Preterm Birth: A Risk-factor for Chronic Kidney Disease?

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The concept of the origin of most chronic illnesses in the prenatal period was introduced by Dr. David Barker, back in the 1990s [1]. This concept was later extended to kidney diseases by Brenner, *et al.* [2]. As more than 60% of the nephrogenesis occurs in the last trimester of pregnancy, it is believed that preterm births before 36 weeks have a lower nephron mass [3]. This results in a decreased estimated glomerular filtration rate (GFR) at birth. However, despite the fewer glomeruli, they manage to achieve a GFR similar to that of a term neonate. This compensatory response due to the single nephron hyperfiltration eventually results in glomerular damage, proteinuria and hypertension, thus setting them on the path of development of chronic renal disease in due time.

In small for gestational age (SGA) newborns; however, the cause for a decreased GFR is different. A difference in the genetic composition of the renal cells with an overall increased rate of apoptosis are the proposed mechanisms [4,5]. The ongoing inflammation along with placental insufficiency in these growth restricted newborns affects the organogenesis, leading to a lower nephron mass [6]. In this issue of the journal, Reddy and colleagues [7] have reported on their study on renal growth and function in appropriate for age (AGA) and SGA preterm neonates with a gestation <35 weeks. They have concluded that preterm infants, especially SGA infants, are at an increased risk of impaired renal function with a poor renal growth at 12 to 18 months of corrected gestational age [7].

The extra-uterine course of each newborn is different. Sepsis, birth asphyxia and use of nephrotoxic drugs may additionally impact the GFR [8]. With an increased risk for renal vascular thrombosis and a poor tubular function, some of these newborns may suffer a second hit, *i.e.* neonatal acute kidney injury (AKI) [9]. These factors predispose this cohort to the development of chronic kidney disease (CKD) in later life [10-12].

As the growth of the kidneys to attain adult

glomerular filtration levels continues till two years of age, the evaluation of kidney function in this dynamic period remains difficult [13]. Therefore, a one-time assessment by a cross-sectional study may potentially lead to biased results. Moreover, baseline renal functions after birth require serial repeated measurements over time to ensure consistency in the results and a valid final outcome.

The use of serum creatinine as a neonatal renal biomarker has been questionable. Being affected by the muscle mass and hydration status, it has a high inter-individual variability among neonates itself [14]. The superiority of Cystatin C over serum creatinine has been extensively studied and evaluated with meta-analyses. Being independent of age, sex, muscle mass and various inflammatory conditions, the constant production rate with a minimal placental transfer makes it a preferred biomarker for estimation of GFR, especially in neonates. Even though, further validation by more extensive studies remains necessary, its importance cannot be undermined.

Iyengar, *et al.* [15] in 2016, studied the kidney growth and changes in GFR during this dynamic period in a cohort of southern Indian infants using serial renal volume measurements by an ultrasound and cystatin C derived glomerular filtration rate. While the renal growth was reported to be slower in the low birthweight and SGA infants, the GFR at 18-24 months of age was similar. This supported the concept of hyper-filtration in the smaller kidneys which may act as a precursor to the development of CKD in the adult life.

Various studies support the concept of the mean renal volume as a surrogate *in vivo* marker for the nephron number in neonates [16,17]. However, the extrapolation of this concept to renal length, as done in the current study, may lead to biased results. Moreover, most of the studies conducted previously for assessment of the renal function and the progression to CKD in this cohort, have enrolled large subject numbers. A small number of total enrolled patients by Reddy, *et al.* [7] might lead to confounded results and hence, a decreased generalizability of the study.

A newer innovative method of assessing nephron number by magnetic resonance imaging (MRI) of the kidney, with cationic ferritin labelled glomeruli is currently being evaluated [18]. The ongoing research in metabolomics with urinary novel biomarkers including beta-trace protein, beta-2 microglobulin, urinary neutrophil gelatinase associated lipocalin, urinary kidney injury molecule, serum cystatin C and uromodulin will open new doors for early detection of kidney injury and better techniques for estimation of GFR in children. The manipulation of the modifiers of nephrogenesis, including variants in the *PAX2* or *RET* genes and epigenetic factors like DNA methylation raises the possibility of development of strategies to extend the period of normal nephrogenesis [19]. Methods to induce *de novo* nephrogenesis postnatally are also currently the focus of ongoing animal experiments [20].

The increasing survival rate of the preterm and SGA babies also puts them at the risk of development of various co-morbidities. It is, thus, imperative that a long-term surveillance plan for early detection of kidney diseases be implemented with appropriate preventive measures to check the progression to chronic kidney disease.

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