Short-Term Gestation, Long-Term Risk: Prematurity and Chronic Kidney Disease

abstract

Thanks to remarkable advances in neonatal intensive care, infants who once had little chance for survival can now enter adulthood. Yet the consequences of premature birth or low birth weight (LBW) on nephrogenesis, final nephron number, and long-term kidney function are unclear. This review focuses on the theory, experimental evidence, and observational data that suggest an increased risk of chronic kidney disease (CKD) for infants born prematurely. Many premature and LBW infants begin life with an incomplete complement of immature nephrons. They are then exposed to a variety of external stressors that can hinder ongoing kidney development or cause additional nephron loss such as hemodynamic alterations, nephrotoxic medications, infections, and suboptimal nutrition. Acute kidney injury, in particular, may be a significant risk factor for the development of CKD. According to Brenner’s hypothesis, patients with decreased nephron number develop hyperfiltration that results in sodium retention, hypertension, nephron loss, and CKD due to secondary focal segmental glomerulosclerosis. Because the risk of CKD in premature and LBW infants has not been accurately determined, there are no evidence-based recommendations for screening or management. Yet with the first generation of infants from the surfactant era only now reaching adulthood, it is possible that there is already an unrecognized epidemic of CKD. We suggest individualized, risk-based assessments of premature and LBW infants due to the increased risk of CKD and call for additional research into the long-term risk for CKD these infants face. Pediatrics 2013;131:1168–1179

AUTHORS: J. Bryan Carmody, MD, and Jennifer R. Charlton, MD, MSc

University of Virginia, Department of Pediatrics, Division of Nephrology, Charlottesville, Virginia

KEY WORDS

Chronic kidney disease, premature infants, low birth weight, acute kidney injury, nephron, secondary FSGS, proteinuria

ABBREVIATIONS

AKI—acute kidney injury
CKD—chronic kidney disease
ESRD—end-stage renal disease
FSGS—focal segmental glomerulosclerosis
GFR—glomerular filtration rate
LBW—low birth weight

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Address correspondence to Jennifer Charlton, MD, MSc, Department of Pediatrics, University of Virginia, Box 800386, Charlottesville, VA 22908. E-mail: jrc6n@virginia.edu

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Improving survival for the smallest, most vulnerable infants is among the great success stories in pediatrics. The advances in neonatal intensive care in the past 50 years have been nothing less than remarkable: according to the most recent data from the Vermont Oxford Network, ∼90% of infants born weighing 501 to 1500 g survive to NICU discharge, and ∼60% of survivors leave the NICU without any major neonatal morbidity.1 It is clear that today, many infants who in another era would have died within a matter of hours are now surviving to adulthood.

The long-term consequences of prematurity or low birth weight (LBW) are less clear. Although there has been a great deal of research into the neurodevelopmental outcomes of premature infants,2–4 the impact of prematurity or LBW on other organ systems is less well understood. There is now evidence from both the basic science and the clinical arenas to suggest that premature and LBW infants who survive the NICU still face serious risks to their long-term kidney health. Here, we review the theory, experimental evidence, and observational data that suggest an increased risk of chronic kidney disease (CKD) for premature and LBW infants and argue for increased surveillance of these patients.

**FETAL ORIGINS OF ADULT DISEASE**

David Barker is credited with the observation that many “adult” diseases may in fact have their origins in fetal life.5,6 To survive in a stressful or nutrient-poor environment, a fetus must make “choices” about how to use scarce resources in a way that maximizes the likelihood of survival in early life, even at the expense of greater susceptibility to chronic illnesses and increased mortality in adulthood. This kind of developmental programming among LBW infants7,8 has been associated with problems including obesity,9 hypertension,10 insulin resistance,11 and coronary artery disease.12 Nephrologist Barry Brenner first applied Barker’s theory to the development of CKD. Building on the observation that human nephron number is widely variable (ranging from 200,000 to 2 million per kidney13), Brenner hypothesized that either a congenital or acquired reduction in nephron number could explain why some individuals are more susceptible to hypertension and CKD.14 Brenner proposed that persons with a decreased complement of nephrons can initially maintain a normal glomerular filtration rate (GFR) as individual nephrons enlarge to increase the total surface area available for renal work.15 Over time, however, this adaptive response becomes harmful. Increased glomerular surface area leads to sodium retention and systemic hypertension, and glomerular hyperfiltration disrupts renal autoregulatory mechanisms, generating intraglomerular hypertension and proteinuria.14,16–18 These processes eventually cause nephrons to become sclerotic and senescent. This in turn leads to additional decline in nephron number and greater hyperfiltration in remnant nephrons, culminating in more rapid nephron dropout and perpetuating renal injury in a vicious cycle14,19 (Fig 1).

**LATE GESTATION IS CRITICAL FOR NEPHROGENESIS**

Although nephrogenesis in humans begins around 9 weeks gestation,20,21 60% of nephrons are formed during the third trimester (Fig 2).22 The entire nephron complement of the human kidney is determined by 36 weeks’ gestation,23 and these nephrons must last for a lifetime because nephrons do not have the ability to regenerate24; even in healthy persons, the number of functional nephrons gradually declines over time, leading to the age-dependent decline in GFR seen in older adults.25

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**FIGURE 1**

According to Brenner’s hypothesis, reduced nephron number (oligonephropathy) leads to hyperfiltration, hypertension, and proteinuria, which perpetuate renal damage and lead to glomerulosclerosis and CKD.16,150 Infants born prematurely have additional risk factors for nephron loss such as nephrotoxins and hemodynamic alterations.
Because there is no mechanism to assess nephrogenesis in a living infant, data on human kidney development in an extrauterine environment is limited to autopsy studies. Although such studies are prone to selection bias, their findings suggest that although nephrogenesis in infants born prematurely continues postnatally, it may be altered. Rodriguez et al performed an autopsy study of 56 premature infants with birth weight <1000 g and found no evidence of postnatal glomerulogenesis after 40 days. Additionally, when stratified by occurrence of acute kidney injury (AKI), defined as a sustained serum creatinine of >2 mg/dL, those infants who experienced AKI had significantly lower radial glomerular counts, or layers of glomeruli. If premature infants have only 40 days from birth to complete nephrogenesis, then those born at 23 to 24 weeks may only develop nephrons until 29 to 30 weeks, in contrast to continuing nephrogenesis until 36 weeks, as in normal gestation.

The developing nephrons in premature infants seem particularly vulnerable to maldevelopment and dysfunction in an extrauterine environment. Sutherland et al performed an autopsy study including 60 infants and found that premature infants had reduced nephrogenic zone width and more mature glomeruli compared with gestational controls at similar postconceptional ages, suggesting early cessation of nephrogenesis or accelerated postnatal renal maturation. Preterm infants also had increased glomerular volume (potentially indicating glomerular hyperfiltration), and up to 13% of their glomeruli were histologically abnormal, with dilation of Bowman’s space and a shrunken glomerular tuft.

FROM THE NICU TO FSGS

Fewer layers of larger glomeruli with more histologic abnormalities suggest that premature infants leave the NICU with a reduced number of functional nephrons, a risk factor for focal segmental glomerulosclerosis (FSGS). It is now clear that all forms of FSGS are diseases of the podocyte. Although the pathologic findings of FSGS can be induced by immunologic mechanisms (primary FSGS), genetic mutations, viruses, systemic diseases, certain drugs, and obesity can all cause podocyte dysfunction or injury, leading to secondary FSGS. Reduced nephron mass is also a well-described cause of secondary FSGS. The subtotal or five-sixths nephrectomy model, in which experimental rats have 1 kidney removed and two-thirds of the second kidney ablated, has been among the best-studied models of FSGS for 80 years, and more recent techniques of experimental podocyte depletion also generate clinical FSGS in a dose-dependent manner. Notably, some animal studies suggest that the presence of hypertension is essential for the development of glomerulosclerosis and that lesions can be avoided if glomerular hemodynamic changes are prevented.

EVIDENCE FROM ANIMAL MODELS

In rats and mice, nephrogenesis continues for 5 to 7 days postnatally, yet premature birth alone still has a profound effect on nephrogenesis. Mice born 1 to 2 days prematurely develop a CKD phenotype by the time they are 5 weeks old, with hypertension, albuminuria, and reduced nephron number. In other rodent studies, reduced nephron number can be induced by prenatal protein restriction or vitamin A deprivation, perinatal exposure to gentamicin, or antenatal exposure to steroids. A closer approximation of the NICU is the baboon model of prematurity in which animals are delivered prematurely and maintained under conditions that approximate those encountered by human infants (including mechanical ventilation and exposure to nephrotoxins such as gentamicin and nonsteroidal antiinflammatory drugs for patent ductus arteriosus closure). Analogous to human studies, premature baboons continued to develop nephrons postnatally, and although there was no alteration in total glomerular number, a high percentage of nephrons had histologic abnormalities.

PREMATURITY: AN UNDERRECOGNIZED RISK FACTOR FOR CKD

To date, there have been no prospective, population-based studies to confirm the association between prematurity or LBW and CKD. Although it is difficult to disentangle the effects of confounders...
such as socioeconomic status in retrospective studies, a systematic review of 31 cohort or case-control studies found a 70% increase in adulthood CKD for LBW infants.66 Although this meta-analysis excluded studies consisting exclusively of extremely LBW or very premature infants, other more inclusive studies have shown similar results. A national registry-based study including all infants born in Norway from 1967 to 2004 found an overall relative risk of 1.7 for the development of end-stage renal disease (ESRD) for infants with birth weight <10th percentile compared with those with weights from the 10th to 90th percentile.57

Clinical signs of oligonephropathy among patients born prematurely may be detectable in childhood.48,49 Two recent case series (each including 50 infants born at <30–52 weeks’ gestation) found that children born prematurely had smaller kidneys and higher blood pressure compared with term controls, even though their GFR remained normal.50,51 Microalbuminuria, an early indicator of kidney disease and a risk factor for future cardiovascular morbidity, is also common among children aged 8 to 11 years who were born prematurely or with LBW.52 The first series of premature infants who developed secondary FSGS was recently reported.54 These 6 patients were all very premature, with gestational ages of 22 to 30 weeks, and presented at an average age of 32 years with nephrotic-range proteinuria, hypoalbuminemia, and lack of edema without other risk factors for secondary FSGS.

**AKI AS A RISK FACTOR FOR CKD**

Acute kidney injury in the NICU is common. Although its overall incidence is difficult to determine given the lack of multicenter studies and variable definitions of AKI, it is clear that smaller and sicker infants most commonly experience AKI (Table 1). Yet because the majority of pediatric patients with AKI are discharged from the hospital with a normal serum creatinine,55 the long-term significance of their renal injury may not be appreciated. It was long taught that AKI is reversible.56 This may be true for AKI caused purely by volume depletion, but it is now clear that intrinsic forms of AKI cause cumulative and irreversible damage. In animal models of acute tubular necrosis, renal regeneration is not complete: there is permanent reduction in vascular density and compromised oxygen delivery.57,58 Regeneration of tubular epithelial cells can result in sustained fibroblast activation, leading to progressive fibrosis even after the initial insult has subsided.59,60 There is now ample epidemiologic evidence associating AKI with the development of CKD, leading some authors even to suggest that the rising incidence of AKI may be partly responsible for the nationwide increase in CKD and ESRD.61 A recent meta-analysis of adult trials found a substantial, exposure-dependent risk of CKD after AKI, with patients who experienced more severe AKI developing CKD and ESRD more frequently.62 Although there are inherent risks in extrapolating the results of adult studies to pediatric patients, it seems likely that nephron loss would have even greater effects on future health for a newborn infant than for an older adult. Moreover, the limited number of pediatric studies have found similar results. Pediatric patients with AKI due to diarrhea-associated hemolytic-uremic syndrome,63 meningococcal sepsis,64 and cardiac surgery65 all have an increased long-term risk of CKD. Beyond these specific populations, a recent single-center PICU study found that 10.3% of all patients with AKI (defined by Acute Kidney Injury Network criteria66) subsequently developed CKD (GFR <60 mL/min/1.73 m²) within the next 1 to 3 years.67 An additional 46.8% of this cohort were deemed “at risk” for CKD based on the presence of hypertension, reduced GFR (60–90 mL/min/1.73 m²), or hyperfiltration (GFR >150 mL/min/1.73 m²).

These studies have been criticized for epidemiologic flaws that prevent the determination of causation; that is, it

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**TABLE 1 Recent Estimates of AKI Incidence in Various Neonatal Populations**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>AKI Definition</th>
<th>Number of Infants</th>
<th>AKI Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viswanathan et al141</td>
<td>Extremely LBW (&lt;1000 g)</td>
<td>Serum creatinine ≥1.5 mg/dL or urine output &lt;1 mL/kg/h</td>
<td>472</td>
<td>12.5%</td>
</tr>
<tr>
<td>Koralkar et al142</td>
<td>Very LBW (&lt;1500 g)</td>
<td>AKIN61</td>
<td>229</td>
<td>18%</td>
</tr>
<tr>
<td>Selewska et al143</td>
<td>Asphyxiated newborns undergoing therapeutic hypothermia</td>
<td>AKIN</td>
<td>86</td>
<td>38%</td>
</tr>
<tr>
<td>Kaur et al144</td>
<td>Infants ≥34 wk gestation with asphyxia (Apgar &lt;7 at 1 min after birth)</td>
<td>AKIN</td>
<td>36</td>
<td>41.7%</td>
</tr>
<tr>
<td>Blinder et al145</td>
<td>Infants &lt;90 d old with congenital heart disease undergoing surgery</td>
<td>AKIN</td>
<td>430</td>
<td>52%</td>
</tr>
<tr>
<td>Gadepalli et al146</td>
<td>Infants with congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation</td>
<td>RIFLE147</td>
<td>68</td>
<td>71%</td>
</tr>
</tbody>
</table>

AKIN, Acute Kidney Injury Network; RIFLE, risk, injury, failure, loss, end-stage renal disease.
could be argued that patients who are predisposed to the development of CKD may also be predisposed to the development of AKI. However, for pediatricians caring for premature infants who have suffered AKI, this distinction is likely academic. Whether AKI in fact leads independently to CKD or simply identifies a subgroup of infants already at risk for CKD, the implications for the child are the same, and the long-term implications of AKI in the NICU ought not be ignored.

**PRACTICE AND POLICY IMPLICATIONS: WHAT ARE PEDIATRICIANS TO DO?**

Worldwide, almost 13 million infants are born prematurely each year, but there is currently no mechanism to identify the infants most at risk for developing CKD due to congenital or acquired low nephron number and no guidelines for screening or follow-up from the American Academy of Pediatrics or other professional association. Pediatricians must therefore use clinical judgment to make an individualized risk assessment for each patient to provide the best care to NICU graduates. Follow-up recommendations are presented in Fig 3.

A careful review of the neonatal history is an essential first step for primary care physicians to identify infants who require the closest follow-up. Note should be made of the infant’s birth weight, gestational age, weight-for-age classification, and any history of AKI. Unfortunately, discharge summaries may not provide all of these details. A systematic review of pediatric and adult discharge summaries found that significant errors and omissions were common. Communicating an infant’s history of AKI to pediatricians may be particularly poor: at our institution, only 21 of 155 (13.5%) of infants who experienced AKI by the Acute Kidney Injury Network criteria from 2008 to 2011 had AKI listed on their NICU discharge summary.

Hypertension may be a clinical indicator of low nephron number because decreased filtration surface area leads to renal sodium retention and elevated blood pressure. Currently the American Academy of Pediatrics recommends measuring blood pressure at health maintenance examinations beginning at age 2.5 years, but we argue that all premature infants should be considered a high-risk group in whom blood pressure screening should occur at earlier visits.

Careful assessment of linear growth at every well-child check is also important. Although growth must be interpreted within the context of the patient’s genetic potential, nutritional status, and neonatal history, practitioners should be alert to the possibility that abnormal growth may reflect CKD. Children with CKD can have impaired linear growth even when the GFR is only mildly to moderately impaired, and both LBW and SGA status were risk factors for impaired linear growth in

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**Figure 3**

Follow up strategies for NICU graduates. In the absence of high-quality evidence, physicians must make an individualized risk assessment of each patient and balance the risks and benefits of any screening strategy. IUGR, intrauterine growth retardation; SGA, small for gestational age.
a prospective cohort of patients with mild to moderate CKD, independent of GFR.77 Assessments of the NICU graduate should continue into adolescence, a time when many children see their pediatrician less frequently. Rapid growth in puberty often unmasks renal dysfunction78 because abnormal kidneys may be unable to accommodate the demands of increased growth. It is also important that adolescent patients, particularly those nearing transition to adult practitioners, be aware of their history of prematurity, understand their increased long-term risk for CKD, and receive counseling regarding modifiable risk factors for CKD progression (such as smoking,79 hypertension,80 or obesity81).

Laboratory tests may be useful in specific circumstances. Whereas an abnormal serum creatinine at NICU discharge or in childhood carries an ominous prognosis, serum creatinine is not a sensitive indicator of long-term CKD risk because increased tubular secretion can maintain a normal plasma creatinine until 25% to 50% of GFR has been lost.82 Pediatricians and neonatologists must therefore not be falsely reassured by normal values. Additionally, the recognition of mildly abnormal creatinine values in children may be challenging. Although the average creatinine for a 2-year-old is 0.3 mg/dL,83 values up to 0.6 mg/dL are often reported as normal by reference laboratories.84 Yet these “normal” values can reflect significantly impaired GFR, as demonstrated in Table 2.

Cystatin C, a nonglycosylated basic protein produced at a constant rate by all nucleated cells,85 is more easily interpretable than creatinine because a single reference range can be used for any child over 1 year of age.86 Cystatin C is a more sensitive marker of mild renal impairment than creatinine,87,88 and mild elevations are seen in preterm infants at 12 to 36 months of age compared with term control subjects.89 However, this test is expensive and not readily available in all areas. Microalbuminuria (urine albumin/creatinine of 30–300 mg/g) is also an early indicator of CKD and represents a therapeutic target for CKD progression.90 Standard urine dipsticks detect only overt albuminuria, but targeted screening of premature or LBW infants could result in earlier detection of CKD. Such screening is already standard of care in certain other high-risk groups, such as children with type 1 diabetes mellitus81 and sickle cell disease.92 Unfortunately, the utility of microalbuminuria as a screening tool may be hampered by a high false-positive rate due to the prevalence of benign proteinurias (such as orthostatic proteinuria93 or exercise-induced proteinuria94) in the pediatric population. For example, in the NHANES, 8.9% of adolescents had microalbuminuria, although the majority of these had no other risk factors for cardiovascular or renal disease.95 Finding elevated levels would therefore require additional testing to distinguish true disease from benign proteinuria.

Screening patients with imaging techniques such as renal ultrasound is theoretically appealing because renal volume at birth is a surrogate for nephron number.96–98 However, in older children or adolescents, competing factors such as patient size, compensatory hypertrophy of remnant nephrons, and additional nephron loss through injury make the relationship between kidney size and nephron number less easily interpretable.99 Although some studies have found smaller renal length or volume in children born prematurely,100 the use of ultrasound or other imaging techniques is expensive and has yet to be validated prospectively.

**INTERVENTION AND EDUCATION**

Any recommendation for increased population-based screening must be tempered by the acknowledgment that there is no specific therapy to slow or arrest the progression of CKD in children born prematurely or with a LBW.101 However, there are nonspecific therapeutic targets for CKD progression such as hypertension,101,102 microalbuminuria,90 and dyslipidemia.90 In particular, inhibition of the renin-angiotensin system (RAS) has been shown to slow CKD progression in adults with proteinuria103 and hypertensive children aged 3 to 18104 and is standard of care in nephropathy related to diabetes.105,106 However, these medications must be used cautiously in children because their side-effect profile is not benign, and they are a well-described cause of AKI, particularly with volume depletion or when given in combination with other medications that decrease renal blood flow.107

Even in the absence of targeted therapies for CKD progression, earlier identification of patients with CKD could provide the opportunity to improve patient outcomes by addressing systemic complications of CKD sooner. Beyond the well-known complications of CKD such as anemia, poor growth, and renal osteodystrophy, many children with CKD have impaired neurocognitive function and reduced quality

### Table 2: Estimates of GFR With “Normal” Creatinine Values for a Hypothetical 2-Year-Old Child With Height 86.4 cm Using the Revised Schwartz Equation

<table>
<thead>
<tr>
<th>Serum Creatinine (mg/dL)</th>
<th>Estimated GFR (mL/min/1.73 m²)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>119</td>
<td>Normal</td>
</tr>
<tr>
<td>0.4</td>
<td>89</td>
<td>Normal</td>
</tr>
<tr>
<td>0.5</td>
<td>71</td>
<td>Stage 2 CKD</td>
</tr>
<tr>
<td>0.6</td>
<td>59</td>
<td>Stage 3 CKD</td>
</tr>
</tbody>
</table>

*GFR = 0.413 × height(cm) / creatinine(mg/dL)140*
of life. Subjects in the CKD in Children (CKiD) reported decreased health-related quality of life compared with healthy children, with lower scores in physical, emotional, social, and school domains.\textsuperscript{108} Additionally, 21% to 40% of children with mild or moderate CKD have below average measures of IQ, academic achievement, attention regulation and executive functioning.\textsuperscript{109,110} Early intervention in these areas could improve school performance and self-esteem.

At the very least, identification of patients with early CKD would facilitate education of the child and parents about the treatments for CKD and allow the opportunity to provide counseling on avoiding risk factors that may accelerate its progression (such as nephrotoxic medications, recurrent urinary tract infections, dehydration, and coexisting urologic issues). Obesity in particular is a modifiable risk factor for CKD progression\textsuperscript{111,112} and one for which both primary care physicians and specialists have an important role in management.\textsuperscript{113}

**RESEARCH HORIZONS**

**Nephrogenesis**

A comprehensive discussion of the molecular mechanisms of nephrogenesis is beyond the scope of this review but has recently been reviewed elsewhere.\textsuperscript{114} Although a number of genetic modifiers of nephrogenesis have been described, such as common variants in the \textit{PAX2}\textsuperscript{115} or \textit{RET}\textsuperscript{116} genes, which are associated with reduced kidney volume at birth, epigenetic factors such as DNA methylation appear to play an equally important role in nephrogenesis.\textsuperscript{117,118} The identification of these potentially modifiable epigenetic factors raises the possibility that eventually strategies might be developed to extend a premature infant’s period of normal nephrogenesis to 36 weeks’ postmenstrual age, allowing their kidneys to attain a normal nephron number despite their premature birth.\textsuperscript{119,120}

**Nutrition**

In rats, who continue nephrogenesis postnatally, nutritional support after birth can restore a normal nephron endowment and prevent adult hypertension after uteroplacental insufficiency.\textsuperscript{121} The potential benefit of improved nutrition for human infants was suggested by a prospective cohort study of premature infants with extraterine growth restriction (growth value \(\leq 10\)th percentile of intrauterine growth expectation based on postmenstrual age at the time of discharge from the hospital).\textsuperscript{50} Compared with infants with intrauterine growth restriction or normal growth status, infants with extraterine growth restriction had lower protein-energy intake during their first week of life and lower GFR than at a mean of 7.6 years follow-up. However, there is also good epidemiologic evidence to suggest that too rapid “catch up” growth for growth-restricted infants may be detrimental.\textsuperscript{122}

Vitamin A is an important regulator of cell proliferation and differentiation and plays a critical role in the determination of nephron mass.\textsuperscript{123–125} Vitamin A deficiency is also common in premature infants\textsuperscript{126} due in part to increased urinary losses of vitamin A.\textsuperscript{127} Although vitamin A supplementation appears to be beneficial in the lung, another branching organ that develops in late gestation, in protecting against chronic lung disease,\textsuperscript{128} there are no clinical data on renal outcomes in humans.

**Experimental Models**

Given the lengthy time horizon between premature birth and the development of CKD, valid experimental models are essential for understanding nephrogenesis and its disruptors. The prohibitive expense of primate research and the normally occurring postnatal nephrogenesis in rodents limits the utility of these models. Newer models such as the premature mouse model\textsuperscript{59} or fetal renal cell culture\textsuperscript{129} may enhance understanding of renal cell differentiation, proliferation, and apoptosis.

**Acute Kidney Injury**

To evaluate the long-term effects of AKI, it is imperative to validate and adopt a consistent definition of AKI.\textsuperscript{130} The use of serum creatinine–based definitions of AKI is problematic because serum creatinine is a measure of function, not injury, and a rise in serum creatinine occurs only after as much as 50% of kidney function has been lost.\textsuperscript{131} Identification and validation of biomarkers would allow earlier detection of AKI in premature infants and permit generalizability between single-center studies.\textsuperscript{132–134} Biomarkers including urine cystatin C, uromodulin, epithelial growth factor, neutrophil gelatinase-associated lipocalin, and osteopontin predict AKI in specific neonatal populations.\textsuperscript{135,136}

**NICU Management**

The role that NICU clinical management strategies play in the development of CKD is largely unexplored. However, NICU patients are commonly exposed to medications that impair nephrogenesis\textsuperscript{137} (such as aminoglycoside antibiotics or prostaglandin synthetase inhibitors) and frequently experience AKI. If these are independent risk factors for CKD, avoidance of such medications or efforts to decrease AKI incidence could lead to better long-term outcomes. Appropriately designed long-term studies are needed.

**Counting Nephrons**

The Brenner hypothesis has been criticized by authors who point out that all supporting evidence is circumstantial given the inability to measure nephron number in a living person.\textsuperscript{138} In experimental animals, cationic ferritin has
been used safely to label the glomerular basement membrane (Fig 4), allowing an accurate count of glomeruli using MRI.\textsuperscript{139,140} If validated, such techniques could provide accurate and noninvasive measurement of glomerular counts for clinical or research purposes in the future.

**SUMMARY**

Thanks to the contributions of our predecessors, contemporary pediatricians can celebrate the extraordinary success story of neonatal intensive care. Today, most of even the tiniest infants will survive, and many of them will leave the NICU without any apparent morbidity. Although many of the original challenges in neonatal intensive care remain, the bigger challenge for the current generation of pediatricians is to continue to improve long-term outcomes for these infants.

Most infants in the NICU begin life with an incomplete complement of immature nephrons. They are then exposed to a variety of external stressors that can hinder ongoing kidney development or cause nephron loss. However, unlike respiratory or infectious diseases, kidney disease is seldom a proximate cause of life-threatening illness for infants while they are in the NICU. Although pediatricians are attuned to the short-term risks associated with prematurity and LBW such as chronic lung disease or neurocognitive delays, the longer-term risk of developing CKD often escapes notice. Yet that risk may be significant. With the first generation of infants from the “surfactant era” only now reaching young adulthood, it is possible that there is already a silent epidemic of CKD in this population.

The evidence reviewed here highlights the risk of renal disease in premature and LBW infants and emphasizes the need for increased awareness among all pediatricians of the significance of low nephron number. Despite a sound theoretical rationale and emerging basic science and epidemiologic data, there is little high-quality evidence from appropriately designed studies with meaningful long-term outcomes to guide pediatricians in the management of these patients. We urge professional organizations, funding agencies, and the entire community of pediatricians to consider this issue, so that the next half-century of neonatal intensive care can match the successes of the past.

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1176 CARMODY and CHARLTON

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39. Silver LE, Decamps PJ, Korst LM, Platt LD,

38. Silver LE, Decamps PJ, Korst LM, Platt LD,
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