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EDITORIAL COMMENT

Novel Risk Factors for STEMI Among Young Women

Does Placental Development Offer a Clue?

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Adverse pregnancy outcomes (APOs) are increasingly recognized for their contribution to short-term maternal morbidity and mortality, and their longer-term impact on adverse cardiovascular events. The pathophysiology of preeclampsia remains incompletely understood but is thought to occur due to impaired trophoblast invasion and incomplete spiral artery remodeling that result in placental ischemia and thereby an increase in angiogenic markers and vascular endothelial dysfunction.[1] Similarly, while diverse etiologies can contribute to intrauterine growth restriction (IUGR), placental insufficiency and malperfusion are key contributors to risk. During pregnancy and the early postpartum period, preterm preeclampsia is a leading cause of adverse maternal and fetal outcomes, including severe maternal hypertension and its downstream complications, pulmonary edema, and diastolic dysfunction.[1,2] However, it is also now widely recognized that the effect of APOs extends beyond pregnancy and is associated with a process of accelerated cardiovascular aging.[3] As such, APOs are associated with increased risk of diverse cardiovascular complications, particularly among patients aged ≤65.[3]

In this issue of *JACC: Advances*, Handmark et al[4] extend our understanding beyond association of APOs with incident coronary artery disease (CAD) by investigating severity of myocardial infarctions (MIs) among young women by history of APOs. As hospitalizations for acute MIs have been increasing particularly among younger women, this represents a vulnerable population for whom a better understanding of risk is required.[5] Among 8,320 patients age ≤65 years presenting with a first MI in Sweden, the adjusted odds of presenting with a ST-segment myocardial infarction (STEMI) was 40% higher among those with a history of preterm preeclampsia (95% CI: 1.05-1.88) and 30% higher for those with a history of delivering a small for gestational age (SGA) infant (95% CI: 1.13-1.50) as compared with patients without these APOs. History of term preeclampsia and gestational hypertension has been associated with increased risk of developing CAD but was not associated with increased risk of STEMI in this analysis. While this and other data sets have described a higher burden of comorbid conditions among patients who have experienced APOs as compared with those who have not, increased risk of STEMI persisted after adjustment for body mass index, diabetes, hypertension, smoking status, and treatment for dyslipidemia.

With this analysis, Handmark et al[4] demonstrate that APOs are not only associated with an increased risk of any future CAD but also a higher-risk MI presentation. Furthermore, not all APOs confer the same risk for STEMI. This is important to consider with an overarching goal of targeting interventions toward patients who may be at greatest risk. However, as the pathophysiology and exact mechanisms by which APOs confer risk remains incompletely understood, targeted therapies are lacking. Aggressive primary prevention strategies comprise the mainstay of current recommendations, which call for patients to be engaged in longitudinal primary care. However, in a recent analysis of patients in the United States, only 58% with hypertensive disorders of pregnancy

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engaged in any longitudinal follow-up at 6 months postpartum.[6] As such, novel means of educating patients and managing risk factors following APOs are greatly needed. Postpartum transition clinics and virtual care strategies have been proposed to bridge the care gap, but the optimal means of improving access and reducing inequities in care (especially in the context of new caregiving responsibilities) remains an area of active investigation.[7] As the current analysis identifies patients with a history of preterm preeclampsia and SGA infants as the highest risk for STEMI, efforts targeted at engaging these highest risk patients may be particularly important.

Traditional cardiovascular risk factors, however, do not account for the totality of risk following APOs. For example, Handmark et al found that increased risk of STEMI among patients with preterm preeclampsia and SGA persisted in their fully adjusted model, which accounts for differences in comorbid risk. Furthermore, in an analysis restricted to women without hypertensive disorders of pregnancy, Handmark et al found that the association between SGA and future STEMI persisted. As both preterm preeclampsia and IUGR seem to share an underlying mechanism of impaired placental development and consequent endothelial dysfunction, further research into the pathophysiology of this process may ultimately yield targeted therapies for both CAD risk reduction but also improved disease-prevention strategies during pregnancy. At present, low-dose aspirin is recommended for pregnant patients identified as high risk for development of preeclampsia for disease prevention.[8] While this strategy has been investigated for IUGR prevention, in the absence of risk factors for preeclampsia it is not currently recommended by the American College of Obstetricians and Gynecologists. Beyond this, evidence-based interventions to reduce the risk of developing either of these APOs are lacking.

Central to better understanding the mechanisms by which APOs increase the risk of future cardiovascular disease is the availability of diverse data sets that capture detailed reproductive histories. Handmark et al were able to leverage the Swedish Medical Birth Register, which afforded an ability to examine diverse APOs more rigorously than other analyses. Many prior observational studies, for example, have grouped all hypertensive disorders of pregnancy together given a lack of granularity in the data, limiting the ability to identify the highest risk patients among this diverse set of disorders. With an increasing recognition of the impact of reproductive risk factors across the lifespan on cardiovascular disease, future cardiovascular studies should intentionally and rigorously capture reproductive risk with sufficient detail to advance our understanding of which patients are at highest risk for adverse outcomes and therefore merit more aggressive preventative care.

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