RESEARCH PAPER

Assessment of Renal Growth and Function in Preterm Infants at Corrected Age of 12-18 Month

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Objective: To assess the kidney growth and function in appropriate for date and small for date (SGA) preterm neonates.

Methods: Appropriate for date and SGA preterm neonates with gestation <35 weeks, at 12-18 months of corrected age, attending the follow-up outpatient clinic of a Tertiary care level III neonatal unit. Renal function was assessed by measuring the serum creatinine level and estimated Glomerular Filtration Rate (eGFR) was calculated by using modified Schwartz formula. Kidney size was determined by ultrasonography using a 5 MHz sector probe with an accuracy of 1.0 mm.

Results: The mean (SD) serum creatinine and eGFR in the 120 children enrolled were 0.39 (0.16) mg/dL and 109.05 (44.66) mL/min/1.73 m^2, respectively. The mean (SD) lengths of right and left kidney were 54.3 (4.9) mm and 55.2 (4.77) mm, respectively. The kidney length, serum creatinine and eGFR were significantly lower in preterm SGA infants as compared to preterm AGA infants.

Conclusion: Preterm infants, especially SGA infants, at 12 to 18 months of corrected age have impaired renal growth with small kidney size.

Keywords: *Chronic kidney disease, Outcome, Prematurity, Sequelae*.

Neonates born preterm are at risk for multiple morbidities because of the organ immaturity. With improved survival of these premature infants, focus is now on short term and long-term morbidities. Prematurity is consistently associated with reduction in number of nephrons. Coupled with prematurity, multiple intrauterine and extra uterine insults may result in developmental maladaptation resulting in immediate, short-term and long-term renal complications. Effect of immaturity of organ systems on post-natal renal function is less well appreciated when compared to pulmonary and neurodevelopmental consequences [1,2]. Preterm infants are reported to have 1.73 times higher odds of developing chronic kidney disease [3].

The kidney length has been previously reported to be lower in preterm small for gestational age (SGA) infants compared with preterm appropriate for gestational age (AGA) infants [4,5]. As there are limited studies evaluating the post-natal kidney function and growth in preterm infants, we designed this study to assess the renal growth and function at 12-18 months of corrected age in preterm neonates with gestation less than 35 weeks at birth. We also compared the kidney growth and function between AGA and SGA infants

METHODS

We conducted this cross-sectional observational study in a tertiary care level III neonatal unit over a period of 2 years from May, 2016 to May, 2018.

Accompanying Editorial: Pages 395-96.

All inborn preterm infants with gestational age <35 weeks at birth (with a minimum gestation of 25 weeks) born after May, 2015 and attending the follow-up clinic up to at least 12 to 18 months of corrected age were enrolled after obtaining a written consent from one of the parents. Infants with major malformations (including renal malformations) were excluded from the study.

The antenatal, perinatal and neonatal details of enrolled infants were collected in a predesigned proforma from the discharge summary, computerized database and case files. This data included maternal details (age, medical and pregnancy related illnesses, medication details, antenatal steroid administration and mode of delivery) and neonatal details (birth weight, sex, the need for resuscitation at birth and Apgar scores at 1 and 5 minutes, incidence of respiratory distress syndrome, patent ductus arteriosus (PDA) – clinical or

echocardiography proven, culture positive sepsis, necrotizing enterocolitis stage II and above, use of nephrotoxic medications like aminoglycosides, metabolic derangements like hypoglycemia, electrolyte disturbances, apnea, jaundice, presence of intra ventricular hemorrhage, retinopathy of prematurity, bronchopulmonary dysplasia, acute kidney injury (AKI) [6] and anthropometry at discharge). Feeding details such as duration of exclusive breastfeeding, type of feeding in the first 6 months, time of initiation of complementary feeding, and illnesses requiring admission in the hospital were also documented.

Renal function was assessed by measuring the serum creatinine levels based on the modified Jaffe method [7] (Alkaline Picrate no deproteinization–Siemens Dimension RXL). Estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine and length of the infants using the modified Schwartz formula (eGFR= k*length in cm/creatinine in mg/dL with k value taken as 0.413) [8]. Kidney size was assessed by ultrasonography using a 5 MHz sector probe (Philips CX50 – Philips Ultrasound, Andover, MA, USA). The probe was placed on the back of the child in a supported sitting position. The kidney was identified in the sagittal plane along its longitudinal axis. Both length and breadth were measured to nearest 0.1 cm in both kidneys. All the measurements were done by a single radiologist who was blinded to antenatal and postnatal details including birth weight group. The expected length of the kidneys for that age and length of the child was estimated from the published normative data of Indian children [9]. Deficit in the length was calculated from the observed and the expected lengths of the kidneys and compared between SGA and AGA infants. With 95% confidence level and 80% power we needed a sample size of 119 to identify a difference in kidney of 1 mm compared to previous normative data [9].

Statistical analysis: Group comparisons for baseline data and outcomes was done using chi-square test or student t test for categorical and continuous variables, respectively. To know the independent effect of variables which are significant on univariate analysis, separate linear regression models were created using SPSS version 23 with kidney length (right and left), estimated GFR, serum creatinine as dependent variable and gestation, growth restriction at birth, sepsis, PDA, use of amikacin, antenatal steroids, singleton, mode of delivery, gender, neonatal AKI as independent variables. *P* value <0.05 was considered as significant.

RESULTS

During the study period, 178 eligible infants attended the follow up clinic at 12 to 18 months of corrected age and among them data for kidney size and function was available for 120 infants (58 parents refused consent). The mean birth weight and the mean gestation of study population was 1242.33 (340.36) grams and 30.32 (2.08) weeks, respectively. Baseline variables including neo-natal morbidities were comparable for AGA and SGA infants except for proportion of infants from multiple pregnancy and preterm pre-labor rupture of membranes (PPROM) in the mother was higher in AGA group and maternal pregnancy induced hypertension (PIH) and antenatal doppler abnormalities were higher in SGA group (***Table* I**).

The mean lengths of the right and left kidneys in the study population were 54.3 (4.9) mm and 55.2 (4.77) mm, respectively. The mean breadths of the right and left kidneys in the study population were 24.6 (2.14) mm and 25.8 (2.26) mm, respectively. The mean creatinine level and mean eGFR in the study cohort were 0.39 (0.16) mg/dL and 109.05 (44.66) mL/min/1.73m^2, respectively. Infants in

Table I Baseline Details of Preterm Infants Enrolled in the Study (*N*=120)

Variable	*AGA group (n=90)*	*SGA group (n=30)*
‡*Gestation (wk)	29.98 (2.1)	31.37 (1.67)
‡*Birthweight (g)	1306.56 (344.12)	1049.67 (246.44)
Male sex	53 (59)	16 (53.3)
ANS coverage	78 (86.7)	26 (86.7)
#Multiple pregnancy	27 (30)	3 (10)
*PIH	28 (31.1)	21 (70)
*Abnormal doppler	20 (22.2)	21 (70)
*PPROM (%)$	44 (49)	3 (10)
#LSCS (%)$	77 (85.6)	30 (100)
APGAR (5min)	8 (5,9)	8 (7,9)
Culture positive sepsis	20 (22.2)	8 (26.7)
HSPDA	17 (19)	7 (23.3)
HIE	2 (2.2)	0 (0)
AKI	5 (5.6)	1 (3.3)
BPD (%)$	8 (9)	4 (13.3)
‡*Reached full feeds (d)	7.14 (5.06)	10.47 (5.84)
‡#Regained birth weight (d)	13.94 (4.41)	11.5 (5.19)
‡CGA at discharge (wk)#	34.65 (2.15)	34.65 (2.15)
‡#Discharge weight (kg)#	1563.11 (201.07)	1484.33 (96)

*Values in no.(%) except ‡mean (SD), *P<0.0001; #P<0.05; ANS – PIH; – Pregnancy induced hypertension; PPROM – preterm premature rupture of membrane; LSCS – lower segment cesarean section; HSPDA – hemodynamically significant; NEC – necrotizing enterocolitis; HIE – Hypoxic ischemic encephalopathy; AKI – acute kidney injury; BPD – bronchopulmonary dysplasia; CGA – corrected gestational age.*

SGA group had higher mean creatinine levels and lower eGFR values and smaller kidneys when compared to AGA group infants (***Table* II**).

On regression analysis with kidney length as the dependent variable, birthweight *Z* score independently predicted the renal growth. With every one-point increase in *Z* score for birthweight, length of right kidney and left kidney improved by 1.52 mm (0.46-2.58 mm) and 1.54 mm (0.51-2.57 mm), respectively. On regression analysis with serum creatinine or GFR as dependent variable, gestation at birth and birthweight *Z* score independently predicted the renal function (serum creatinine levels and estimated GFR levels). With every week increase in gestation at birth and increase in birthweight *Z* score by 1 point, eGFR increased by 5.48 mL/min/1.73m^2 (0.27-10.69) and 14.34 mL/min/1.73m^2 (2.66-26.02), respectively. With every week increase in gestation at birth and increase in birth weight z score by 1 point, serum creatinine levels decreased by 0.01 mg/dL and 0.035mg/dL, respectively.

DISCUSSION

In this cross-sectional observational study, we evaluated the renal function and growth at 12 to 18 months of corrected age in preterm infants with gestation <35 weeks at birth. At 12 months age, the average reported kidney size is 57 mm [9] and the reported serum creatinine values vary from 0.17 to 0.36 mg/dL [10]. In comparison to published norms for the age, preterm infants of this study had lower kidney growth and function and it was significantly compromised in preterm SGA infants in comparison with preterm AGA infants. The reason for this reduced renal growth and function in our preterm infants may be due to intrauterine growth restriction, preterm birth and postnatal factors like hyperoxia, exposure to toxic medications (aminoglycosides, non-steroidal anti-inflammatory drugs, *etc*.) and extra uterine growth restriction. The extra uterine insults in the neonatal period on the immature kidney may result in reduced nephron number, glomerular and tubular injury and may further predispose these children to long-term complications in later life. In the studies that evaluated preterm SGA infants [4,5], prematurity and weight for gestational age had significant effect on kidney growth at 12 and 18 months of corrected age. Our conclusions are similar but the parameters used for measuring the renal growth are different – kidney volume in Schimdt, *et al*. [5] and relative kidney length in Drougia, *et al*, [4]. Contrary to these findings, Hotoura, *et al*. [11] did not find any difference in mean kidney length between SGA and AGA infants at 12 months of chronological age. Differences in the baseline characteristics and differences in time points of assessment may be reasons for these differences in renal outcomes.

Table II Renal Growth and Function in Preterm Infants at Corrected Age of 12-18 Month (*N*=120)

Variable	*AGA group (n=90)*	*SGA group (n=30)*	*P-value*
Serum creatinine, mg/dL	0.4 (0.18)	0.5 (0.09)	0.005
eGFR, mL/min/1.73m^2	115.6 (48.41)	89.4 (21.37)	0.005
Kidney length, mm			
Right	55.4 (4.0)	51 (6.0)	< 0.001
Left	56.2 (3.88)	52.3 (5.97)	<0.001
Kidney breadth, mm			
Right	24.7 (2.16)	24.3 (2.08)	0.36
Left	25.7 (2.45)	25.9 (1.60)	0.71
Growth deficit, mm			
Right	-2.7 (4.4)	-6.0 (6.37)	0.002
Left	-1.9 (4.06)	- 4.7 (6.0)	0.005
*Expected kidney length, mm	57.9 (2.3)	57.8 (2.24)	0.93

*All values in mean (SD); AGA – appropriate for gestational age; SGA – small for gestational age; eGFR – estimated glomerular filtration rate; *for corresponding body length.*

In our study, we have measured the renal function by calculating estimated GFR from serum creatinine levels using modified Schwartz formula. No previous study has evaluated the renal function at 12 to 18 months of corrected age or during infancy among preterm infants. Similar to our study, a study by Rodriguez-Soriano, *et al*. [12] reported significantly reduced GFR in preterm children compared to term controls. Other studies did not find any difference in renal function in terms of GFR in preterm infants compared to term infants in childhood [13-15]. Some authors have evaluated renal function using Cystatin c levels and have found that extremely low birthweight infants have higher levels when compared to term infants at a mean chronological age of 6.7 years, and ages 7 - 11 years, respectively [16,17].

Evaluation of both renal growth and function, and availability of renal data in 70% of infants approached for the study are the main strengths of this study. Cross-sectional design and estimation of renal function by creatinine levels renal growth only by renal length (unlike renal volume), and lack of data on blood pressures are the main limitations.

Preterm infants at 12 to 18 months of corrected age have reduced renal growth and lower kidney function. Compared with AGA preterm infants, SGA preterm infants are at an increased risk for impaired renal function and poor renal growth. All preterm infants and more so the SGA preterm infants should be tracked for development of chronic kidney disease in adolescence and adult life.

WHAT THIS STUDY ADDS?

- Preterm infants, especially preterm small-for-gestational age infants, are at an increased risk of poor renal growth and impaired renal function.

Ethical approval: Institutional Ethics Committee of Fernandez Hospital; No. 19/20016 dated June 27, 2016.
Contributors: KVR: concept, study design, data collection, written the manuscript; DP: data collection; DM: performed Renal ultrasound for all children; MS, SM: reviewed the manuscript.
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