Journal of the American Heart Association

EDITOR'S NOTE

JAHA Spotlight on Pregnancy and Its Impact on Maternal and Offspring Cardiovascular Health

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The growth and development of a fetus during pregnancy requires complex interactions between the mother and the growing fetus such that reciprocal signaling between the two modifies the cardiovascular structure and function of the mother to adapt to the physiologic demands of the growing fetus. In this issue of the *Journal of the American Heart Association* (*JAHA*), a Spotlight collection of articles examines critical elements of these processes and describes their effects on fetal development and on the short- and long-term health of both the mother and the child.

The communication between the mother and the developing embryo begins shortly after fertilization and before implantation when maternal and embryonic signals prepare the uterus for successful embryo implantation and placental development.[1] Central to this process is vascular growth and remodeling which helps provide a healthy placenta capable of appropriately nourishing the developing embryo. This important process can be compromised by suboptimal cardiovascular health of the mother. Conditions such as obesity, hypertension, diabetes, and smoking can impact the cardiovascular health of the mother and impair the vascular development and function of the placenta, resulting in increased risk of pregnancy loss, fetal growth impairment, and abnormal fetal development and can lead to lifelong health issues for the child and for the mother.[2–5]

As described in Sharma et al in this issue,[6] the cardiovascular health of pregnant women is strongly affected by social determinants. In their study, the investigators examined 1433 pregnant women across the United States and scored them for 38 variables across 6 social domains (economic stability; neighborhood, physical environment, and social cohesion; community and social context; food; education; and health care system). They determined that ≈50% of women in the highest quartile for adverse social determinants of health had suboptimal cardiovascular health as determined by the presence of 2 or more cardiovascular risk factors (obesity, hypertension, diabetes, smoking, high cholesterol/dyslipidemia, and physical inactivity) and were therefore at risk for poor pregnancy outcomes. They stressed the urgent need for social assessment of pregnant women and women considering pregnancy to reduce cardiovascular risk profiles, improve pregnancy outcomes, and improve maternal health.

Suboptimal cardiovascular status during pregnancy predisposes to pregnancy complications and adverse pregnancy outcomes (APOs) such as new-onset hypertensive disorders of pregnancy including gestational hypertension and preeclampsia/eclampsia, the rates of which have nearly doubled across the United States over the past 14 years as noted by Cameron et al[7] in this issue. The rates of these hypertensive conditions have increased in both rural and urban areas with the greatest rise in urban areas and with racial and ethnic asymmetries that suggest an important contribution of social determinants of health. They note

Key Words: cardiovascular diseases ■ pregnancy ■ women

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that identification of the individual and environmental factors that are supporting the overall increase in incidence and the persisting racial and ethnic asymmetries will require further study.

A central feature of preeclampsia and related hypertensive disorder of pregnancy is impaired placental function.[8] Poor placental health can lead to trophoblast necrosis and the release of pro-inflammatory factors into the maternal circulation. These inflammatory agents can cause maternal vascular injury and vasoconstriction, resulting in maternal hypertension and vascular remodeling. Circulating cell-free DNA released by damaged cells can be an important marker of tissue injury and the stress response. In this issue, Cushen et al[9] examined circulating cell-free DNA regulation and determined that preeclampsia was associated with aberrant circulating cell-free DNA dynamics compared with healthy controls. As such, cell-free DNA dysregulation may serve as an important marker and potentially pathogenic stimulus of hypertensive disorders of pregnancy such as preeclampsia.

Pregnancy-induced inflammation and vascular remodeling can have important short- and long-term effects on maternal cardiovascular health. During the pregnancy, this can result in maternal hypertension and preeclampsia. Postpregnancy, as noted by Park et al[10] in this issue, hypertensive disorders of pregnancy were associated higher incidence of developing a cardiac arrhythmia in the year following the pregnancy. Although lethal arrhythmias were uncommon, there was an >2-fold increase in incidence of atrial flutter/fibrillation in patients with preeclampsia compared with normotensive pregnancies in their study of >2 million women in the Korea National Health Insurance database. They noted that pregnancy-induced hypertension, which was diagnosed in ≈1.8% of the cases, occurred more commonly in those patients with higher prepregnancy cardiovascular risk profiles.

The long-term impact of preeclampsia and other pregnancy complications on the cardiovascular health of the mother and the resulting implications for clinical cardiovascular screening and cardiovascular disease (CVD) risk assessment were examined in a number of articles in this issue. In a large study of 2 134 239 women in the Swedish birth registry, Cederlöf et al[11] noted that pregnancy complications (defined as preeclampsia and/or eclampsia, gestational hypertension, gestational diabetes, preterm birth, small for gestational age, and/or stillbirth) occurred in 19.1%. Each type of pregnancy complication was associated with all-cause and cardiovascular mortality, frequency of hospitalization for CVD, and earlier CVD onset. Of note, very preterm birth and stillbirth—2 pregnancy complications whose maternal CVD effect had not been well-described—were determined to be significant risk factors for later maternal CVD with those mothers who delivered an extremely preterm infant having a 2.2-fold increased risk of hypertension within 10 years following the pregnancy. While Fraser et al[12] noted that the risk of CVD after adverse pregnancy might not rise to levels that support widespread CVD screening for that indication alone, Naz et al determined that adding the presence/absence and number of APOs improved the risk prediction accuracy of the Framingham Cardiovascular Risk Score,[13] and both studies supported the need for healthy lifestyle counseling in women who have had an APO. The greater the number of APOs, the greater the risk, with 3 or more APOs associated with a hazard ratio of 2.48 for a significant maternal cardiovascular event (stroke, transient ischemic attack, death from cerebrovascular or coronary artery disease, unstable angina, coronary disease, or suspected myocardial infarction).[13]

On the positive side, long-term maternal cardiovascular health can be improved by breastfeeding. In a meta-analysis of 8 studies involving >1 million women, Tschiderer et al[14] in this issue determined that lifetime breastfeeding duration was progressively associated with reductions in CVD risk with reduced risk of coronary disease, stroke, and fatal cardiac events.

An impaired maternal–fetal environment can also have profound and lasting effects on fetal development and child health.[15] Exposures early in gestation can lead to disorders of organ and tissue formation. Congenital heart defects, which are caused by abnormal formation of the heart, can be caused by genetic factors or environmental insults. In this issue, Harvey et al[16] examine 1 modifiable environmental factor, alcohol intake, which they demonstrated was associated with a specific set of structural cardiac defects. Their retrospective review of the hospital discharge records from the California Office of Statewide Health Planning identified just over 16 000 pregnancies where there was a maternal diagnosis of an alcohol-related condition out of >5 million pregnancies examined. In those ≈16 000 pregnancies there was a significantly increased risk of coronary heart disease with ≈2- and 3-fold increase in risk of conotruncal and endocardial cushion defects, respectively.

In addition to its effects on organ and tissue development, an impaired maternal–fetal environment may lead to important lasting effects on cardiovascular function in the offspring. In a rat model, male and female offspring of hypertensive pregnancies exhibit high-fat-diet–induced hypertensive response sensitization (an exaggerated response to vasoconstrictors such as angiotensin-II and tumor necrosis factor-α). In female offspring, this response is significantly attenuated. In this issue, Xue et al[17] demonstrated that this protection against high-fat-diet–induced hypertensive response is dependent on estrogen signaling and that maternal hypertension during pregnancy compromises

this protective effect by augmenting central nervous system–driven sympathetic activity. The study highlights several important effects of cardiovascular health in the offspring of pregnancies affected by maternal hypertension, most importantly that the effects last into adulthood and differentially affect males and females because of gender-dependent neurohormonal differences. It also reinforces prior work that prenatal programming may potentiate the effect of a "second hit" such as a high-fat diet or obesity on cardiovascular risk in the offspring even into adulthood.[18]

Abnormal cardiovascular responsiveness may be an important contributor to the findings of Savla et al[19] in this issue, who determined that an impaired maternal–fetal environment, defined as maternal gestational hypertension/preeclampsia, gestational diabetes, and/or smoking during pregnancy, was associated with 6-fold increase in the risk of death after neonatal palliative surgery to treat hypoplastic left heart syndrome, a severe congenital heart defect where the left side of the heart does not develop, leaving the child with only a single functioning ventricle. Out of 273 children with hypoplastic left heart syndrome in this single-center study, 26% were exposed to an impaired maternal–fetal environment and had a 50% 1-year survival compared with an 89% survival in those not exposed to an impaired maternal–fetal environment. Not surprisingly, the subjects with impaired maternal–fetal environment had lower birth weights and were more likely to be born prematurely (<37 weeks gestation). The authors concluded that optimizing prenatal care should be an important part of the care of patients and families with hypoplastic left heart syndrome.

In this issue, Limperopoulos et al[20] reviewed the importance of the findings of Salva et al and placed them within the context of the emerging body of literature on the effect of the prenatal environment on postnatal child health. They advance the concept of prenatal pediatrics to emphasize that the medical field may need to re-envision prenatal care to optimize postnatal health. Better optimization of maternal–fetal health can substantially improve the short- and long-term health of the offspring, especially in those instances such as critical congenital heart disease, in which the newborn's health and ability to survive and thrive when facing the challenges of neonatal cardiac surgery is so dependent on optimal physiologic responsiveness. They call for increased cooperation between pediatric and obstetrical providers to provide personalized and precise care during every pregnancy in order to optimize clinical outcomes, especially in those offspring with critical health conditions.

The emerging message is that adverse pregnancy outcomes are driven in part by abnormal placental function, which can be a byproduct of maternal cardiovascular risk factors such as obesity, diabetes, smoking, and hypertension. These cardiovascular risks are associated with social determinants of health that show racial and ethnic asymmetries, the underpinnings of which are not well understood caused at least in part by an underrepresentation of minority groups in studies examining the association of cardiovascular disease and adverse pregnancy outcomes. Therefore, high-risk cardiovascular profiles increase the risk of APOs, which in turn activate inflammatory pathways that further compromise cardiovascular function, affecting future pregnancies and the long-term cardiovascular health of the mother. Strategies aimed at improving women's cardiovascular health, such as healthy lifestyle promotion, weight management, and exercise, may be critical in reducing adverse pregnancy outcomes and mitigating the effects of a complicated pregnancy on the long-term health of the mother.

The impact of the prenatal environment on the long-term health of the offspring is also being increasingly recognized. Given that prenatal cardiovascular risk profiles in the mother will directly influence the life-long cardiovascular risk profile of the offspring, improving maternal health and the maternal–fetal environment will be a critical step in addressing health disparities and reducing nongenetic or environmental transmission of cardiovascular risk from one generation to the next. The optimization of maternal–fetal health will have an important impact on overall population health with a direct, immediate, and potentially dramatic effect in those children with significant health conditions such as critical congenital heart disease.

ARTICLE INFORMATION

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Disclosures

None.

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