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EDITORIAL COMMENT

What Is the Impact of Maternal Hypertension on Offspring Cardiac Structure and Function?*

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Hypertensive disorders of pregnancy (HDPs) affect approximately 15% of childbearing women[1,2] and include chronic hypertension, gestational hypertension (GH), preeclampsia, and eclampsia. GH is defined as a systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg occurring after 20 weeks of gestation in a previously normotensive woman.[3] Preeclampsia is defined by the same BP criteria but is further characterized by end-organ dysfunction in the form of proteinuria (≥300 mg per 24-hour urine collection or protein/creatinine ratio of ≥0.3 mg/dL or 2+ protein on urinalysis) or at least one of the following clinical features: thrombocytopenia (platelet count <100,000 × 10^9/L), renal insufficiency (serum creatinine >1.1 mg/dL or a doubling of the serum creatinine in the absence of renal disease), pulmonary edema, elevated liver transaminases (>2× normal concentration), or new-onset headache unresponsive to medications.[3] Women with HDPs have an increased lifetime risk for cardiovascular diseases, including chronic hypertension, coronary artery disease, heart failure, and stroke.[4,5] Although HDPs have been associated with increased risk of hypertension in offspring,[6] the mechanism is not well understood. Furthermore, differences in cardiac structure have been observed in women with HDPs vs their normotensive counterparts, both in the peripartum setting[7] and over the longer term,[8] which may be at least partially driven by progression to chronic hypertension.[9]

To date, the impact of exposure to HDP on the newborn heart has been less extensively studied, with mixed findings regarding differences in cardiac structure and function among exposed vs unexposed offspring. Experimental models of GH using a chronically hypertensive atrial natriuretic peptide knockout mouse found that their offspring developed significant left ventricular (LV) hypertrophy associated with a restrictive mitral inflow pattern and interstitial myocardial fibrosis.[10] Similar findings have been seen in infants born to mothers with HDP in small studies. Narin et al[11] demonstrated that infants born to mothers with preeclampsia (n = 15) compared with term neonates (n = 17) were found to have impaired diastolic function with a lower mitral peak E-wave velocity and a lower E/A ratio on echocardiography performed within 24 hours of birth. Cetinkaya et al[12] observed a reduced LV end-diastolic dimension, peak E-wave velocity, peak A-wave velocity, and E/A ratio in infants born to mothers with preeclampsia compared with those born to normotensive mothers.

In the study in this issue of *JACC: Advances*, Vøgg et al[13] used the Copenhagen Baby Heart Study, a prospective, population-based cohort, to examine the effect of HDP on term infants using echocardiography performed within 60 days of birth. The authors found that infants exposed to preeclampsia (n = 745) had a significant increase in septal LV wall thickness

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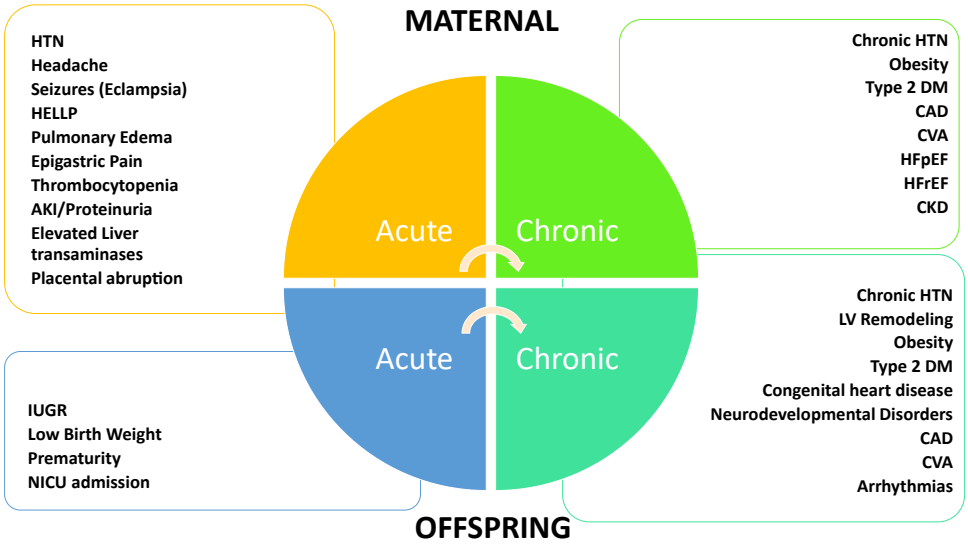
FIGURE 1 **Hypertensive Disorders of Pregnancy: Acute and Chronic Impact on Maternal and Offspring Outcomes**



AKI = Acute kidney injury; CAD = coronary artery disease; CKD = Chronic Kidney Disease; HELLP = Hemolysis, elevated liver enzymes, low platelet count; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; IUGR = Intrauterine growth restriction.

(adjusted mean difference 0.05 ± 0.02 mm; $P = 0.004$), posterior wall thickness (0.04 ± 0.02 mm; $P = 0.009$), increased LV internal diameter (0.12 ± 0.06 mm; $P = 0.04$), and larger LV end-diastolic volume (0.21 ± 0.10 mL; $P = 0.03$) when compared with those unexposed to HDP (n = 17,384). Infants exposed to preeclampsia demonstrated a significant increase in fractional shortening and stroke volume and abnormal diastolic indices: lower peak E-wave velocity and lateral mitral annular tissue Doppler a' velocity. However, adverse remodeling and changes in systolic and diastolic function were not seen in those infants (n = 469) exposed to GH.

Offspring in this study exposed to preeclampsia, but not GH, demonstrated cardiac morphological and functional alterations in the newborn period. The extent to which preeclampsia and GH have shared vs distinct pathophysiologies is incompletely understood and remains controversial; the difference in offspring cardiac findings in this study may be interpreted as further evidence of pathophysiologic differences. Human genetic analyses indicate that gestational hypertension is more directly linked to chronic hypertension predilection, whereas maternal preeclampsia genetics are more complex and multifactorial.[14] Davis et al[15] found elevated levels of 4 indices of angiogenesis-related factors (sFlt-1, PIGF, sFlt-1/PIGF ratio, and sEng) in patients with GH and preeclampsia, with higher values in the latter suggesting that GH might be a subclinical or attenuated form of preeclampsia. Preeclampsia may also be a separate entity characterized by the release of placental antiangiogenic factors into the maternal circulation, crossing the placenta and altering the vasculature of the offspring. The histopathology seen in preeclampsia is characterized by acute atherosis (fibrinoid necrosis of the placental vessel wall with lipid-laden "foamy" macrophages and a mononuclear perivascular infiltrate) and may be associated with vascular ectasia and thrombi.[16] These angiogenic and hypoxic effects in addition to increased placental resistance may lead to an increase in LV afterload and subsequent LV hypertrophy and LV dilation as seen in this study.

There are many strengths to study. To date, this represents the largest systematic study comparing LV structural and functional echocardiographic parameters in infants born to mothers with preeclampsia and GH to those without HDP. Echocardiographic analysis was performed in a blinded fashion with good intra- and inter-observer agreement. The limitations of the study include lack of follow-up echocardiographic data beyond 60 days. It is not clear if infants with adverse LV remodeling had persistent LV changes

beyond 2 months and the clinical significance of observed differences is currently unclear. Importantly, infants studied were delivered at term; prior work has linked preterm birth, which commonly accompanies preeclampsia (especially severe preeclampsia), with cardiac fibrosis in young adulthood.[17] Finally, infants in this study were born to mostly White women, and therefore, these findings may not be generalizable to racial and ethnic minorities.

What is the relevance of this study's findings beyond the newborn period? Prior data suggest adolescents exposed to maternal preeclampsia and GH have thicker LV walls and smaller LV end-diastolic volume vs unexposed offspring.[18] A study in adolescents aged 12 years found those born to a mother with HDP had increased LV mass that was proportional to blood pressure.[19] By the age of 20 years, up to 30% of young adults with clinical hypertension had a maternal history of HDP.[20] Finally, these offspring born to mothers with preeclampsia and GH also have an increased risk for the development of stroke.[21] **Figure 1** displays the reported acute and chronic effects on pregnant women and their offspring exposed to HDP. Further work is needed to clarify long-term prognostic implications and whether these relationships reflect direct causal effects and/or shared risk factors such as genetics or environmental exposures.

This study by Voegg et al provides a window into the effects of HDP on perinatal cardiac structure and function, with alterations noted particularly in offspring of pregnancies complicated by preeclampsia. In addition to clarifying longer term prognostic implications, an equally important question for future research is whether prepregnancy and antepartum interventions may confer benefits for long-term offspring cardiometabolic health in addition to improving obstetric and neonatal outcomes. Optimization of perinatal care including systematic monitoring of hypertension and implementing effective and timely interventions may mitigate adverse cardiac remodeling in the offspring and reduce long-term cardiovascular risk. Finally, it is critical to include a diverse cohort in these investigations as there are significant differences in health outcomes between racial and ethnic groups.

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