Is Maternal Blood Pressure the Key to Vascular Dysfunction in Preterm Offspring With Elevated Blood Pressure?

Barbara T. Alexander

An inverse association between birth weight and systolic blood pressure was first noted by Barker et al. Since then experimental studies have not only substantiated this finding but also provided insight into the potential mechanisms by which adverse influences during critical periods of fetal life lead to increased blood pressure and cardiovascular risk. Recent studies indicate that early postnatal influences may also greatly impact cardiovascular risk in the adult, suggesting that the critical window of programming extends beyond the prenatal period to early postnatal life. Although influences in early life as determinants of cardiovascular risk are widely accepted, the specific influence of gestational age has only recently been acknowledged. Moreover, the mechanism(s) that contribute to high blood pressure in preterm infants, notably the potential role of maternal blood pressure status, has not yet been explored.

The original studies by Barker et al investigated blood pressure as a link between the intrauterine environment and later cardiovascular risk. The noted inverse relationship between birth weight and blood pressure was not associated with gestational age, suggesting that poor fetal growth, not preterm birth, was the major factor contributing to high blood pressure in low birth weight offspring. In this issue of Hypertension, Lazdam et al demonstrate that preterm birth, per se, is also a critical influence on later cardiovascular risk. Importantly, the authors also provide evidence that one mechanism by which preterm birth leads to high blood pressure occurs through programmed changes in vascular phenotype that appear to be influenced by maternal blood pressure during pregnancy.

Blood pressure is higher in low birth weight children born from hypertensive pregnancies, indicating that the maternal milieu of a hypertensive pregnancy may enhance the programming of cardiovascular risk. Impaired vascular function is one mechanism thought to contribute to high blood pressure in low birth weight offspring. Thus, Lazdam et al tested the hypothesis that the vascular phenotype of preterm offspring might be altered by maternal hypertension during pregnancy. The authors report that an increase in blood pressure in preterm offspring of hypertensive pregnancies was associated with an increase in carotid artery intimamedia thickness, a marker of hypertensive vascular damage and indicative of future risk for cardiovascular morbidity and mortality. In addition, flow-mediated vasodilation, an assessment of vascular function, was also impaired in these individuals.

Interestingly, blood pressure was also increased in preterm offspring of normotensive pregnancies; yet, carotid artery intimamedia thickness was not increased in this preterm cohort. Flow-mediated vasodilation was also not reduced, suggesting that maternal hypertension leads to programming of a vascular phenotype that is not observed in preterm offspring from normotensive pregnancies. However, changes in vascular health were not just limited to the preterm offspring from hypertensive pregnancies; arterial stiffness was increased in the preterm cohort from normotensive pregnancies. Thus, Lazdam et al noted that differences in maternal blood pressure status during pregnancy are associated with divergent vascular outcomes in preterm offspring; yet, the causative factors that differentially create these distinct vascular phenotypes are yet to be elucidated.

An earlier study found reduced flow-mediated vasodilation in preterm children to depend on accelerated postnatal growth, suggesting that postnatal influences could be a contributing factor in the programming of impaired endothelial vascular function in preterm individuals. Whether the difference in vascular phenotypes reported here between preterm offspring born to normotensive pregnancies or preterm offspring born to hypertensive pregnancies is because of differences in the postnatal environment is not clear. Information related to the rate of postnatal weight gain in preterm offspring and how that correlates with maternal blood pressure was not reported in the current study. The authors do report that preterm individuals were significantly shorter at the time of the follow-up study at 20 years of age, but they had similar body mass index and weight, suggesting that adult metabolic factors are likely not the cause of the disparate vascular phenotypes. In general, preterm infants demonstrate impaired postnatal growth regardless of whether they are appropriate or small for gestational age. Thus, postnatal influences that alter growth trajectories may not be critical mediators of the different vascular phenotypes observed in the preterm cohorts in this study.

Cheung et al reported that an increase in arterial stiffness in preterm offspring in their study was related to intrauterine growth restriction. However, aortic stiffness was not increased in preterm offspring from hypertensive pregnancies in the current study. Furthermore, Lazdam et al did not observe a difference in birth weight between the 2 preterm cohorts, suggesting that the increase in arterial stiffness in the preterm offspring of normotensive pregnancies was most likely not the result of slow fetal growth. Vascular stiffness

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can be an adaptation to increased blood pressure. However, in the current study blood pressure at the 20-year follow-up was similar in both preterm cohorts (≈10 mm Hg higher) relative to term controls, indicating a need for additional studies to delineate the underlying mechanisms that differentially program impaired vascular function in preterm offspring.

If growth during gestation and growth during early postnatal life are not primary mediators of the divergent vascular phenotypes observed in preterm offspring of normotensive versus hypertensive pregnancies, subsequently is poor maternal health the key? The importance of maternal health is implicated in the hypothesis of the developmental origins of adult health and disease. In the study by Lazdam et al., pre eclampsia accounted for 85% of the cases of hypertensive pregnancies. The environmental milieu of a hypertensive preeclampsia involves activation and production of numerous endothelial and humoral factors that mediate maternal vascular dysfunction. In addition, adverse influences from the ischemic placenta may also play a key role in the development of the vascular phenotype of the fetus before birth. In the absence of hypertension in pregnancy, however, other factors must contribute to the programming of altered vascular phenotype and higher blood pressure in preterm offspring. A positive family history of cardiovascular disease that includes genetics and common environmental factors that interact with preterm birth could be a causative factor in the programming of later cardiovascular risk. However, the probability is low that similar genetic and environmental influences would occur only in preterm offspring of normotensive pregnancies.

Spontaneous preterm birth can result from a number of different stimuli, including fetal distress, infection and inflammation, and genetics. The cause of preterm birth in the normotensive pregnancies is not provided in the study by Lazdam et al.; however, stressful stimuli related to the cause of spontaneous preterm delivery cannot be ruled out as an adverse influence that may affect vascular development in these preterm offspring. Other factors that may contribute to increased risk for preterm birth include the age of the mother (typically younger), ethnicity (highest for black infants), and socioeconomic factors, all of which are not reported for the preterm cohort in the study by Lazdam et al. All of these factors may contribute to altered vascular development in this preterm group. Thus, further investigation is needed to clearly address the cause of preterm birth in normotensive pregnancies and how preterm birth from a normotensive pregnancy correlates with programmed changes in vascular function and higher blood pressure in preterm offspring.

In conclusion, the differential effect of a normotensive versus a hypertensive pregnancy on vascular function in preterm offspring is a novel finding and indicates a key role for the maternal environment in the programming of cardiovascular risk. Future studies are needed to establish how distinctive influences from diverse maternal environments differentially program vascular dysfunction in preterm offspring.

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