

Assessment of kidney function in preterm infants: lifelong implications

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Abstract

This educational review will highlight the historical and contemporary references that establish a basic understanding of measurements of kidney function in the neonate and its relevance for the life of an individual. Importantly, the differential renal function of preterm infants relative to term infants has become paramount with the increased viability of preterm infants and the realization that kidney function is associated with gestational age. Moreover, neonatal kidney function is primarily associated with absolute renal mass and hemodynamic stability. Neonatal kidney function and its early developmental progression predict lifelong cardiovascular and renal disease risks. Validation of estimation equations of kidney function in this population has provided important reference data for other investigations and a clinical basis for prospective and longitudinal follow-up. Future research should be directed towards a better understanding of surrogate markers of kidney function from infancy through adulthood. Pediatric nephrologists should be aware of the developmental aspects of kidney function including the importance of the congenital nephron endowment and the preservation of kidney function throughout a lifetime.

Key summary points

- Nephrogenesis occurs in utero in concert with other organ systems by branching morphogenesis, including the lungs,

pancreas, and vascular tree, with over 60 % of nephrons being formed during the last trimester.

- Infants born preterm before 36 weeks' gestation are in active nephrogenesis and are at increased risk of having a decreased nephron endowment from prenatal and postnatal genetic and epigenetic hazards that will impact the patient for a lifetime.

- Post-natal adaptation of kidney function is directly proportional to the number of perfused nephrons, estimated by total kidney volume (TKV), mean arterial pressure (MAP), and gestational age.

- Accurate measurement of glomerular filtration rate (GFR) in infants is problematic due to the unavailability of the gold standard *inulin*. The traditional use of creatinine to estimate GFR is unreliable in preterm infants due to its tubular reabsorption by immature kidneys and its dependence on muscle mass as an endogenous marker. Alternative endogenous markers to estimate GFR are cystatin C and beta trace protein (BTP).

- Long-term follow-up of renal function in those born preterm should be life long and should include assessment of GFR, total kidney volume (TKV) relative to body surface area (BSA), and cardiovascular risks including hypertension and vascular stiffness.

Keywords Nephrogenesis · Nephron endowment · Total kidney volume · Cystatin C · Preterm · Neonates

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Introduction

Despite many decades of careful scientific investigation, the *accurate assessment of kidney function in the preterm infant* remains elusive [1, 2]. Nephrogenesis is intended to be complete by 36 weeks' gestation in utero [3, 4]. Preterm infants are

born during active nephrogenesis, making them particularly vulnerable to alterations imposed by the extra-uterine environment [5, 6]. The individual adaptive kidney function will depend on the *effective* nephron mass (or surface area), which is proportional to the number of perfused and fully formed glomeruli [7]. It is inversely proportional to the area of the “nephrogenic zone” composed of incompletely formed glomeruli in various stages of development immediately below the renal capsule [7, 8]. Among preterm infants, the number of nephrons formed during the first 4–6 weeks of post-natal life will determine that individual’s nephron endowment for a lifetime [9]. Taking advantage of this “window of opportunity” to support active extra-uterine nephrogenesis through judicious clinical management may be the most important determinant of the preterm infant’s final nephron endowment [10]. For example, management of the preterm infant commonly includes the use of nephrotoxic medications and correcting hemodynamic instability related to environmental stress [11–13]. Epigenetic exposures including environmental pollutants can also contribute to kidney injury in the developing fetus and child [14]. In addition, genetic predisposition plays a role in determining risk for chronic kidney disease (CKD). For example, African Americans have a higher rate of preterm birth and new evidence suggests that carrying the *APOL1* risk allele, which is associated with focal segmental glomerulosclerosis (FSGS), may be an additive risk for CKD progression in these infants [15]. To that end, it is important to assess the preterm infant’s renal size and function from the outset [16–18]. Understanding the limitations and applications of endogenous markers of kidney function relative to gestational age and post-natal development should allow early recognition of acute kidney injury (AKI) [19–21]. This, in turn, should lead to more systematic longitudinal surveillance of renal size and function in infants after their perinatal course [13, 17–21]. For many neonatal intensive care units, this will require a cultural change and we make an appeal for broader adoption of the clinical assessment tools described herein.

In this review, we will emphasize the strong association of *structure and function* in neonatal kidneys especially regarding the transition from the intrauterine to a potentially *hostile* extra-uterine environment. We will also consider kidney size and function in the perinatal period and their implications for the life course of individuals. The maturation of renal function from birth to early childhood will be examined according to post-natal physiologic and structural adaptations. Methodologies for the “true” measurement of kidney function in infants will be analyzed from a historical perspective. The limited data available validating current estimation equations of glomerular filtration rate (eGFR) applicable to the neonatal population will also be summarized [22–24]. This review is an ambitious endeavor with a goal of guiding continued translational research in the field of human renal-functional

maturation. Most importantly, we provide an important educational update on current directions in neonatal renal functional assessment.

Nephrogenesis and congenital nephron endowment

The human kidney forms from three primordial “attempts” beginning with the primitive, but obligatory anlage, called the “*pronephros*” at about 3 weeks’ gestation and lasting for only 3–5 days [3, 4, 25–27]. The pronephros never functions but provides the pattern of ciliated epithelial cells that are reminiscent of the proximal tubular epithelial cells that will compose a major part of the human nephron [4, 25–27]. With the regression of the pronephros, the *mesonephros* emerges as a much more complex structure with nephrotomes and filtration bundles developing around the incursion of the Wolffian duct into the mesonephric mesenchyme. Subsequently, the mesonephric nephrons begin their involution and the Wolffian duct gives rise to the ureteric bud, which starts its incursion into the *metanephric mesenchyme*, giving rise to the *metanephros*, the third anlage and true human kidney. From the 5th gestational week, the ureteric bud has begun sequential branching into the *metanephric mesenchyme* propagated by a complex system of signaling molecules emanating from both tissues [25–27]. By the 20th gestational week, the fetal urine comprises 80 % of the amniotic fluid at a rate of approximately 800 ml per day (300 ml/kg fetal weight/day) [28, 29]. The fetal urine flow rate is 2–5 ml/h at 20–25 weeks’ gestation; 5–10 ml/h by 26–30 weeks’ gestation, and 15–30 ml/h by 31 to 40 weeks’ gestation [28, 29].

The kidneys form in parallel with other organ systems by a process of “branching morphogenesis” [25–27]. Of profound interest and scientific relevance, these various organ systems share genetic and physiologic functional determinants within the “fetal origins of adult disease paradigm” [30–32]. Among the organ systems that develop by “branching morphogenesis” are the lungs, pancreas, vascular tree, and kidneys [30–32]. As a consequence, parallel burdens of post-natal maturation, and growth may impact insulin resistance, vascular stiffness, chronic lung disease, as well as early renal senescence [28–32]. Over 80 % of the nephrons form during the last trimester, with a rapid succession of “nephron generations” from the cortico-medullary junction extending up to the “nephrogenic blue zone” under the capsule [3–5]. From 22 to 36 weeks’ gestation, 10–12 generations of nephrons form, similar to the rings of a tree [3–5]. With cessation of glomerulogenesis, the nephrogenic zone disappears [25, 26]. Thereafter, only tubular and vascular growth and interstitial tissue expansion occurs [25, 26]. The glomerular epithelial cells are cuboidal in shape and the capillary loops are poorly perfused, receiving less than 2 % of the fetal cardiac output [28, 29]. It appears that the epithelial cells decrease in density as the nephrons expand with the inner glomeruli becoming

more “mature”, while those of the outer cortex are the last to expand, making them the more vulnerable to adverse circulation ex-utero [27]. If birth occurs prematurely during active nephrogenesis, there may be potential for ongoing or even accelerated nephrogenesis [5, 6, 33]. However, our knowledge of ongoing nephrogenesis in preterm humans is limited to a few postmortem studies [5, 6, 33]. Rodriguez et al. showed that extra-uterine nephrogenesis was active until 40 post-natal days in extremely preterm infants. Among those infants who survived >40 days, a full complement of nephrons was never achieved compared to term newborns [5]. Moreover, those infants who had AKI, defined as a serum creatinine >1.5 mg/dl (133 mM/l), had fewer nephron generations compared to those without AKI [5]. Sutherland et al. [33] conducted an autopsy study of preterm infants ranging from 24 to 35 weeks’ gestation and showed active or even accelerated nephrogenesis with a high percentage of morphologically abnormal glomeruli, including “atubular” and cystic glomeruli, which would not be able to function [33]. The same group has demonstrated similar morphology in a non-human primate model of prematurity [34]. In the final analysis, preterm birth is an independent risk factor for a decrease in one’s nephron endowment [5, 6, 33, 34].

Importantly, a low nephron endowment has been linked to the development of hypertension and cardiorenal disease in adult life [35]. As pertains to renal organogenesis, there is a wide normal distribution in the “congenital nephron endowment” [36, 37]. This has been confirmed in numerous other studies, with a tenfold variance in nephron numbers

(Nglom) ranging from approximately 200,000 to over 2,000,000 per kidney [37–44]. Epigenetic and environmental influences play a prominent role in the nephron endowment, which may be affected by simple genetic variants or polymorphisms within a given population accounting for the wide normal distribution that has been described [37, 45]. Nyengaard also described the positive correlation between the human nephron endowment and kidney size by gram weight across all age ranges [37]. Of note, renal size and nephron numbers are 10–15 % less in females, beginning at an early age [37].

Since the number of nephrons in each kidney is determined before term birth, and the size of the kidney must accommodate the size of the infant, the nephron density (Dglom) or Nglom per gram kidney weight is at least 10× greater during infancy and gradually declines until maturation when the final mature kidney mass is obtained. At each age, there is a wide confidence interval following the normal distribution that is found [37–45]. In Fig. 1a, we have plotted the regression equation of a composite of data points extracted from references that provided kidney size with nephron numbers per kidney over an age range from <3 months of age to >60 years of age in postmortem kidneys from subjects with preserved renal function [37–45]. Similarly, the glomerular density relative to kidney size is plotted in Fig. 1b. Both relationships are significant and the graphic depiction of glomerular number (Nglom) and density (Dglom) relative to advancing age and kidney weight provides a clear representation of the renal structural changes that occur from birth to maturation. After 40 years of age, there is a gradual loss in Nglom through

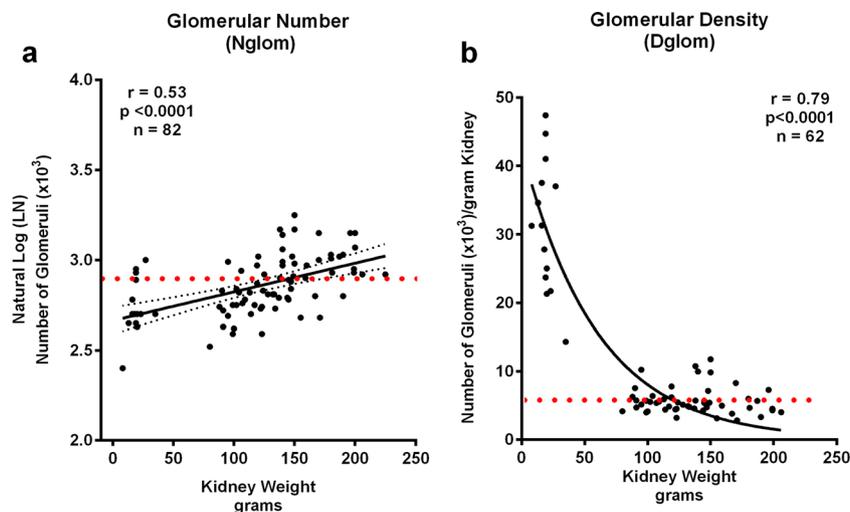


Fig. 1 a Linear regression of the Natural Log (LN)₁₀ of glomerular number (Nglom) per kidney ranging from kidney weights of 20 g to >200 g at autopsy from individuals with normal kidney function ranging in age from <3 months to >60 years. Data were extracted from references [35–42]. The red line indicates the average Nglom = 813,000 with an average mature kidney weight of 150 g. **b** Non-linear regression of the

glomerular density (Dglom) as the number of glomeruli (N/glom) per gram kidney weight. The data were extracted from references [35–42] and included kidneys at autopsy from individuals with normal kidney function ranging in age from <3 months to >60 years. The red line indicates the average Dglom = 5500 or Nglom = 825,000 in an average kidney weighing 150 g

senescence manifest as glomerular sclerosis and GFR declines by 10 ml/min/1.73 m² each decade [46]. Its relevance for preterm infants is paramount, since there is evidence that low nephron endowment and preterm birth lead to early senescence with a higher set-point for the onset of progressive CKD [24, 46, 47].

A recent educational review on the determinants of nephron number in early life covers the subject well and is recommended for more comprehensive reading [45]. However, the methodologies devoted to the actual counting of nephrons deserve closer attention since there is an important research effort directed towards being able to assess the nephron endowment in the living individual for prediction of cardio-renal longevity as well as to determine the suitability for kidney donation [48, 49]. Hinchcliffe et al. first devised the “disector” method for estimating glomerular number and size, and determined from autopsied infants that those with intrauterine growth restriction had fewer nephrons [50]. Shortly thereafter, Hinchcliffe described the “medullary ray glomerular counting” method; now called the “radial glomerular counts” of nephron generations, which provides not only an estimate of nephron numbers but allows an assessment of the stages of active nephrogenesis in preterm infants [51]. The “gold standard” has become the “dissector/ fractionator” method, which is laborious, expensive, and requires the destruction of the tissue [48, 49, 52]. More recently, the injection of cationic ferritin followed by ex vivo MRI scanning in animals appears to be a promising technique directed towards developing methodologies for in vivo studies [53]. Until then, we must rely on surrogate and easily accessible modalities for assessing renal mass, such as renal ultrasound, while we continue to refine other non-invasive methods of clinical assessment of nephron mass in infants and small children currently limited to experimental use [54–56].

Post-natal physiologic and structural adaptations

Birth is a hemodynamically intense event that has been characterized as one of the most dangerous moments of a lifetime. The fetus has been completely protected and nurtured within the amniotic fluid and perfused through a blood circuit of low oxygen tension [28, 29]. The physiologic, structural, and functional alterations of the kidneys in transition from the fetal to the extra-uterine environment include an abrupt increase in renal perfusion pressure mediated by an increase in the percentage of cardiac output received by the kidneys from 3 to 25 %. There is also a gradual decrease in filtration fraction (FF) from as high as 50 % to a mature level of 20 % after the glomerular capillary resistance decreases and tubular growth and expansion occurs. Filtration fraction (FF) is the ratio of GFR over renal plasma flow (RPF); $FF = GFR/RPF$. At birth, both GFR and RPF are low due to the low perfusion pressure, high blood viscosity, and increased efferent arteriolar tone [12,

13]. Ultimately, the GFR will equal 120 ml/min/1.73 m² and the RPF will be over 600 ml/min/1.73 m² giving a FF of 20 % at full maturation. This FF is higher and takes longer to mature in preterm infants. This may also partially explain the “back diffusion” of creatinine described in preterm infants who have persistently elevated serum creatinine and low urinary creatinine excretions with appropriate renal function in the first weeks of life [57, 58].

Glomerular perfusion is dependent on local and systemic mediators of afferent and efferent arteriolar tone, with the primary humoral mediators being prostaglandins for afferent relaxation and the renin–angiotensin–aldosterone system maintaining efferent arteriolar constriction [28, 29]. The extremely sensitive glomerular-tubular feedback at the juxtaglomerular apparatus (JGA) may insert a potentially damaging reflex that can acutely constrict the afferent arteriole through the generation of adenosine in response to anoxia or hypotension [28].

Measurement of glomerular filtration in infants by exogenous markers

Historically, *inulin* and its analog *sinistrin* have been considered the “gold standard” for measurement of GFR in infants and, to date, have not been replaced [59]. It is a naturally occurring polysaccharide that is a derivative of the Jerusalem artichoke and other legumes such as chicory. It meets the essential criteria for accurate measurement of GFR, including being freely filtered through the glomerulus and neither being secreted nor re-absorbed in its transit down the nephron [16, 60]. Moreover, it must *not* be metabolized or protein bound after injection. Importantly, it must be safe and innocuous for clinical investigations in infants and children. During the early years of investigation into the renal function of infants, there were a number of studies that reported inulin clearances relative to gestational and post-natal age [61–71]. These studies were considered the foundation for the assessment of neonatal kidney function and development. Unfortunately, the product is no longer readily available for clinical use and, as will be discussed below, has been supplanted by estimation equations [16, 60]. Other direct measures of GFR include non-radioactive iothalamate [72]. Although it is partially protein bound and there is possible tubular secretion, it is inexpensive and, in the neonate, closely approximates inulin clearance [72]. Iohexol is a non-radiopaque contrast agent used in the measurement of GFR in children with CKD, but has not been validated in infants [23, 73].

Estimation of GFR by endogenous markers

Despite the imperative for having a reliable assessment of GFR in the neonate, the performance of tedious clearance

studies, especially in sick infants, is impractical. As a consequence, endogenous markers of GFR have been sought with the construction of estimating equations [22, 23, 73, 74]. To serve as an accurate marker of GFR, the plasma solute must be freely filtered across the glomerular membrane and neither secreted nor reabsorbed along the tubular network. It must be solely excreted via the kidney and the endogenous production rate must be constant. The endogenous markers that have been applied in the assessment of neonatal kidney function across gestational age groups are creatinine, cystatin C, and beta-trace protein (BTP) [17, 74–81]. Using a composite analysis of historic clearance studies and contemporary estimating equations applicable to infants, Table 1 and Fig. 2 have been provided as a resource [62–68].

Schwartz and others, using inulin clearances in their early clinical investigations, provided reliable data that allowed the derivation of estimating equations from serum creatinine values [23, 73, 74]. More recently, the Schwartz equation has been modified using iothexol clearances in a large cohort of children with CKD (CKiD study) [74]. The need for the adjustment of the Schwartz constant “k” by 25 % from 0.55 to 0.413 was due to the adoption of the enzymatic assay for serum creatinine over the historical Jaffe method, which decreased the results by 20–25 % [74]. Pottel et al., in a meta-analysis of creatinine-based estimating equations, have provided the *Flanders equation*, which adjusts the k by age so that those subjects <3 years of age can have more accurate assessment of GFR [81]. Similarly, Zappitelli et al. have provided iothalamate clearances in infants and children and applied estimating equations using cystatin C and creatinine [76]. More recently, Filler et al. have extensively reviewed the application and potential advantages of using BTP in estimating GFR in neonates [79].

In summarizing the benefits of applying estimating equations for the accurate assessment of GFR in infants, it is

evident that creatinine-based formulas lack accuracy. However, creatinine assays are universally standardized, readily available, and inexpensive. Cystatin C-based equations have been validated in infants and children and are independent of body mass and age [74–77]. Cystatin C-based equations are consistent with inulin and iothexol clearances and do not require length measurements [74–77]. Although novel, BTP may be a potential alternative to cystatin C; but the most accurate BTP estimating equations still contain creatinine and height [79]. Both cystatin C and BTP assays are not routinely available in the hospital chemistry laboratory as standard assays and are from 10–15 times more expensive [79]. Combined equations offer greater accuracy and are included in Table 2; but the univariate equations offer the best bedside assessments. Therefore, current recommendations would be to use a univariate cystatin C equation followed by the modified Schwartz equation adjusted by the Flanders’ constant in infants <2 years of age [16, 23, 74, 81].

Towards normative charts for creatinine, cystatin C, and eGFR

In prior years, experts have called for the adoption of normative charts for infants and children to be able to interpret measures of renal assessment similar to growth curves with the calculation of z-scores or percentiles relative to the normal pooled data [82]. Traditionally, the dogma has been to dismiss elevated serum creatinine in preterm infants during the neonatal period as unreliable. However, there is growing concern among pediatric nephrologists and neonatologists that failure to recognize kidney injury during the neonatal period may result in a lack of surveillance for the development of progressive kidney disease [13, 17, 83].

Table 1 provides the mean ± standard deviation (SD) calculated for preterm and term infants at birth and at 3, 6, and 12 months post-conceptual age for serum creatinine, cystatin

Table 1 A table of reference values compiled from the literature [17, 74–81]

	Preterm	Term	3 months	6 months	12 months	24 months	36 months
Scr mg/dl	0.7 ± 0.3	0.5 ± 0.1	0.4 ± 0.2	0.3 ± 0.2	0.3 ± 0.1	0.3 ± 0.2	0.3 ± 0.2
ScysC mg/l	1.42 ± 0.21	1.33 ± 0.20	1.20 ± 0.26	0.98 ± 0.22	0.85 ± 0.22	0.72 ± 0.12	0.72 ± 0.10
S _{BTP} mg/l	1.79 ± 0.56	1.27 ± 0.27		0.84 ± 0.35		0.68 ± 0.17	0.74*
GFR _{INULIN} ml/min/1.73 m ²	44 ± 9	55 ± 8	60 ± 17	87 ± 22	96 ± 12	105 ± 17	111 ± 19
eGFR _{cr} ml/min/1.73 m ²	24 ± 7	46 ± 10	63 ± 8	92 ± 10	105 ± 12	120 ± 17	113 ± 10
eGFR _{cysC} ml/min/1.73 m ²	46 ± 10	54 ± 8	61 ± 10	78 ± 8	92 ± 12	112 ± 10	112 ± 8
eGFR _{BTP} ml/min/1.73 m ²	46 ± 7	63 ± 13		94 ± 39		115 ± 29	106 ± 8

*Upper limit of range for adults [78]

Scr: serum creatinine; mg/dl: milligrams/ deciliter; ScysC: serum cystatin C; mg/l: milligrams/liter; S_{BTP}: serum beta trace protein; GFR_{INULIN}: glomerular filtration rate measured by inulin; ml/min/1.73 m²: milliliters/minute/1.73 meters²; eGFR_{cr}: estimated GFR by creatinine; eGFR_{cysC}: estimated GFR by cystatin C; eGFR_{BTP}: estimated GFR by beta trace protein

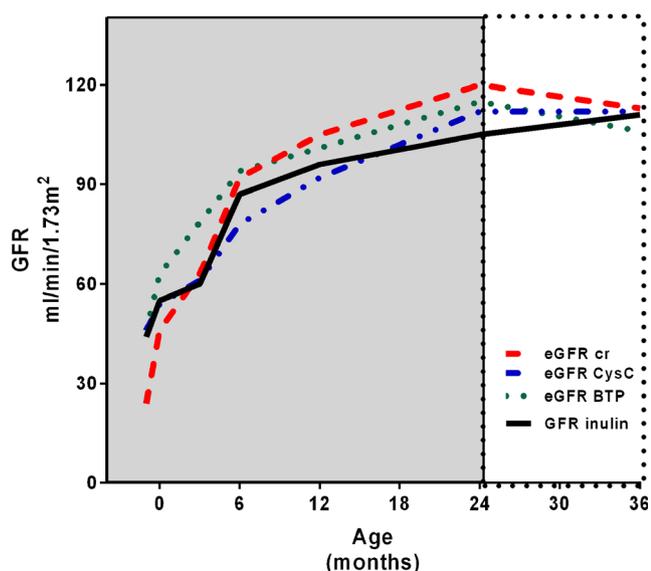


Fig. 2 Plot and comparison of the estimated glomerular filtration rates (eGFR) derived from three endogenous markers: creatinine (cr), cystatin C (CysC), and beta trace protein (BTP) in colors against the measured inulin clearance from preterm birth through the first 36 months of life. At birth, especially in the preterm infant, eGFRcr markedly underestimates GFR-inulin; whereas GFR CysC and GFR BTP closely approximate measured or “true” GFR. After 6 months, GFRcr and GFR BTP overestimate and GFR CysC underestimate “true” GFR. It is not until 3 years of age that all the eGFR seem to accurately assess GFR. Data are derived from references used to develop Table 1 [17, 74–82]

C, and eGFR [74–82]. Table 2 provides a summary of the estimating equations most applicable to infants during the first 2 years of life with the caveat that none have been adequately validated in infants [74–82].

Total kidney volume in the assessment of kidney function

In the early post-natal period, maintenance of GFR is dependent primarily on gestational age, total kidney volume (TKV), and mean arterial pressure (MAP) [15]. Within days, with hemodynamic stability, the healthy neonate has adjusted to the extra uterine environment and 15–20 % of cardiac output is distributed to the kidneys [7, 26, 27]. However, maturation of GFR to adult levels will take almost 2 years in the healthy infant and is directly related to maturation and growth of the kidney and increase in the surface area of those glomeruli that were present at birth (nephron endowment).

Preterm birth imposes immediate and potential long-term alterations in kidney size and function. Infants born before 36 weeks’ gestation during active nephrogenesis will have a decreased number of filtering nephrons and the GFR will be proportionate to the number of nephrons being perfused. The GFR will also be a function of the gestational age since renal size in utero follows gestational growth curves [17]. In a small autopsy study of term neonates ($n=15$) glomerular number correlated to kidney weight [43]. This is consistent with adult autopsy studies in various populations, suggesting that nephron endowment can be estimated by following kidney size [35–42]. Even more compelling is that kidney size individualized to body surface area (BSA) correlates closely with kidney function across all age groups [15, 16, 83–85]. Individual kidney volume can be measured using the equation for an ellipsoid: $\text{volume} = \text{length} \times \text{width} \times \text{depth} \times 0.523$ and then left and right kidney volumes can be summated for the TKV

Table 2 Estimating equations most suitable for application to infants

Pediatric eGFR equations (ml/min/1.73 m ²)	References
Creatinine and length	
$eGFR = 0.413 \times \text{Length (cm)} / \text{Cr}$	[23] Schwartz et al. J Am Soc Nephrol 2009; 20:629–637
$eGFR = [0.0414 \times \ln (\text{Age}) + 0.3018] \times \text{Length (cm)} / \text{Cr}$	[81] Pottel et al. Pediatr Nephrol 2012; 27:973–979
Cystatin C alone	
$eGFR = 70.69 \times (\text{CysC})^{-0.931}$	[74] Schwartz et al. Kidney Int 2012; 82:445–453
$eGFR = 75.94 \times (\text{CysC})^{-1.170}$	[76] Zappitelli et al. Am J Kidney Dis 2006; 48:221–230
Beta trace protein	
$eGFR = 10^{(1.902 + (0.9515 \times (\text{Log}_{10} (1/\text{BTP})))}$	[78] Benlamri et al. Pediatr Nephrol 2010; 25:485–490
$eGFR = -35.2 + 122.74 \times (1/\text{BTP})^{0.5}$	[79] Abbink et al. Clin Biochem 2008; 41:299–305
Combined equations	
$eGFR = 3.98 \times (\text{Length (cm)} / \text{Cr})^{0.456} (1.8 / \text{CysC})^{0.418} (30 / \text{BUN})^{0.079}$	[74] Schwartz et al. Kidney Int 2012; 82:445–453
$eGFR = (43.82 \times e^{0.003 \times \text{length(cm)}}) / (\text{CysC}^{0.635} \times \text{Scr}^{0.547})$	[76] Zappitelli et al. Am J Kidney Dis 2006;48:221–230

eGFR: estimated glomerular filtration rate; cm: centimeters; Cr: creatinine; ln: natural log; CysC: cystatin C; Log₁₀: log to base 10; BTP: beta trace protein; BUN: blood urea nitrogen; e = natural log = 2.7183; Scr: serum creatinine

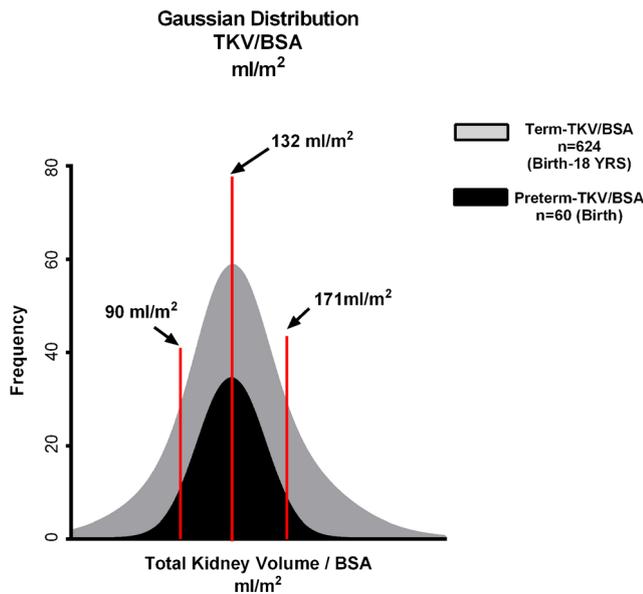


Fig. 3 The Gaussian distribution of total kidney volume (TKV) factored by body surface area (BSA) in milliliters (ml) per meter² (ml/m²). The predominant distribution is derived from the data of 624 healthy German individuals from <1 month to 18 years of age [85]. The mean and 90 % confidence intervals define the normal distribution of kidney mass and, by inference, “nephron endowment” since kidney volume correlates closely with kidney weight [54]. An individual whose TKV/m² falls below the 10th percentile (<90 ml/m²) should be observed closely for development of chronic kidney disease (CKD) due to nephropenia. The darker curve within the larger German cohort is data from our cohort of 60 preterm infants [17]. This demonstrates that preterm infants have a similar *normal distribution* of nephron endowment at birth and suggests that they have the potential for normal attainment of nephron mass in the extra-uterine environment. Most importantly, preterm infants should be followed sequentially for kidney growth by TKV/m² throughout childhood

(ml) [54, 55, 85]. Ultra-sonographers can estimate these measurements from standard renal ultrasound images [54, 55, 85].

Moreover, there is a normal Gaussian distribution of TKV individualized to BSA (TKV/m²=ml/m²) when measured by non-invasive renal ultrasound from birth to adulthood [85]. A cross-sectional study of renal ultrasounds in 624 healthy German children from birth to 18 years of age showed an average TKV/m² to be 132 ml/m² with the 10th and 90th percent confidence interval being 90 and 171 ml/m², respectively [85]. In a separate Canadian cohort of 136 full-term healthy Caucasian infants <3 months of age, an identical curve was generated with the mean TKV/m²=132±29 ml/m² [43]. Most recently, the Generation R study of over 6000 Dutch children followed prospectively since birth used TKV as a marker of kidney health and have shown subtle but significant differences in kidney function at 6 years of age [86, 87].

When the Gaussian distribution of TKV/m² of the normal population of 624 infants, children and adults was superimposed on that of 60 preterm infants at birth from our cohort, the remarkable observation was that they were similar [17, 85]. This corroborates previous studies that nephron mass and presumed nephron endowment is normally distributed and similar in preterm infants at birth (Fig. 3). The implications are significant in that, if active nephrogenesis can be supported to fruition post-natally, then the preterm infant could potentially achieve a nephron endowment similar to that of a term infant. It also suggests that individuals whose TKV/m² falls below the 10th percentile have an inherent risk for “oligonephropathy” and should be monitored for hypertension and progression to CKD.

In seeking more accurate and alternative estimates of GFR in infants and children, it has become evident that TKV should be considered in the baseline and longitudinal assessment of neonatal kidney function and has implications for the individual’s renal longevity [13, 14, 16, 17].

Conclusions

In summary, it is well documented that being born prematurely confers an increased risk of CKD in adulthood. This review has highlighted the key factors likely underlying this phenomenon, namely the importance of the congenital nephron endowment. The extra-uterine environment of the preterm infant is often taxed with various insults such as nephrotoxic drug exposure and hemodynamic instability that may negatively affect the short window of ongoing nephrogenesis. Subsequently, obesity, recurrent AKI, and the natural aging process will all negatively impact the nephron endowment. Hence, early identification and periodic screening of these at-risk preterm individuals should allow for mitigation of injury and preservation of their nephron endowment and renal function over the life span. As more data accumulate, especially in larger diverse cohorts, such as the Neonatal Kidney Collaborative (NKC), NCT02443389, a scoring system may be forthcoming that incorporates the degree of prematurity, AKI, renal size, and other relevant factors to be validated for better stratification of future risk of CKD among these infants [19]. In a recent review, Carmody and Charlton proposed a screening algorithm including measuring blood pressure, renal function, and proteinuria for these at-risk patients [83]. Providers could consider screening these patients every 6 months to 1 year with well child visits and refer to specialists when appropriate. Future research efforts should focus on prospective longitudinal studies of preterm infants to identify more specific screening timelines and areas for early therapeutic intervention to mitigate the morbidity of CKD. Finally, as in most circumstances, the onset of cardiovascular and renal

complications of being born preterm and/or of low birth weight will likely not manifest until early adulthood. Mechanisms for effective transition of care to adult providers must include highlighting these concerns.

Questions

1. The human kidney forms from which sequential developmental stages?
 - a. Pronephros, metanephros, mesonephros
 - b. Antinephros, neonephros, humanonephros
 - c. Metanephros, mesonephros, pronephros
 - d. Pronephros, mesonephros, metanephros
2. What is considered the “gold standard” for measurement of GFR in infants?
 - a. Iohexol
 - b. Inulin
 - c. Creatinine clearance
 - d. Para-aminohippurate clearance
3. An endogenous marker of GFR must fulfill all of the following criteria except it:
 - a. Must be freely filtered by the glomerular barrier
 - b. Must be secreted and reabsorbed by the renal tubule at an equal rate
 - c. Must be produced at a constant rate
 - d. Must not be protein bound
4. The nephron endowment is determined by which of the following:
 - a. Intra-uterine environment
 - b. Genetic polymorphisms of intra-uterine drivers of nephrogenesis
 - c. Prematurity and post-natal completion of nephrogenesis
 - d. All of the above
5. Which of the following subjects does not have oligonephronia?
 - a. Six-year-old born 36 weeks preterm with a serum creatinine of 0.4 mg/dl and a TKV/m² = 160 ml/m²
 - b. Fifteen-year-old obese male with unilateral renal agenesis with a TKV of 135 ml and a BSA = 2.00 m²
 - c. Three-year-old born extremely preterm and low birth weight with serum creatinine of 0.6 mg/dl and a TKV/m² = 85 ml/m²
 - d. Six-year-old born at term with IUGR who is growing well along the 15th percentile for length and the 50th percentile for weight.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest.

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Answers to questions

1. D
2. B
3. B
4. D
5. A