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Renal Parenchymal Area Growth Curves for Children aged 0 to 10 months

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Abstract

Purpose—Low renal parenchymal area (RPA), the gross area of the kidney in maximal longitudinal length minus the area of the collecting system, has been associated with increased risk of end stage renal disease during childhood in boys with posterior urethral valves, but normal values do not exist. We aimed to increase the clinical utility of this measure by defining normal RPA values during infancy.

Materials and Methods—In a cross-sectional study of children with antenatally-detected mild unilateral hydronephrosis **evaluated between 2000-2012**, we measured the RPA of normal kidney(s) (**opposite the kidney with mild hydronephrosis**) imaged by ultrasound from birth to 10 months **post-gestational age**. We used the LMS method to construct unilateral, bilateral, and side and sex-stratified normalized centile curves. The z-score and centile of total RPA of 12.4cm²

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at 1-2 weeks post-gestational age, which has been associated with increased risk of kidney failure before 18 years among boys with posterior urethral valves, were determined.

Results—975 normal kidneys of children 0-10 months were used to create RPA centile curves. At the 97th centile for the unilateral and single stratified curves, the estimated margin of error was 4.4-8.8%. For the bilateral and double stratified curves the estimated margin of error at the 97th centile was 6.6-13.2%. Total **RPA** $<12.4\text{cm}^2$ at 1-2 weeks post-gestational age has a z-score of -1.96 and falls at the 3rd percentile.

Conclusions—These normal RPA curves may be used to track kidney growth among infants and identify children at risk for chronic kidney disease progression.

Keywords

congenital anomalies of kidney and urinary tract; ultrasonography; infant

Introduction

Congenital abnormalities of the kidney and urinary tract (CAKUT), including obstructive uropathy and kidney dysplasia, account for 50-60% of chronic kidney disease (CKD) in children and are the most common cause of childhood end stage renal disease (ESRD).¹⁻³ However, in clinical practice, there is remarkable heterogeneity in time to ESRD and need for renal replacement therapy, making long-term outcomes difficult to predict.^{3, 4} There is a need for biomarkers available during the first months of life that identify infants at risk of early CKD progression. Identifying patients at highest risk would help guide therapy for those most likely to benefit from early treatment (e.g. renin-angiotensin blockade) and spare those patients at low risk of progression potential treatment-associated harms.^{2, 5, 6-8} The current convention, to use nadir creatinine at one year of age as a predictor of outcome, leaves a significant period of uncertainty regarding prognosis until this information becomes available.^{9, 10} Furthermore, as glomerular filtration rate normally increases over the first 2 years of life, serum creatinine during the first months is a poor predictor of long-term outcomes.

One biomarker that may identify high-risk patients early in life is renal parenchymal area (RPA). RPA is the gross area of the kidney in maximal longitudinal length minus the area of the collecting system.¹¹ Shortliffe first described RPA as a measurement to assess kidney function in children with vesicoureteral reflux and to monitor kidney growth.^{4, 11-13} RPA “corrects” for hydronephrosis, estimating the functional area of the kidney better than renal length or bipolar thickness, and correlates well with renal volume determined by MRI.^{1, 14} RPA may measure the functional reserve of the kidneys, with smaller areas associated with decreased nephron mass and greater likelihood of CKD progression. Our group recently reported that total (bilateral) RPA $<12.4\text{cm}^2$ on first post-natal ultrasound of boys with posterior urethral valves (PUV) is associated with an increased risk of ESRD before age 18 years.¹⁵ Because it is available immediately after birth, RPA may predict risk of CKD progression in children with CAKUT prior to the appearance of later biomarkers, such as nadir creatinine or proteinuria. However, normal RPA growth curves do not exist, limiting its

clinical utility. Our aim is to increase the utility of RPA in the management of children with CAKUT by providing normal RPA values during infancy.

Methods

Population and Study Design

This was a cross-sectional study designed to define normal RPA in infants. The population was identified by searching the outpatient billing database at the Children's Hospital of Philadelphia (CHOP) for infants evaluated for hydronephrosis before 6 months post-gestational age (PGA) in the Urology clinic from 2000-2012 using ICD-9 codes 591 and 753.1 (hydronephrosis and other obstructive defect of renal pelvis and ureter, respectively).

We excluded children with bilateral hydronephrosis, unilateral hydronephrosis greater than Society of Fetal Urology (SFU) grade 2, chromosomal abnormalities, cardiac disease, glomerular kidney disease, and anatomical abnormalities affecting kidney size such as collecting system duplication and **dysplasia**. The age at ultrasound of children meeting eligibility criteria, but born prematurely (<37 weeks gestational age) was calculated as the number of weeks since birth minus the number of weeks prior to 37 weeks gestational age at which the infant was born.

All renal ultrasound images were reviewed. Data from the contralateral normal kidney in patients with unilateral mild hydronephrosis was used. Data from both kidneys in patients with bilateral normal kidneys on post-natal ultrasound was utilized. Our rationale was that mild hydronephrosis is generally a benign finding that stabilizes or resolves spontaneously in 98% of patients without affecting the growth or function of the affected or contralateral kidney.¹⁶⁻¹⁹ For patients with multiple ultrasounds, each kidney measurement was included as a separate data point, which is consistent with the methods used by the World Health Organization to generate growth curves.²⁰ The CHOP Institutional Review Board approved this study.

Determination of RPA and Collection of Patient Data

We calculated the RPA using a recently described semi-automated method, which increases the speed with which RPA can be measured and has excellent validity compared to manual RPA measurement and low inter- and intra-observer variability (**less than 10%**).²¹

Briefly, the image of the kidney in greatest longitudinal dimension was imported into MatLab. The investigator then selected points around kidney, which the software used to outline the kidney contour.²⁰ The outline was manually adjusted to maximize precision. When a **small amount** of collecting system dilation was visible, points were placed within the collecting system, which the software used to define the collecting system borders.²⁰ RPA was automatically calculated as the gross kidney area minus the collecting system.

Patient data were abstracted through chart review, and included kidney laterality, age at time of ultrasound, sex, race, and gestational age. Data were collected and managed using Research Electronic Data Capture hosted at CHOP.²²

Creation of Standardized RPA Centile Curves and Statistical Analysis

RPA curves were constructed using LMSChartmaker Pro v2.5 and the LMS method described by Cole.²³ The LMS parameters describe the skew (L for lambda; power transformation), the median (M for mu) and the coefficient of variation (S for sigma) for each monthly RPA measurement. This approach uses Box-Cox transformations to remove data skewness at each age interval, allowing for the creation of normalized centile standards for anthropometric data.²⁴ The Centers for Disease Control uses this method for pediatric growth curves.

In determining the margin of error, we assumed that the coefficient of variation for RPA would be 0.05-0.1, higher than the variation previously observed in normal renal length, and that our data would be right skewed and therefore L would be negative, as is true for most anthropomorphic measurements.²⁵ For negative L values, higher centiles have maximal variance. Variance also increases as S increases and sample size (**n**) decreases.^{23, 26} We thus assumed that the maximum variance would exist at the upper age limits, where data were most sparse, and the 97th centile. For this reason, we reported only the margin of error at the 97th centile to provide the most conservative estimate of the accuracy of our curves.²³

Side and sex-specific curves were created by stratifying the original data. A total (bilateral) RPA curve, representing the combined RPA of the left and right kidneys, was also constructed. Since we had more data points for right than left kidneys, we randomly sampled right kidney values within each one-month age strata, matched these to left kidneys by closest age, and summed the RPAs to obtain the total RPA. We defined the age limit for each curve to maintain a margin of error of <15% at the 97th centile, which is a reasonable level of precision for anthropometric data curves.²⁵

Plotting RPA of Children with PUV

Our group previously demonstrated that total RPA <12.4cm² on first post-natal ultrasound is associated with increased risk of ESRD before age 18 years in boys with PUV.¹⁵ In order to demonstrate the clinical applicability of the RPA curves, we plotted this value on the curves and calculated its z-score:²³

$$z = \frac{(RPA/M)^L - 1}{LS}$$

The z-score (standard deviation score) is a normally distributed variable for which the mean equals zero and the standard deviation is one. Z-scores thus can be readily converted to a centile value allowing comparison of an individual to “normals” for a given variable.

Results

Of 1935 patients identified, 610 were eligible for inclusion (**Figure 1**), yielding 1301 data points, each representing a single kidney at a given age. Most data existed for 0-3 months PGA with the number of kidneys decreasing with age. Centile curves were created using data from all eligible kidneys up to 10 months PGA since data at older ages was too sparse

to maintain the desired precision. Descriptive characteristics are summarized in the **Table**. Fewer data points were available for the stratified and total RPA curves; thus, a cut off of 7 months PGA was chosen to maintain precision at the 97th centile.

Figure 2 is the standardized RPA centile curves created from all 975 kidneys. The 9-10 month age stratum had the fewest data points. At this age, the margin of error at the 97th percentile was 4.4-8.8%.^{23, 26} **Figure 3** shows the total RPA curves for ages 0-7 months constructed from the sum of matched left and right kidneys. Although a lower age cutoff was used, fewer data were available, resulting in a maximal error of 6.6-13.2%.²²

Figure 4 demonstrates the RPA centile curves stratified by either side or sex, which have a maximal error of 4.4-8.8% at the 6-7 month age range and 97th centile.²² **Figure 5** shows the curves stratified by both side and sex. For the female left and right and the male left curves there were very few data points in the 6-7 month age range, giving a margin of error of 6.6-13.2% at the 97th centile. The male right kidney curve had more data points with a maximal margin of error of 4.4-8.8%.²²

Finally, we plotted total RPA of 12.4cm² at 1-2 weeks, below which an increased risk of ESRD has been demonstrated in boys with PUV.¹⁵ Using **Figure 3**, 12.4cm² is approximately at the 3rd percentile of normal, with z-scores of -1.82 and -1.96 at 1 and 2 weeks PGA, respectively.

Discussion

These RPA growth curves provide a reference for the functional area of the kidney during infancy. Similar to somatic growth curves, patients' RPA values can be compared to normal values for their age. As demonstrated by the PUV example, if the patient's RPA falls at a low centile, this may indicate lower nephron mass and increased risk of CKD progression. These curves will also facilitate the development of more robust risk prediction models for CKD progression that can incorporate imaging in addition to serum and urine biomarkers.

Shortliffe *et al.* previously constructed a growth chart of RPA for children from birth to 21 years, but this prior study was limited by a smaller sample size (120 patients versus 975 kidneys) and a greater age range (0-21 years versus 0-10 months), and did not normalize RPA values.¹¹ In addition to the increased precision of the RPA curves presented in this study, the LMS method used provides centiles for each age, and normalizes the data and corrects for skewness. Additionally, compared to renal length, RPA is better correlated with renal function and volume, particularly in the setting of hydronephrosis.^{4, 11-14, 25} RPA may therefore be more useful for estimating **children's** risk of CKD progression.

The curves presented here offer distinct advantages that can be applied in diverse clinical settings. The unilateral RPA curves (**Figures 2, 4, and 5**) allow monitoring of individual kidney growth. The overall curves (**Figure 2**) are the most precise as they are derived from the most data. However, the stratified curves, (**Figures 4 and 5**), offer the advantage of being specific to sex and/or kidney side. It is notable that left kidney RPA at a given age is visibly larger than right kidney RPA, supporting the previous finding by Abidari *et al.*²⁸ The differences between the female and male curves are less obvious, with male RPA values

greater than corresponding female values at younger ages and becoming increasingly similar as age approaches seven months. The stratified curves may thus be more useful in tracking growth of an individual kidney since they best reflect the specific growth trajectory of that particular kidney.

The total RPA curves (Figure 3) reflect the combined kidney area and allow overall functional area of the kidney to be assessed and tracked. The predictive value of RPA for CKD progression is likely greatest when considered for both kidneys collectively since the combined area of the kidneys determines overall renal function. These curves are thus most useful in infants with CAKUT at risk for CKD.

Although we used a semi-automated method to measure RPA, radiologists can report RPA or RPA can be calculated manually by measuring the gross kidney area minus the area of the collecting system. This can be easily performed using ImageJ, an open access Java image processing program developed by the National Institutes of Health.²⁷ Additionally, many ultrasounds can determine the renal and collecting system areas during real-time sonography using the planimetry function.¹¹ This decreases the time needed to measure RPA without significantly increasing the study length and allows RPA to be easily assessed and tracked each time follow up imaging is performed.

Our curves should be interpreted with respect to their limitations. First, they were derived from primarily white, male, right kidneys. It is possible that our results may not be generalizable to other patient populations with different characteristics. Second, data from infants born prematurely were included in our study. Although we corrected for gestational age, it is uncertain whether prematurity or low birth weight may change the trajectory of normal renal growth and development. However, only 7.8% of the data points in the overall curves were from children born <37 weeks; therefore the effect of prematurity is likely minimal. Additionally, it is likely that weight would be directly associated with RPA. Hence, the distribution of RPA values at any given age should account for variation in RPA due to differences in weight.

Third, fewer data points were available for the upper age ranges because most children had more imaging studies early in life. Despite the smaller sample size at older ages, our maximum margin of error was estimated to be 8.8% for the overall and single stratified curves and 13.2% for the double stratified and total RPA curves. This value seems high; however, when compared to the variance of standardized growth curves for stature, weight and BMI used commonly in pediatrics this represents a reasonable variance for anthropologic data.²⁶ A larger sample size, particularly at the upper age ranges and extending through the entire period of renal growth would allow for the creation of more accurate centile curves that could be used throughout childhood as opposed to exclusively during infancy.

Finally, ultrasound images used to calculate RPA and create our curves were obtained at a variety of outside institutions as well as our own. Factors such as the experience of the ultrasound technician and probe type and size were variable, which may have created

additional variance that we did not account for. However, this variation should also increase the generalizability of the curves.

Conclusions

This study provides the first age-specific normalized RPA centile curves for infants up to 10 months old. These curves may be used to track kidney growth in infants and identify patients falling off the RPA growth trend early in life, much the same way as length and weight curves are used in general pediatric practice. Additionally, these curves allow for greater applicability of RPA to a broad range of congenital abnormalities and may obviate the need to have specific cut points for each individual disorder. **In combination with our group's previous findings**, total RPA below the 3rd centile is associated with increased risk of ESRD during childhood for boys with PUV.¹⁵ Future studies should determine the marginal improvement of incorporating RPA into risk prediction models for CKD progression.

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Abbreviations

CAKUT	congenital anomalies of kidney and urinary tract
RPA	renal parenchymal area
VUR	vesicoureteral reflux

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Figure 1. Flowchart of subject inclusion

975 kidneys were included in the single kidney normalized RPA centile curves. Subsets of this cohort were used for the creation of the total RPA curves and curves stratified by gender and/or laterality.

Figure 2. Single Kidney normalized centile curves of RPA in children aged 10 months
Curves represent the 3rd, 10th, 25th, 50th, 75th, 90th and 97th centiles respectively. RPA is measured in cm². N=975.

Figure 3. Total RPA normalized centile curves for children aged 7 months
Curves represent the 3rd, 10th, 25th, 50th, 75th, 90th and 97th centiles. RPA is measured in cm². N=308.

Figure 4. Stratified normalized centile curves for single kidney RPA in children aged 7 months stratified by kidney side (A, B) and subject sex (C,D)

Curves represent the 3rd, 10th, 25th, 50th, 75th, 90th and 97th centiles. RPA is measured in cm². A) Left kidneys, n=308; B) Right kidneys, n = 553; C) Female kidneys, n = 321; D) Male kidneys; n = 540.

Figure 5. Sex and side specific normalized centile curves for single kidney RPA in children aged 7 months

Curves represent the 3rd, 10th, 25th, 50th, 75th, 90th and 97th centiles. RPA is measured in cm². A) Female left kidneys, n=122; B) Female right kidneys, n = 199; C) Male left kidneys; n= 186; D) Male right kidneys, n=354.

Table

Demographic characteristics of total cohort.

	N	Percentage
Total Kidneys	975	100
Left	348	35.7
Right	627	64.3
Male	623	63.9
Female	352	36.1
Asian	53	5.4
Black	157	16.1
White	599	61.4
Other/ Not Reported	166	17

Characteristics of all kidneys included in RPA centile curves for children aged 10 months.