evaluation of traditional risk factors (hypertension, diabetes, smoking, and so forth), review of APOs, history, physical examination (including blood pressure, body mass index, and waist circumference), and laboratory testing (including glycosylated hemoglobin and lipids).

In this younger population, where primary prevention is important to prevent disease development, the American cholesterol guidelines include APOs as "risk enhancers" for atherosclerotic CVD (ASCVD) risk that may allow clinicians to personalize decisions regarding statin use.[14] Patients with a borderline (5%-7.5% risk) or intermediate (7.5%-<20%) ASCVD risk score may benefit from discussion or earlier use of a statin if risk enhancers, such as APOs, exist. If the risk decision is still uncertain, the coronary artery calcium score may help guide the decision regarding statin therapy. It is recommended that patients with a positive coronary artery calcium scan consider statin therapy. Studies have noted that APOs are associated with higher rates of ASCVD on computerized tomography imaging.[15,16]

Lastly, evaluation in the postpartum period should include counseling regarding lifestyle modifications, including weight reduction, dietary recommendations, physical fitness, management of depression, and possible medication treatment if needed. Research has shown that improved awareness of CVD risk in women is associated with preventive actions, highlighting the importance of early education and counseling.[17,18]

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