Preterm Birth and its Impact on Renal Health

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Summary: Preterm birth occurs in approximately 10% of all births worldwide. Preterm infants have reduced nephron numbers at birth in proportion to gestational age, and are at increased risk of neonatal acute kidney injury as well as higher blood pressure, proteinuria, and chronic kidney disease later in life. Rapid catch-up growth in preterm infants, especially if resulting in obesity, is a risk factor for end-stage kidney disease among children with proteinuric renal disease. Preterm birth, however, is a risk factor not only for the infant because mothers who deliver preterm have an increased risk of having subsequent preterm deliveries as well as hypertension, cardiovascular disease, and renal disease later in life. Preterm birth in a female infant is also a risk factor for her future risk of having a preterm delivery, gestational hypertension, and gestational diabetes, which in turn may impact the development of fetal kidneys and the offspring's risk of hypertension and renal disease. This intergenerational programming cycle, therefore, perpetuates the risks and consequences of prematurity. Interruption of this cycle may be possible through optimization of maternal nutrition and health as well as careful antenatal care, which may in turn reduce the global burden of hypertension and renal disease in subsequent generations.

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Preterm birth is defined as a birth before 37 weeks of gestation and very preterm is defined as birth before 32 weeks.[1] Preterm infants often are born with a low birth weight (LBW), either related to low gestational age per se, or from superimposed growth restriction resulting in a birth weight that is small for gestational age (SGA). Both preterm birth and growth restriction have been associated with an increased risk of chronic diseases in later life. This risk is not limited to the infant because a mother who delivers prematurely also may be at increased risk of renal and cardiovascular disease, and a mother who herself was born prematurely may be at increased risk of having a complicated pregnancy and delivering a preterm infant.

The global incidence of preterm birth is approximately 10%, which is similar in both high- and low-income countries, although reasons may differ.[2,3] In high-income countries, preterm birth may occur with advanced maternal age, maternal obesity, assisted reproduction, multiple gestations, and chronic maternal illness, whereas in lower-income settings, young maternal age, maternal stunting and low body weight, preeclampsia, maternal infections, and socioeconomic disadvantage may be more frequent causes (Fig. 1). The contribution of preterm birth to global mortality has decreased over the past decade, but the years of life lived with disabilities after preterm birth have not yet decreased.[4,5] Furthermore, these data do not capture the long-term programming impact of preterm birth on later-life chronic disease risk, which may be under-recognized, but is an important contributor to the global burden of renal and cardiovascular diseases. The phenomenon whereby stresses experienced during fetal and early postnatal life impact organ development and increase the risk of later-life chronic disease is termed *developmental programming*.[6] Initial studies focused on LBW as a marker of risk for later-life cardiovascular disease.[7] Since then, LBW also has emerged as a surrogate marker for low nephron number, and low birth weight is now a recognized risk factor for later-life hypertension and chronic kidney disease (CKD).[8] This article discusses the association of preterm birth and growth restriction with programming changes in the kidney, and the risk of hypertension and renal disease in later life both for the infant and mother.

PRETERM BIRTH AND NEPHRON NUMBER

Given the fact that nephron number does not increase after birth, Brenner et al[9] hypothesized that individuals born with kidneys with fewer nephrons would be at increased risk for hypertension and renal disease later in life. This paradigm has been termed the nephron number hypothesis. In human beings, nephrogenesis generally continues in utero until the 36th week of gestation, with little evidence of nephrogenesis occurring postnatally in term infants.[10] In preterm infants, however, it has been observed that nephrogenesis can

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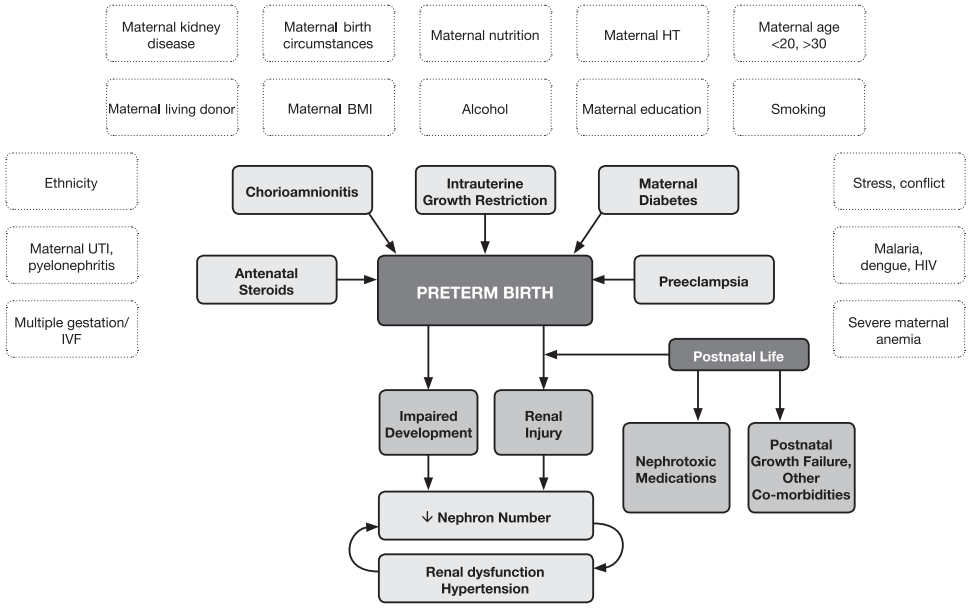

Figure 1. Risk factors for preterm birth and factors impacting renal programming in the infant. Adapted with permission from Sutherland et al.[15] BMI, body mass index; HIV, human immunodeficiency virus; HT, hypertension; IVF, in vitro fertilization; UTI, urinary tract infection.

continue up to 40 days after birth, however, the nephrons formed tend to mature prematurely and remain abnormal.[11] Nephron number in human beings is known to be proportional to gestational age (Fig. 2).[11] Growth-restricted fetuses at various gestational ages were found to have fewer nephrons than those with appropriate weights for gestational age.[12] How preterm birth may impact nephrogenesis is not known, but it has been suggested that multiple factors may contribute sequentially including growth restriction in utero, the alteration of the neonatal redox state occurring at birth with the transition from relative hypoxia in utero to high oxygenation ex utero, as well as nutrition and pharmacologic interventions required postnatally, which all affect the developing kidney.[13]

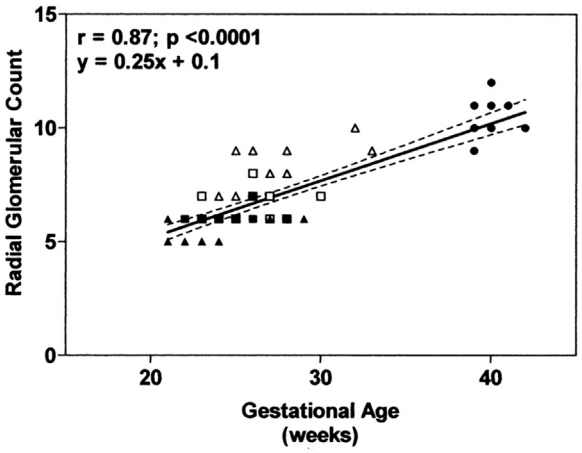

Figure 2. Linear regression analysis of radial glomerular counts with increasing gestational age; closed triangles, preterm fewer than 40 days after birth, with renal failure; closed squares, preterm fewer than 40 days after birth, without renal failure; open squares, preterm 40 days or more after birth, with renal failure; open triangles, preterm 40 days or more after birth, without renal failure; and closed circles, term birth. Reprinted with permission from Rodriguez et al.[11]

There is a broad range of risk factors for preterm birth including maternal body weight (both high and low), acute and chronic maternal illness, assisted reproduction, multiple gestations, extremes of maternal age, and preeclampsia, among others (Fig. 1).[14,15] Table 1 shows both animal and human risk factors for a preterm birth and their potential independent effects on programming of offspring nephron number and blood pressure. Human data are sparse, but tend to be consistent with animal findings. Whether renal programming in preterm infants results purely from arrested or abnormal kidney development after a preterm birth or is impacted additionally or synergistically by the risk factors that led to preterm birth, or results from the frequent growth restriction that accompanies preterm birth, are difficult to dissect and have not been well studied. Most likely a preterm infant experiences multiple hits of varying severity during kidney development, which ultimately impact long-term risk. For example, two important risk factors for preterm birth include preeclampsia/eclampsia and maternal diabetes. Preeclampsia/eclampsia occurs in up to 5% of pregnancies worldwide, whereas gestational diabetes, although not screened for systematically, has been reported in up to 25% of pregnant women in some countries.[16,17] Placental ischemia associated with preeclampsia or hyperglycemia

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