Editorial Commentary

Breaking a Mother’s Heart
Circulating Antiangiogenic Factors and Hypertension During Pregnancy Correlate With Specific Cardiac Dysfunctions

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It is clear that a past history of preeclampsia in any pregnancy is a major risk factor for the development of cardiovascular disease later in that woman’s life. However, it is not clear what molecular and physiological changes occurring during preeclampsia cause such long-term problems. Thus, there is a need for increased understanding of the acute damage occurring during pregnancies complicated by preeclampsia or any hypertensive disorder of pregnancy (HDP), so that preventative therapeutics can be developed to protect mothers post-partum. Along these lines, previous research has demonstrated that women with any HDP have subclinical cardiac dysfunction at the end of pregnancy. In addition, antiangiogenic factors have been implicated in the pathogenesis of preeclampsia and HDP and their sequelae, but whether these molecules play a role in resulting cardiac dysfunction remains unknown.

In the current issue of Hypertension, Shahul et al describe a case-control clinical study examining the relationship of global longitudinal strain (GLS), an echocardiographic measure that detects subtle left ventricular dysfunction (and thereby an early measurement of subclinical cardiac dysfunction), and circulating antiangiogenic factors in pregnant women with or without various HDPs, including preeclampsia, gestational hypertension, and chronic hypertension. In the study, the authors document positive correlations between plasma concentrations of antiangiogenic factors soluble fms-like tyrosine kinase-1 (sFlt1) and soluble endoglin with GLS during the third trimester of pregnancy. It is important to note that the relationship between worsening GLS and the antiangiogenic factors remained regardless of clinical diagnosis (preeclampsia versus gestational or chronic hypertension). Because these different types of hypertensive disorders differ in pathogenesis, the strength of the relationship between the circulating factors and GLS is impressive and supportive of the concept that these factors may directly affect cardiac function during any form of HDP.

Although the significance of the subclinical effects of HDP on the cardiovascular health of the mother and a possible contribution of antiangiogenic factors are highlighted, there is still work to be done. As the authors point out, the current study only investigated the correlation between antiangiogenic factors and cardiac function at a single, later-pregnancy time point. Yet at this time, it is not clear whether this correlation actually highlights a causal relationship and whether antiangiogenic factors actually drive cardiac dysfunction. Pharmacological inhibition of vascular endothelial growth factor (functionally mimicking the actions of sFlt1) seems to cause new-onset cardiac dysfunction in humans during chemotherapy, supporting the notion that angiogenic dysfunction may drive cardiac dysfunction. Positive implication of these factors in the development of cardiac dysfunction does not, however, preclude the alternative possibility that subclinical alterations in cardiac structure or function may predispose a woman to elevations in antiangiogenic factor expression, especially when cardiovascular function is challenged by pregnancy. In addition, these correlations do not rule out a confounding effect of hypertension on GLS during pregnancy as hypertension positively correlated with antiangiogenic factors and may be an alternative or additional causative factor on GLS throughout gestation. Nor does the study rule out the action of immunologic mechanisms that are seen earlier in gestation in the development of preeclampsia and other HDPs as severe dysfunctions in cardiac structure or function may predispose to elevations in antiangiogenic factor expression, vice versa, or both or neither. Whether interference with these antiangiogenic factors can prevent or reverse pathological changes in cardiac structure and function (during, following, or outside pregnancy) remains an exciting hypothesis, which requires future study.

Although the current study highlights the correlation between antiangiogenic factors and GLS during pregnancy, the demographics of the study population prevent extensive dissection of the relationship. For example, GLS was impaired the most in the preeclamptic group, but this group also exhibited the highest blood pressure, maternal age, body mass index, and most severe intrauterine growth restriction. In other studies, age, blood pressure, and body mass have all been reported to contribute to changes in GLS. Despite
controlling for some of these factors in the regression analyses, the association between sFlt1 levels and worsening GLS persisted. Further study in a larger cohort is needed to examine the true effects of these covariates on the sFlt1–GLS relationship and to gain clinically useful information particularly because intrauterine growth restriction, as an example, can result from multiple independent mechanisms (ie, infectious, immune, genetic, and vascular). Thus, whether these variables modulate cardiac dysfunction or the relationship between antiangiogenic factors and cardiac dysfunction requires additional investigation.

In short, the study by Shahul et al. clearly highlights a relationship between HDP and worsened GLS, which correlates with changes in antiangiogenic factors sFlt1 and soluble endoglin. In concert with other publications, it is easy to hypothesize that the antiangiogenic factors may directly contribute to the cardiac dysfunction. Dissecting the causality of this relationship and exploring the potential therapeutic implications of modulating angiogenic function—or the systems that precede and initiate the production of antiangiogenic factors to cause preeclampsia and other HDP—may prove beneficial both during pregnancy and throughout the mother’s life (Figure).

Figure. The authors have previously demonstrated that antiangiogenic factors are upregulated in preeclampsia and, in the case of soluble fms-like tyrosine kinase-1 (sFlt1), can lead to symptoms of preeclampsia in rodents. The current understanding of preeclampsia involves an initiating event that stimulates the production of antiangiogenic factors, which then leads to the symptoms of preeclampsia, including global longitudinal strain (GLS). The authors conclude that these antiangiogenic factors may be directly responsible for GLS in preeclampsia. However, Figure 1 in their article highlights a positive correlation of GLS with sFlt1 and soluble endoglin (sEng) in all patients, including control pregnancies and those with chronic or gestational hypertension (HT) without preeclampsia. Therefore, the study supports the broader concept that sFlt1 and sEng may cause GLS even in the absence of preeclampsia, which is an exciting and important discovery beyond obstetric cardiovascular medicine.
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