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Prematurity and Future Kidney Health: The Growing Risk of Chronic Kidney Disease

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Abstract

Purpose of review—The purpose of this review is to describe the role prematurity plays in the development of chronic kidney disease (CKD), and to discuss potential reasons for this association including decreased nephron mass, as well as post-natal insults such as neonatal acute kidney injury (nAKI).

Recent findings—New observational studies in humans and experimental studies in animal models have strengthened the association between prematurity, low birth weight, and CKD. Growing evidence suggests increased susceptibility to CKD is caused by decreased nephron mass at birth. Beginning with a low nephron count may cause only subtle abnormalities during childhood, however may result in CKD, hypertension and albuminuria in adolescence or adulthood. Recent studies in premature infants reveal a high incidence of nAKI, which may also contribute to ongoing CKD risk.

Summary—Children born at low birth weights (both due to prematurity and/or intrauterine growth restriction) show increased risk of kidney dysfunction during adulthood. A better understanding of the modulators of nephron mass in premature infants as well as the effects of the extrauterine environment is essential. Additionally, improved awareness of at-risk infants is important as is early evaluation and detection of kidney dysfunction, allowing interventions to slow the progression to CKD.

Keywords

Kidney development; Prematurity; Kidney disease; Chronic Kidney Disease; Acute Kidney Injury

Introduction

Approximately 15 million infants worldwide are born prematurely each year. In the United States, 50,000 infants each year are born at less than 28 weeks of gestation. Dramatic improvements in neonatal intensive care, advancements in our understanding of neonatal physiology, and implementation of therapies (such as prenatal glucocorticoids and surfactant

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Conflicts of interest

None

replacement) have led to improved survival of premature infants. The most recent data from the Vermont Oxford Network demonstrate that approximately 90% of infants born weighing between 500g and 1,500g survive to discharge.[1]

However, despite an improvement in survival, long-term morbidity remains high, and premature infants account for massive resource utilization during their lifetimes. While increased attention has been focused on neurodevelopmental outcomes for these infants, morbidity related to kidney health has been largely neglected.[2] Over the last decade, the critical care and nephrology communities have demonstrated that kidney dysfunction portends poor short and long-term outcomes, independent of comorbidities and interventions, both in children[3*] and adults.[4]

This review highlights the role of developmental programming and the importance of late gestation and post-natal nephrogenesis on nephron mass, evaluates recent experimental evidence, and observational data that support the role of prematurity as a risk factor for chronic kidney disease.

A Theoretical Framework and the Importance of Late Gestation for Nephrogenesis

There are two hypotheses that form the framework for reduced nephron number and its impact on kidney health. The first, that of prenatal origins of adult disease, is credited to David Barker who made the observation that many “adult” diseases appear to have their origins in fetal life.[5] This conclusion, drawn initially from epidemiologic associations between low birth weight and adult hypertension, is commonly called the Developmental Origins of Health and Disease (DOHaD) hypothesis.[5] Evidence for this “fetal programming” exists for premature infants that go on to develop coronary artery disease[6], hypertension[5], and obesity[7] later in life.

Brenner extended this principle to kidney development, suggesting that fetal stressors result in reduced nephron number at birth, predisposing individuals to CKD.[8–10] Human nephron number is highly variable, ranging from 210,000 to 2.7 million, with this variability hypothesized to contribute to an individuals’ susceptibility to kidney disease.[11,12] Nephrons do not regenerate; therefore, the nephrons present in neonates at time of birth must last a lifetime. Even in healthy adults, the number of functional nephrons decrease over time, leading to an age-dependent decline in glomerular filtration rate (GFR).[13] Brenner’s theory, also known as “nephron under-dosing” posits that over time individual nephrons increase their available surface area to compensate for decreased nephron number, an adaptive response that becomes maladaptive.[10] Glomerular surface area increases leading to systemic hypertension and sodium retention, disrupting renal auto-regulatory mechanisms and worsening proteinuria and hypertension.[14] This in turn leads to nephron sclerosis, resulting in additional decline in nephron number and more rapid nephron dropout in a deleterious and additive process (Figure 1).[15]

Prematurity leads to a decrease in nephron mass. Nephrogenesis begins during the sixth week of gestation and continues through the 36th week, with nearly 60% of nephron

development occurring during the third trimester of pregnancy.[16] While nephrogenesis may continue in premature infants for up to 40 days following birth, these nephrons are abnormal and age at an accelerated rate.[17] However, despite this post-natal kidney development, premature infants are still left with a decreased number of nephrons. For example, a premature infant born at 26 weeks of gestation, despite 40 additional days of nephrogenesis, will only have nephron development until 32 weeks in contrast to continuing nephrogenesis to 36 weeks in term gestation. In infants born prematurely, autopsy studies have found decreased areas of development with abnormally formed and mature glomeruli suggesting early cessation of nephrogenesis.[16,18]

Animal Studies Implicating Decreased Nephron Number

Experimental models support these theoretical frameworks, as models of reduced nephron number (5/6 nephrectomy in rats) demonstrate early onset renal disease.[19] In mouse models, where nephrogenesis occurs for 5-7 days following birth, prematurity impairs post-natal nephron formation. Prematurely born mice have decreased nephron number and decreased kidney volume compared to mice born at full gestation. Clinical outcomes mirror pathologic findings, as mice born several days prematurely develop CKD with hypertension and albuminuria by 5 weeks old.[20]

Non-human primate models (such as the baboon) appear to be a closer approximation to premature humans, in that they continue to form nephrons postnatally. Studies of kidney pathology from premature baboons in which conditions similar to Neonatal ICU settings (including mechanical ventilation and nephrotoxic medications) are replicated have described decreased nephron number and abnormal glomerular histology during the time of post-natal nephrogenesis.[21]

Prematurity as a Risk Factor for CKD

To date, there are no prospective, population-based studies that confirm the association between prematurity and CKD. The original studies by Barker as part of the DOHaD hypothesis were unable to distinguish between prematurity and intrauterine growth restriction (IUGR) as the cause of low birth weight (LBW). Examining the impact of prematurity alone is challenging as many infants born prematurely also have IUGR, as well as multiple medical problems and medication exposures.[8] Despite these confounders, studies have repeatedly demonstrated strong associations between fewer glomeruli and a higher risk of proteinuria, hypertension, salt sensitivity of blood pressure and progressive CKD.[10,22,23]

The best-studied marker for adverse intrauterine environment is LBW. A meta-analysis including more than 2 million individuals from 31 studies found that LBW was associated with an approximately 80% increased odds of albuminuria, 80% increased odds of a sustained low GFR, and an approximately 60% increased odds of end-stage kidney disease in later life compared to their normal birth weight counterparts.[24] The largest study to analyze this association was a Norwegian registry-based study conducted from 1967 to 2004 which found a relative risk of 1.7 for the development of end-stage kidney disease for all

infants with birth weights <10th percentile.[25] A large national registry-based study including over 20,000 persons born from 1924 to 1944 and followed until death found that both prematurity and LBW were associated with increased risk of CKD (based on ICD-9 codes), with infants born less than 34 weeks having a 2.6-fold increased risk of developing CKD.[26**]

Studies of long-term kidney function following premature birth have been in children and adolescents. Despite this relatively short period of follow-up, several studies have described associations between premature birth and increased urinary albumin excretion and reduced GFR. [27,28*] Among a cohort of adolescents born prematurely, infants with LBW were 1.4 times more likely to have microalbuminuria and a decreased GFR, and those who also had IUGR had a 2.4 fold increase in albuminuria.[28*, 29] A recent case-control study of Japanese children with childhood onset CKD found that 21% of CKD cases were attributable to LBW and a strong correlation was observed between prematurity and CKD (as defined by a GFR <90 ml/min/1.73m²).[30*] Additionally, infants born prematurely appear to have smaller kidneys on renal ultrasound which may reflect decreased nephron number compared to their age matched controls. [27,31**]

Using the NIH-sponsored Chronic Kidney Disease in Children (CKiD) study, of the 489 children in the CKiD cohort, 17% were LBW (< 2,500 g), 13% were premature, 15% were small for gestational age, and 41% were admitted to a neonatal intensive care unit; all of these percentages are more common than rates in the general population.[32] While changes in renal function in adolescence or young adulthood are often subtle, these abnormalities may progress to overt kidney dysfunction or leave children susceptible to secondary kidney injuries.

Acute Kidney Injury as a Second Hit

Premature neonates are at high risk of neonatal acute kidney injury (nAKI), which may further decrease nephron number and potentiate progression to CKD. This increased nAKI risk is due to many factors, including vasomotor nephropathy (impaired vasoregulation of the glomerulus), low GFR during the first several weeks of life, tubular immaturity, exposure to nephrotoxins, and an increased risk of renal vascular thrombosis.[33] nAKI is common in critically ill neonatal populations, with increased risk in infants with perinatal asphyxia[34], congenital heart disease[35], sepsis[36], in addition to prematurity.[37] While the incidence of nAKI has long been challenging to determine given variable definitions, a recent multicenter retrospective cohort study reported an incidence of nAKI of 48% in those born before 29 weeks of gestation.[38*]

Previously, it was assumed that those who survive an episode of AKI recovered kidney function without long-term sequelae; however, over the last decade, data from animal models[39], critically ill children[40,41] and adults[42,43] with AKI suggest that survivors are indeed at risk for development of CKD. Animal models of AKI show reduction in vascular density and oxygen delivery[39], as well as sustained fibroblast activation and progressive fibrosis even after recovery of kidney function.[44]

Investigators have hypothesized that acute hypoxic, hyperoxic, ischemic, septic and nephrotoxic insults between birth and termination of glomerulogenesis are a second hit to the premature kidneys and appear to alter renal development and/or nephron mass potential (Figure 2).[45] In premature infants undergoing post-natal nephrogenesis, this has significant ramifications. In both human autopsy studies[16] and animal studies[18], post-natal development was affected by occurrence of AKI as well as exposure to nephrotoxins such as gentamicin and non-steroidal anti-inflammatory drugs. Additionally, in infants with nAKI there is evidence of accelerated renal maturation, decreased number of immature glomeruli, and abnormally formed and hypertrophied glomeruli compared to gestational age matched controls.[16]

Many studies in pediatric patient populations have demonstrated that AKI is associated with CKD development. Mammen et al. recently described a long-term follow-up study of 126 critically ill children with AKI without pre-existing CKD.[41] Over the 1 to 3 year follow-up period, 49/126 (38.9%) children developed CKD (as defined by a GFR <90 ml/min/1.73m²). [41] Another recent study found that children with nephrotoxin associated AKI had a high risk of kidney dysfunction, with 70 of the 100 patients followed having evidence of residual kidney damage (GFR <90 ml/min/1.73m², hypertension, or proteinuria) 6 months after discharge.[46]

Studies about the long-term implications of nAKI and associations with CKD in premature infants are limited to small single center retrospective reports.[47] Compared to term neonates, premature and low-birth weight infants with nAKI have twice the rates of albuminuria, CKD (developing as early as 1 year), and end-stage kidney disease (4.5-18 years after birth).[47] Risk factors for progression include an urine protein to creatinine ratio >0.6 mg/g and a serum creatinine of >0.6 mg/dL at 1 year of age and a body mass index of $>85^{\text{th}}$ tile.[47]

A meta-analysis of 8 longitudinal studies evaluating kidney function of children diagnosed with nAKI found that among the 293 children followed, 53 (18%) had evidence of CKD. [48**] A recent long-term follow-up study assessed renal function in 34 premature infants with and without nAKI at age 3 – 7 years, finding that infants with nAKI had a higher likelihood of kidney dysfunction (65% vs. 15%) based on GFR, elevated urinary protein excretion, or systemic hypertension.[49**] While much more remains to be learned about the role of nAKI and other post-natal insults in prematurely born children, nAKI appears to impact post-natal nephrogenesis and may lead to a greater decline in kidney function.

Monitoring the ex-Premature Infant for CKD

Pediatricians caring for children born prematurely should have an elevated suspicion for kidney dysfunction, and frequently assess risk of CKD, including a review of the birth history, neonatal course, and childhood health status.[50*] Based on experimental and observational data, all premature infants are at increased risk of kidney dysfunction due to decreased nephron number. While attention to neonatal diagnoses is important, caution must be used as documentation of nAKI is often poor, with one recent study finding that only 13.5% of infants with nAKI had it listed on their NICU discharge summaries.[37]

Much progress has been made in coordinated follow-up programs for premature infants. While evaluation is often focused on neurodevelopmental outcomes,[51] we suggest that these “High Risk” clinics are an ideal opportunity to evaluate infants and children for kidney dysfunction. We propose a risk stratification system to identify infants at the time of hospital discharge based on their gestational age as well as hospital complications, to recommend the location and intensity of kidney function monitoring. (Figure 3)

Kidney dysfunction in former premature children can be detected in childhood with reduced renal volume, microalbuminuria, or systemic hypertension. Recent recommendations for blood pressure monitoring include early and frequent evaluation in infants born <32 weeks gestation, IUGR, those with any neonatal complication requiring intensive care, and those with umbilical line placement.[52*] Infants with chronic lung disease of prematurity represent an understudied group that may be at higher risk for kidney dysfunction and in which closer monitoring may be indicated.[53] Hypertension may be an early clinical indicator of low nephron number in premature infants particularly those with IUGR or other neonatal exposures, and therefore blood pressure screening should be initiated early at all well-child visits starting at 1 year of age.[50*] Additionally, monitoring for appropriate extrauterine growth is essential as rapid weight gain during infancy, childhood or adolescence may place prematurely born children at higher risk of CKD.

Early identification of kidney disease is crucial, as clinical examination (high blood pressure) or laboratory findings (albuminuria) often exist before overt symptoms of kidney dysfunction, and interventions exist to slow progression of CKD. We propose that in premature infants screening should be performed as part of coordinated follow-up programs whenever possible, with coordination between pediatric nephrologists and primary care providers. While the evaluation for kidney dysfunction in the ex-premature infant is beyond the scope of this review, evaluation should include but not be limited to monitoring of growth, laboratory evaluation of kidney function, urinalysis for assessment of microalbuminuria, and blood pressure monitoring.

Future Directions and Research Focus

In order to improve detection and screening programs, future research should focus on improved identification of infants at risk of CKD. The factors most associated with CKD in premature infants need to be fully elucidated. Longitudinal studies of premature infants throughout childhood and adolescence will allow for further insight and risk-factor identification. Additionally, new methods of assessing nephron number in living children may allow further risk stratification with non-invasive imaging. New methods including ultrasound-based imaging [54*] as well as use of cationic ferritin as a MRI-detectable contrast agent[55] have recently been proposed as innovative methods of assessing nephron number.

The well-known limitations of using serum creatinine to diagnose AKI are compounded in premature infants due to confounding from maternal creatinine and interrupted nephrogenesis. Further identification and validation of biomarkers (such as cystatin c, uromodulin or others) or new strategies to define impaired kidney function in premature

neonates beyond serum creatinine may allow for improved identification of kidney injury in this population.

Finally, laboratory-based research exploring the genetic modifiers of nephrogenesis as well as epigenetic factors which modulate development is ongoing.[56*] Identification of these factors suggest that some are modifiable. One promising focus of ongoing animal experiments include exploration of strategies to extend a premature infant's post-natal nephrogenesis to increase nephron number despite premature birth.

Conclusions

With the successes of neonatal care, premature infants are surviving into adulthood. Growing evidence from animal models and observation studies demonstrate that these infants are at increased risk of kidney dysfunction. Improved awareness of prematurity, LBW, IUGR, and decreased nephron mass as risk factors for CKD may increase early identification of infants with evidence of kidney dysfunction. Recognition by neonatologists of nAKI and documentation and discussion of the risks of prematurity on future kidney health will improve identification of those at highest risk. Pediatricians should monitor growth, blood pressures, urinalysis, and kidney function in all prematurely born infants as early as the first year well-child visit. Referral to a pediatric nephrologist in those at highest risk and those who experience nAKI may be warranted. A coordinated effort by neonatologists, nephrologists, and primary care providers is needed to not only identify infants at high risk of CKD but to advocate for early evaluation and referral as appropriate. This may allow for future avoidance of risk factors that may accelerate progression and addressing modifiable risk factors wherever possible. Ongoing research is essential in order to improve outcomes in these infants. A better understanding of post-natal nephron development and quantification of nephron number along with avoidance of ongoing insults in the NICU in those at highest risk combined with improved monitoring and treatment are essential in order to reduce the number of prematurely born infants who go on to develop CKD.

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Key Points

- Premature infants are at increased risk of chronic kidney disease, likely due to decreased nephron number and exposure to post-natal nephrotoxins.
- Neonates born prematurely are at high risk of neonatal acute kidney injury (nAKI), which may further decrease nephron number and potentiate progression to CKD.
- Pediatricians caring for children born prematurely should have an elevated suspicion for kidney dysfunction and evaluate the risk for each patient, allowing appropriate monitoring and referrals.
- Early evaluation of markers of kidney dysfunction including blood pressure, serum creatinine, urinalysis and urine albumin to creatinine ratio should be done in all at risk patients as early as 2 years of age.
- A coordinated effort by neonatologists, nephrologists, and primary care providers is needed to identify infants with early signs of CKD to avoid risk factors that may accelerate progression, and to address modifiable risk factors wherever possible.

Fig 1. Multiple hits of damage due to renal disease programming

Reproduced from [15] Luyckx VA, Bertram JF, Brenner BM et al. Effect of fetal and child health on kidney development and long-term risk of hypertension and kidney disease. *Lancet* 2013;382 (9888):273–83.

Fig 2. Pathophysiologic mechanisms of decreased nephron number and progression to renal dysfunction

Reproduced from [45] Brophy PD, Shoham DA, Charlton JR et al. Early-life course socioeconomic factors and chronic kidney disease. *Adv Chronic Kidney Dis* 2015;22 (1): 16–23

Fig 3. Recommended strategy for evaluation of renal dysfunction in premature infants. While there are not yet any evidence based screening approaches, risk stratification should be made and clinical and laboratory parameters monitored

Source: Original