Pediatric Nephrology (2020) 35:543–546
https://doi.org/10.1007/s00467-019-04465-7

EDITORIAL COMMENTARY

Big equation for small kidneys: a newly proposed model to estimate neonatal GFR

Abby Basalely[1] · Diane Liu[1] · Frederick J. Kaskel[1]

Received: 24 June 2019 / Revised: 13 December 2019 / Accepted: 18 December 2019 / Published online: 31 January 2020

Background

Rapid assessment of glomerular filtration rates (GFR) in infants is imperative for both drug dosing and recognition of acute kidney injury (AKI) [1–3]. This is especially important in low birth weight and preterm neonates who have an increased risk of AKI and development of chronic kidney disease (CKD) [4]. However, obtaining accurate estimates of GFR in term and preterm infants has been challenging. Serum creatinine, the traditional biomarker of filtration, is dependent upon muscle mass and age-dependent renal excretion. Creatinine values in newborns are further complicated by the fact that infant creatinine levels are reflective of maternal creatinine levels in the first few days of life and creatinine is reabsorbed by immature tubules [5, 6].

Traditional urinary clearances using the gold standard marker inulin have been used in the seventies to provide the basic information on the development of glomerular filtration rate [7, 8]. GFR is low at birth with a value close to 20 ml/min per 1.73 m^2 in term neonates. It is lower in premature infants. GFR develops rapidly after birth, its value doubling within the first 2 weeks of life. It develops at a somewhat lower velocity in very premature infants [9].

Recent studies by Vieux et al. [10] have assessed the urinary clearance of creatinine during the first 28 days of life of premature infants with various gestational ages, ranging from 27 to 31 weeks. They provided regression lines for estimating the expected value normal creatinine clearance at different gestational and postnatal ages. The results of these studies were in agreement with the reference values established previously using inulin as a marker [7, 8].

However, estimating GFR by the traditional urinary clearance has an important drawback: it requires precisely timed collections of urine. For these reasons, methods without the need for urine have been sought after.

In 1976, Schwartz et al. published the first method of non-invasive estimation of GFR in children [11]. The researchers created a model to calculate eGFR in children 6 months–18 years old, challenging the original estimation based on adults:

$$\text{Creatinine Clearance} = \frac{\text{UCr} \times \text{V}}{\text{SCr}}$$

UCr is urinary creatinine (mg/dL), SCr serum creatinine (mg/dL), and V urinary flow rate (mL/min).

Schwartz et al. maintained that utilization of a ratio dependent on serum creatinine production did not take into account muscle mass, which varies in growing children. They performed a multivariate linear regression modeling of GFR initially measured by 24-h creatinine clearance studies demonstrating that the ratio of height in centimeters (cm) to SCr was the most significant predictor of GFR. Height was multiplied by the constant of 0.55 (L/SCr), the coefficient derived from multivariate linear regression:

$$\text{eGFR ml/min/m}^2 = \frac{0.55 \times \text{height (cm)}}{\text{SCr (mg/dL)}}$$

They subsequently validated their model directly measuring GFR via single-injection inulin clearance in 77 of the pediatric patients.

In 1984, the group sought to develop an estimation of GFR in term infants [12]. They evaluated creatinine clearance in 137 infants aged 5 days–1 year, for which clearance was measured directly by single-injection inulin in 63 infants. The same relationship of height in cm/SCr was substantiated, but the coefficient of 0.55 grossly overestimated GFR. Based on models built specifically for that population, a new constant of

Abby Basalely and Diane Liu contributed equally to the preparation of this manuscript. AB and DL are trainees on an NIH T32 NIDDK 5T32DK007110- 46.

✉ Frederick J. Kaskel
fkaskel@montefiore.org

[1] Department of Pediatrics, Division of Pediatric Nephrology, The Children's Hospital at Montefiore Bronx, 3326 Bainbridge Avenue, Bronx, NY 10467, USA

0.44 was developed for term neonates.

$$\text{eGFR ml/min/m}^2 = \frac{0.44 \times \text{height (cm)}}{\text{SCr (mg/dL)}}$$

Creatinine-based prediction models of eGFR for premature and low birth weight infants without kidney disease were introduced by Brion et al. in 1986 [13]. Brion, in collaboration with Schwartz, hypothesized that lower muscle mass in low birth weight and preterm infants would result in overestimation of eGFR based on the term infant equation. They evaluated SCr levels, UCr levels, and the plasma disappearance curve of inulin in 118 preterm and 84 term infants. The authors concluded that in premature and low birth weight infants, a lower constant of 0.33 should be used in estimations of GFR as it more accurately takes into account for their lower muscle mass:

$$\text{eGFR ml/min/m}^2 = \frac{0.33 \times \text{height (cm)}}{\text{SCr (mg/dL)}}$$

In 2009, using 349 children aged 1–16 years old who were enrolled in the chronic kidney disease in children (CKid) study, Schwartz et al. developed a simplified "bedside" GFR calculation utilizing a universal constant of 0.413 [14]:

$$\text{eGFR ml/min/m}^2 = \frac{0.413 \times \text{height (cm)}}{\text{SCr (mg/dL)}}$$

This prediction model was subsequently validated by Staples et al. in a cohort of 573 predominantly healthy children, between 1 and 16 years of age, without kidney disease [15].

As SCr varies in children with cachexia and/or CKD, models employing serum cystatin-C (CysC), a cysteine proteinase produced by nucleated cells, as a biomarker of clearance have also been proposed in children. In a cohort of CKD and transplant patients, Zappitelli et al. proposed an estimation that incorporated serum CysC into a single model with height and SCr [16]:

$$\text{eGFR ml/min/m}^2 = \left(43.82 \times e^{0.003 \times \text{Ht}}\right) / (\text{CysC} \cdot 0.635 \times \text{SCr} \cdot 0.547)$$

Abitbol et al. in 2014 found an agreement between GFR extrapolated from six inulin clearance studies and GFR calculated based on Zapitelli's combined equation in preterm and term neonates [17]. The study examined serum CysC levels and SCr levels within the first week of life for 60 preterm infants with gestational age (GA) 25–< 37 weeks and 40 term infants. All serum values were obtained > 48 h from birth. Creatinine-based estimates of GFR using the bedside Schwartz equation underestimated clearance in the cohort by over 20%. The study concluded that CysC is a superior biomarker of clearance to SCr and improves the accuracy of noninvasive modeling of term and preterm neonatal glomerular filtration rates.

Results of the Wilhelm-Bals et al.'s study

In this issue of *Pediatric Nephrology*, Wilhelm-Bals et al. conducted a single-center, prospective study in newborns from Switzerland comparing clearance measured by single-injection inulin and a new prediction model including weight and creatinine in term and preterm neonates [18]. Those with birth weight < 800 g, hemodynamic instability, and severe anemia were excluded. The group compared their prediction model with the Brion et al., Zapitelli, and combined Zapitelli models [16]. Forty-eight infants were included in the study and inulin clearances were measured during days 1–6 of life in 44 patients (41 preterm neonates and 3 term neonates). The authors initially considered candidate variables of height, GA, weight, creatinine, and cystatin C. All variables except for cystatin C were found to be significantly correlated with inulin clearance on bivariate analysis. Multivariate linear regression was utilized to develop a parsimonious prediction model. Cystatin C, GA, log (creatinine), and weight were considered potential predictors. GA and cystatin C were ultimately removed from the model as they were not found to be significant predictors of GFR. The final model after correcting for the logarithmic transformation of serum creatinine was:

$$\text{Predicted eGFR ml/min/m}^2 = 2.32 \times (\text{weight (g)})^{0.64} / (\text{creatinine } (\mu\text{mol/L}))^{0.62}$$

This model gave a mean prediction error of − 0.8 ml/min/1.73 m^2 (95% CI − 3.0–1.4), performing slightly better in this population than the neonatal Schwartz equation, which gave a mean prediction error of 2 ml/min/1.72 m^2 (95% CI − 0.6–2.6). The mean prediction error was much higher for the Zappitelli and combined Zappitelli equations, which were 28.5 ml/min/1.72 m^2 (95% CI 24.6–232.3) and 28.3 ml/min/1.72 m^2 (95% CI 24.9–31.7), respectively.

Significance and generalizability

While this study is the first to utilize weight as a predictor of GFR in a cohort of predominantly preterm neonates during the first week of life, there are significant limitations before it will be accepted as a valid technique. The proposed eGFR model highlights the unique relationship between preterm and term neonates' eGFR and gestational age, height, and cystatin C. The significance of infant weight in the model may reflect the

strong correlation between body weight and nephron number, thus affecting GFR. Although it is not clearly stated by the authors, it could be speculated that weight and GA were collinear variables within the model and thus, both were not included, which has been seen in other models [17].

One limitation of the use of weight as a model variable is that the authors do not specify whether the birth weight or the weight at the time of serum creatinine determination should be used in the equation. Term infants lose up to 10% of birth weight within the first week of life, with even greater losses in preterm infants. Utilizing weights other than birth weight could substantially affect GFR estimates and further clarification should be provided in future studies.

Infant height, a predictor in the majority of eGFR formulas, was not included in the initial full model even though it was significantly correlated to eGFR. Although the authors explained that they had a small sample size, the rationale for not including length in the model is not fully explained. Leger et al. developed a pharmacokinetic population model based on serum creatinine levels to estimate GFR utilizing weight and height in a cohort of children 8 months–18 years of age [19]. Further studies should assess whether height improves the prediction of GFR. This is important, as length has long been used in the signature formulas to estimate childhood GFR.

Another important limitation of this study is that the use of single-injection inulin clearance to directly measure GFR has not been validated in a large sample of premature infants. Urinary inulin clearance studies in neonates using inulin infusion were first described in 1975 by Guignard et al. [7]. These studies demonstrated a rapid increase in GFR in the first month of life, and a doubling of the GFR in the first 15 days of life. Coulthard showed that the continuous infusion of inulin method without urine collection gave a relatable result only when inulin was constantly infused for 24 h [20]. This finding was ascribed to the slow rate of inulin diffusion into the extracellular space of neonates. Using the 24-h inulin infusion method as a reference value, the same author found that the single-injection method correlated poorly with GFR when the single-injection clearance was estimated over 2 h. Similarly, in 1979, Fawer et al. showed that the single-injection inulin technique overestimated the urinary clearance of inulin by up to 30% in the first week of life [21].

The study also did not find cystatin C to be a significant predictor of GFR, which is discrepant from prior reports in the literature. As mentioned previously, Abitbol et al. demonstrated cystatin C to be a superior biomarker of clearance as compared with serum creatinine. Another study, also from Sweden, found no significant relationship between gentamicin clearance and measured cystatin C (the same study also did not find a strong relationship with creatinine) [22]. The debate as to whether cystatin C crosses the placenta is still, to some extent, unresolved. Contrary to what had been postulated previously, cystatin C may cross the placenta, but to a smaller extent than serum creatinine. One could suggest that Abitbol only looked at values after 48 days of life, while this paper looked at those on the first postnatal day, which may account for discrepancy of the findings. Alternatively, as suggested by the authors, the lack of significant correlation may be due to the small sample size. Regardless, the low intra-individual variability of cystatin C measurements in this study further lends support to use of cystatin C to detect AKI in this population.

As the cohort studied did not include extremely low birth weight infants, infants with AKI, or those with any hemodynamic instability and only 3 term neonates were included, the equation reflects GFR measured in a relatively healthy preterm cohort. This calculation can only be used within the first few days of postnatal life. Additionally, as all participants were of European descent, the model becomes less generalizable to a diverse worldwide population. This is of particular significance considering that African Americans have a higher risk of being born preterm and carrying the *APOL1* risk allele [23].

Conclusion

The new model proposed by Wilhelm-Bals et al. offers a novel approach to predict GFR in preterm infants that needs validation. The study highlights the need to conduct studies and derive specific population-based calculations of eGFR as neonatal renal physiology is very different than infants older than 1 month of age. Further validation in a larger sample of ethnically diverse patients is needed to reexamine the relationship of GFR and cystatin C in this population, in addition to considering the inclusion of height in the model. Hopefully, future work will lead to more understanding of how to best assess GFR in preterm infants.

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