Preterm Birth
A Novel Risk Factor for Higher Blood Pressure in Later Life
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There is compelling epidemiological and experimental data that suggest that blood pressure in later life can be programmed by adverse influences during fetal life. Evidence for the theory of developmental programming of adult health and disease was first based on the geographical association of deaths from heart disease to death rates among newborn infants. This observation led to the hypothesis that undernutrition during fetal life permanently alters the physiology, structure, and metabolism of an individual leading to heart disease in later life. Poor fetal growth, the link to infant mortality, was also associated with systolic blood pressure (SBP), a known risk factor for heart disease; however, this association was independent of gestational age. In this issue of Hypertension, de Jong et al present their findings from a thorough and systematic review of the literature followed by a meta-analysis to determine whether preterm birth predicts a higher SBP in later life. Their results indicate that individuals born preterm have a higher SBP in later life than infants born at term (2.5 mm Hg). Although this difference in SBP is small, it is similar to the increase observed in studies linking birth weight and SBP, indicating that preterm birth, not unlike poor fetal growth with birth at term, may also program an increase in later cardiovascular risk. However, the study by de Jong et al provides no direct insight into potential mechanisms. Thus, if preterm birth predicts higher blood pressure in later life, then what are the mechanisms and do they differ from those that program higher blood pressure after poor fetal growth?

Higher blood pressure programmed in response to poor fetal growth has been extensively investigated, and insight from numerous experimental studies indicates a key role for the kidney, vasculature, and neuroendocrine systems. The kidney mediates the long-term control of blood pressure through the maintenance of electrolyte and fluid homeostasis. In humans, nephrogenesis is complete by 36 weeks’ gestation; however, nephron number is reduced in low birth weight individuals, an observation supported by numerous animal models of poor fetal growth. Compensatory glomerular hypertrophy and a reduction in glomerular filtration rate are associated with a marked increase in blood pressure in animal models of prenatal nutrient restriction, suggesting that hypertension programmed in response to an adverse prenatal influence may result from impaired sodium filtration as a result of reduced glomerular filtration rate. However, experimental models that mimic the human condition of poor fetal growth also demonstrate vascular dysfunction and indicate a potential role for the renin-angiotensin and sympathetic nervous systems in the programming of high blood pressure. Thus, these observations suggest that impaired growth during fetal life results in alterations in structure and physiology that impact disease risk in later life. Moreover, these studies indicate that prenatal programming is multifactorial and, despite different methods of prenatal insult, often results in programming of similar mechanistic pathways. Recent studies also demonstrate that accelerated postnatal growth after poor fetal growth enhances the risk of hypertension in adulthood, suggesting that postnatal influences also contribute to later increases in SBP. Thus, prenatal and postnatal influences contribute to the programming of higher blood pressure that originates in response to poor fetal growth; however, are the mechanistic pathways involved in the increase in SBP in response to poor fetal growth the same as those after preterm birth?

Observations that preterm birth confers a risk for higher blood pressure have only recently been suggested, and animal models to study the mechanisms by which preterm birth leads to increased blood pressure are very limited. A recent study from Sutherland et al reports that preterm birth before completion of nephrogenesis does not result in a reduction in nephron number in a nonhuman primate model of preterm birth. These results suggest that nephrogenesis continues after preterm delivery; yet, how completion of renal development beyond the fetal milieu and whether it is impacted by the abrupt renal adaptation to extrauterine life are not clearly known. Lazdam et al demonstrated recently that vascular structure and function are impaired in young adults born preterm that exhibit an increase in SBP in adult life. However, whether changes in vascular structure and function are the result of preterm birth or whether they are attributed to the associated elevation in SBP is not clear. Thus, the question remains, what is the trigger for a later increase in SBP in preterm individuals?

Experimental models of developmental programming demonstrate that heritable mechanisms programmed by poor fetal growth may involve environmentally induced epigenetic modifications that program long-term changes in the phenotype of the developing fetus without changing the underlying DNA sequence. Preterm birth is often associated with
maternal and neonatal distress. Thus, vulnerability of the preterm infant to intrauterine and extraterine environmental cues in early life suggests that epigenetic mechanisms may contribute to increased blood pressure in individuals born preterm. However, the effect of imprinting may not be limited to the influence of an individual’s preterm birth. The causes of preterm birth are varied, but recurrent preterm birth is prevalent in women born spontaneously preterm or with a family history of preterm delivery, indicating a transgenerational effect for preterm birth. The occurrence of intergenerational inheritance of programmed phenotype from the F0 generation to the F2 in the absence of direct exposure to the environmental insult indicates that epigenetic imprinting of genes may be permanent. Thus, one could speculate that programming of higher SBP in individuals born preterm may originate directly from influences in their early life; however, programming of higher SBP linked to preterm birth may also have its origins from previous generations (Figure).

In summary, this study by de Jong et al provides extensive evidence that preterm birth programs higher SBP in later life. In light of findings from the Developmental Origins of Health and Disease paradigm, the complex etiology of preterm birth, and influences exerted by a family history that predisposes to preterm birth, the mechanisms that link higher blood pressure in individuals born at preterm are most likely complex and warrant the development of appropriate animal models of preterm birth for more extensive investigation into cause and effect.

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**References**

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