Brief Review

Preterm Birth and Hypertension Risk
The Oxidative Stress Paradigm

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Preterm Birth

The majority of epidemiological studies in developmental programming have explored the influence of low birth weight (irrespective of gestational age) on long-term chronic disease in individuals born during the first half of the 20th century.[1,2] Low birth weight neonates may represent infants born at term with intrauterine growth restriction (IUGR) or born preterm with or without IUGR. As such, there is emerging interest in the effects of preterm birth alone (beyond birth weight and IUGR) on specific aspects of human development and long-term health.

Approximately 10% of all births worldwide are preterm (before 37 completed weeks of gestation).[3] Besides being of low birth weight, preterm neonates are suddenly and prematurely exposed to the extrauterine environment at a time when organogenesis is incomplete. Exposure postnatally to factors such as high oxygen concentrations,[4] medications[5] (including glucocorticoids),[6] and inadequate nutrition[7] likely adversely influence postnatal growth and ongoing organ development. In addition to possible genetic and epigenetic factors that may contribute to hypertension risk (including hypertension-related complications of pregnancy), a multitude of aspects related to both intrauterine and extrauterine growth, as well as the postnatal environment, may all play an important role in the programming of hypertension in individuals born preterm. In this review, we will highlight, in particular, the potential effect of oxidative stress associated with preterm birth on neonatal development and future disease risk.

Evidence From Epidemiological Studies: Preterm Birth and an Increased Risk of Developing Hypertension

The survival of neonates born at low and very low gestational ages is recent in the history of medicine and has increased remarkably over the last few decades. The first generations of survivors of very preterm birth are currently just reaching adulthood and as such are providing emerging evidence of chronic health conditions, such as hypertension. The link between preterm birth and hypertension risk (independent of birth weight) has been clearly demonstrated in a number of epidemiological studies. A significant inverse correlation between systolic blood pressure and gestational age at birth has been consistently observed from childhood to adulthood in preterm-born individuals[8–21]; in particular, a recent meta-analysis demonstrated that systolic blood pressure in preterm-born children and young adults was an average of 2.5 mm Hg (95% confidence interval, 2.6–5.0 mm Hg) higher than those born at term.[21] We have also recently shown in a population-based study in Quebec, Canada, that women born preterm, particularly if birth occurred <32 weeks gestation, had an increased risk (independent of birth weight) of pregnancy complications (including gestational diabetes mellitus, gestational hypertension, and preeclampsia), as well as chronic hypertension compared with women born at term.[22] It is to be noted, however, that many studies have not taken into account the effect of other confounding factors, such as chronic lung disease, that have effect on exercise capacity and thus cardiovascular health.

Possible Contributors to Increased Hypertension Risk in Neonates Born Preterm

The increased risk of hypertension evidenced in neonates born preterm is likely to be multifactorial in origin, with preterm birth resulting in alterations to cardiac, renal, and vascular development/function, as well as neural pathways.

Vascular

Preterm birth may disrupt or even prematurely arrest proper development of the vascular tree, resulting in stiffer arteries, a restricted vascular bed, and relatively narrowed blood vessels, all predisposing to endothelial dysfunction and arterial hypertension.[23,24] Preterm birth often results from an abnormal pregnancy, with conditions such as preterm premature rupture of membranes, uteroplacental insufficiency, and preeclampsia being major causes of medically induced preterm birth. Therefore, it is to be noted that impairments to vascular system development may initially occur before preterm birth via IUGR and exposure to an inflammatory and antiangiogenic environment.[25,26]

In humans, elastin synthesis in arterial walls peaks toward the end of gestation (near term) and then declines very rapidly after birth.[27,28] Arterial distensibility and elasticity depend largely on the ratio of elastin to the more rigid collagen in

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