



Reference ranges for ultrasound measurements of fetal kidneys in a cohort of low-risk pregnant women

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Abstract

Purpose Alterations in renal dimensions may be an early manifestation of deviation from normality, with possible repercussions beyond intrauterine life. The objective of this study was to establish reference curves for fetal kidney dimensions and volume from 14 to 40 weeks of gestation.

Methods This is a prospective longitudinal study of 115 Brazilian participants in the “*WHO multicentre study for the development of growth standards from fetal life to childhood: the fetal component*”. Pregnant women with clinical and sociodemographic characteristics allowing the full potential fetal growth were followed up from the first trimester until delivery. These women underwent serial sonographic evaluation of fetal kidneys. The longitudinal, anteroposterior and transverse diameters of both fetal kidneys were measured, in addition to calculation of kidney volume. By quantile regression analysis, reference curves of renal measurements related to gestational age were built.

Results Standard normal sonographic values of renal biometry were defined during pregnancy. Reference values for the 10th, 50th and 90th centiles of different fetal kidney measurements (longitudinal, anteroposterior, transverse and volume) from the 14th to the 40th week of gestation were fitted.

Conclusion The reference curves presented should be of the utmost importance for screening and diagnosis of alterations in renal development during the intrauterine period.

Keywords Fetal kidney · Obstetric ultrasound · Prenatal diagnosis · Reference growth curves · Kidney measurement

Introduction

Advances in ultrasonography have made the intrauterine environment much more accessible, enabling a detailed evaluation of the fetal structures and enhancing knowledge of the anatomy, morphology and development of the fetus.

Among the diverse alterations that may be detected by ultrasound, approximately 20% involve the urinary tract [1]. A broader knowledge of the sonographic aspect of the fetal kidney, from a morphologic, structural, echogenic and dimensional perspective is of critical importance for

ensuring the evaluation of kidney development [2]. Deviations from normality may appear or begin as mild dimensional changes. Ultrasonography has a high sensitivity and specificity and is a test used to detect deviations from normal limits [3].

The advantage of knowing the normal pattern of renal growth in the fetus lies not only in the detection of malformations. Many studies have associated kidney length measurements with the correct determination of gestational age in the second and third trimesters [4–10]. Fetal kidney dimensions have also been associated with fetal growth restriction [11–15] and future problems in adult life such as high blood pressure and kidney disease [16]. Furthermore, the normal development of fetal kidneys is essential to the adequate production and maintenance of amniotic fluid [17, 18].

Interest in kidney dimensions began in the 1980s and some reference curves have already been published [19–25]. Nevertheless, there is some divergence between their results. Many were not validated in their ability to determine

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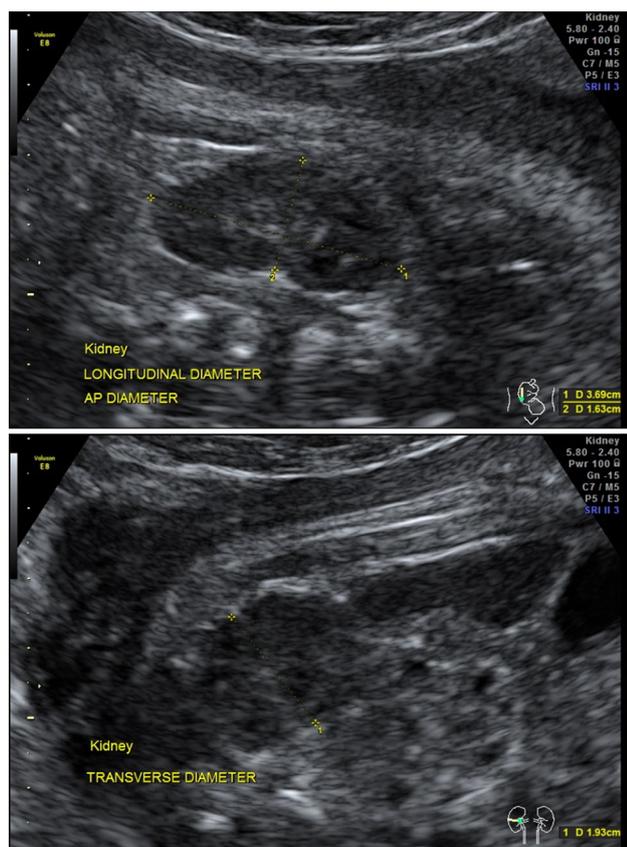


Fig. 1 Ultrasound scan showing the measurements of the diameters of a fetal kidney

gestational age versus crown-rump length. Some were restricted to specific gestational periods and specific populations without ethnic diversity. Others were transversally constructed with values measured with different samples at each gestational age. Some failed to measure the kidney in its three dimensions [23].

The aim of this study is to construct reference curves for sonographic measurements of fetal kidneys related to gestational age in low-risk pregnancies, based on a prospective longitudinal study of pregnant women without any important restrictive clinical, nutritional and social factors.

Methods

This is a complementary analysis of data from the Brazilian center participating in the prospective multicenter study entitled “*WHO multicentre study for the development of growth standards from fetal life to childhood: the fetal component*” [26]. This was a prospective cohort study with low-risk pregnant women receiving follow-up from the first trimester of pregnancy to delivery, in 10 different countries, to systematically obtain fetal anthropometric measurements

throughout pregnancy. Study protocol was published previously [26] and obtained approval from the WHO Research Ethics Review Committee, in addition to approval from the local research ethics committee of each center (in Brazil, Local IRB letter of approval 406/2008). Each woman signed an informed consent form before entering the study. For estimating sample size, the data from Van Vuuren et al. [23] reporting a mean longitudinal diameter at 28 weeks of gestational week of 30.5 mm and a standard deviation of 2.04 mm were used. Assuming a type I error of 5% and a type II error of 20%, the minimum sample size for gestational age was estimated as 33 cases.

The selection of participants involved inclusion and exclusion criteria of the primary study. Pregnant women seen at the ultrasound sector of the Department of Gynecology and Obstetrics of the University of Campinas and prenatal clinics in the city of Campinas were invited to participate in the study. Pregnant women with health, nutritional, environmental and socioeconomic conditions that were considered good and did not interfere with fetal growth were selected. Included in the study were pregnant women aged 18–40 years, with a BMI ranging from 18 to 30 kg/m² (excluding women of low weight or morbid obesity), with singleton pregnancies, who lived close to study location and in altitudes lower than 1500 m, with gestational age according to the date of the last menstrual period between 8 and 12 weeks and 6 days at the time of study entry, confirmed by the CRL (crown-rump length) measurement, and socioeconomic status and level of education that could not interfere in fetal growth. Pregnant women were excluded from the study in case of: current smoking or smoking in the past 6 months; use of medications (including fertilization treatment); current or previous evidence of clinical pathological conditions; current or previous evidence of gynecologic and obstetric conditions; history of repeated abortions, preterm childbirth (<37 weeks) or low birthweight (<2500 g); and the presence of major fetal malformations in the current pregnancy.

Of the 157 pregnant women participating in the multicenter study in the Brazilian center, 115 women also underwent complementary assessment by sonographic measurements of the fetal kidneys. Examinations were performed in the ultrasound sector of the Women’s Hospital of the University of Campinas from February 2013 to August 2014 by three selected sonographers, trained and certified for the multicenter study. The first ultrasound test occurred from 8 to 12 weeks and 6 days. Gestational age was confirmed by measurement of the crown-rump length. Subsequent visits were scheduled at 4-week intervals, corresponding to assessments at 14, 18, 24, 28, 32, 36 and 40 weeks. Fetal kidney measurements were obtained from study participants at clinical and sonographic follow-ups.

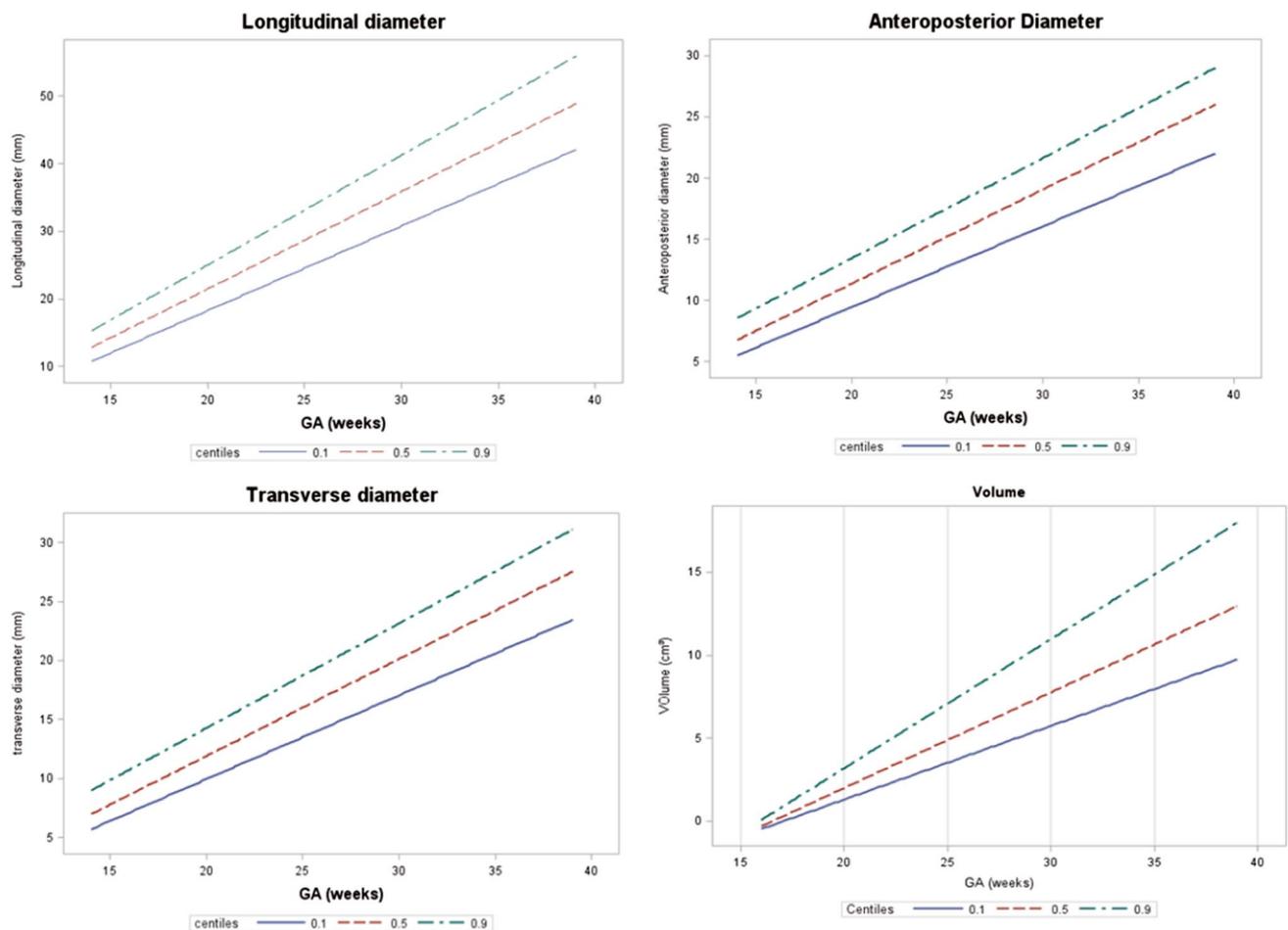


Fig. 2 Curve of values for the fitted 10th, 50th and 90th centiles of longitudinal, anteroposterior and transverse diameters and volume of fetal kidneys according to gestational age

Only one machine was used to perform sonographic measurements (Voluson Expert E8, General Electric, Kretz Ultrasound, Zipf, Austria), which was the same used in all centers participating in the major study. A multifrequency (6–12 MHz) endovaginal transducer was used in the first exam (8 s–12s6d) and a multifrequency (4–8 MHz) convex volume abdominal transducer was used in the remaining exams. Both kidneys (right and left) were measured in their three diameters (longitudinal, anteroposterior and transverse) and their volumes were calculated by the formula for ellipsoid structures $Vol = (\pi/6) \times L \times AP \times T$, where L , AP and T are the measures of the longitudinal, anteroposterior and transverse diameters, respectively.

Longitudinal and anteroposterior kidney diameters were obtained in the fetal sagittal plane, in which the diameters were considered to be maximum and perpendicular to each other. Perpendicular to this plane, in the transverse plane of the fetus, at the site of the renal pelvis, the transverse kidney diameter was obtained. In all measurements, magnification

of the image was appropriate and calipers were placed from the outer border to the outer border of structures (Fig. 1).

Initially, the percentage distribution of sociodemographic and gestational characteristics was described for the sample of women. To describe kidney measurements according to the topographic location of the organ and fetal gender, tables of descriptive statistics of these measurements were constructed with the mean, median, standard deviation, and minimal and maximal values. To compare measurements between the right and left kidneys, the ANOVA test for repeated measures was used. Data were rank transformed due to a not normal distribution of measurements. To compare the mean measurements between male and female fetuses, the Mann–Whitney test was used. The volume of each kidney was estimated by the formula previously specified. This measure was normalized later, using a Box-Cox transformation [27].

Using quantile regression analysis, reference curves of kidney measurements related to gestational age were fitted with their respective 10th, 50th and 90th centiles, using

Table 1 Characteristics of women ($n = 115$)

	<i>N</i>	%
Maternal age (years)		
18–24	17	14.8
25–29	31	26.9
30–34	47	40.9
≥ 35	20	17.4
BMI (Kg/m ²)		
Normal (18–24.99)	74	64.4
Overweight (25–29.99)	41	35.6
Ethnicity		
Caucasian	111	96.5
African	4	3.5
Parity		
Nulliparous	72	62.6
Multiparous	43	37.4
GA at birth (weeks)		
< 37	5	4.3
37–38 weeks 6 days	41	35.7
39–40 weeks 6 days	63	54.8
≥ 41	6	5.2
Fetal gender		
Male	59	51.3
Female	56	48.7
Birthweight (g)		
< 2500	4	3.5
2500–3999	104	90.4
≥ 4000	7	6.1
Apgar score at 5 min		
< 7	1	0.9
≥ 7	114	99.1
Total	115	100%

equations derived from original measurements for each percentile at each gestational age (Fig. 2). The significance level adopted for this study was 5%.

Results

Sample characteristics of 115 low-risk pregnant women participating in this study are shown in Table 1. The vast majority of pregnant women included were white (96.5%) and nulliparous (62.6%) and about 40% were aged between 30 and 34 years. Slightly more than a third (36%) of the women were overweight at the beginning of the study. The majority of births were full term (96%). A low proportion of newborn infants had a 5-min Apgar score lower than 7 (0.9%) and low birthweight index (< 2,500 g) of 3.5%.

During the follow-up period of these 115 pregnant women, a total of 736 kidneys were measured (368 right kidneys; 368 left kidneys). Comparing kidney measurements, no significant differences were observed between the right and left kidneys. In a comparison of mean measurements between male and female fetal kidneys, there were also no significant differences (Table 2).

Figure 2 shows reference curves built by quantile regression analyses for each measurement related to gestational age. Using equations generated from measurements (Box 1), the 10th, 50th and 90th centiles were fitted for each gestational age with estimated values that are shown in Table 3.

Box 1 Equations for fitting the 10th, 50th and 90th centiles for each fetal kidney measurement according to gestational age

Longitudinal diameter

P10: – 6.7886 + 1.2523 (GA)	P50: – 7.3808 + 1.4423 (GA)	P90: – 7.4750 + 1.6250 (GA)
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Anteroposterior diameter

P10: – 3.7400 + 0.6600 (GA)	P50: – 4.0300 + 0.7700 (GA)	P90: – 2.9036 + 0.8175 (GA)
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Transverse diameter

P10: – 4.2333 + 0.7095 (GA)	P50: – 4.5143 + 0.8214 (GA)	P90: – 3.3906 + 0.8844 (GA)
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Volume

P10: – 7.5804 + 0.4440 (GA)	P50: – 9.5355 + 0.5765 (GA)	P90: – 12.3775 + 0.7781 (GA)
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Discussion

The current study enabled the construction of reference curves for fetal kidney measurements by ultrasonography throughout pregnancy in a sample of low-risk Brazilian pregnant women. Furthermore, dimensions of the left and right fetal kidneys and kidney dimensions between female and male newborn infants do not show any significant differences. The great advantage of this study is that it is complementary to a comprehensive prospective longitudinal study, with a rigorously selected population that received follow-up care in a standardized manner. Any health conditions or nutritional/socioeconomic factors that might interfere in fetal growth were excluded. Owing to the prospective and longitudinal nature of the study, the measurements obtained are useful not only to compare kidney size at a certain gestational age, but also to evaluate and determine kidney growth and development throughout pregnancy.

Many previously published studies only analyzed kidney length and used this measure as a tool to calculate gestational

Table 2 Measurements of longitudinal, anteroposterior and transverse diameters and volume of fetal kidneys according to the side and gender of the fetus

Measurements ^a	Side	<i>N</i>	Mean	Median	SD	Min	Max	<i>P</i> value*
Longitudinal	R	368	27.26	28.50	12.15	3.00	53.30	0.4400
Longitudinal	L	368	27.43	28.30	12.09	2.70	52.30	
Anteroposterior	R	368	14.40	14.45	6.53	1.40	30.60	0.7966
Anteroposterior	L	367	14.55	14.90	6.59	1.70	29.50	
Transverse	R	367	15.35	15.40	7.07	1.40	35.40	0.8910
Transverse	L	368	15.37	15.40	7.15	1.50	36.20	
Volume	R	367	4971.90	3344.90	4902.10	3.08	27,570	0.6401
Volume	L	367	5025.20	3235.10	4981.30	3.60	21,282	
Measurements ^b	Gender	<i>n</i>	Mean	Median	SD	Min	Max	<i>P</i> value*
Longitudinal	M	190	28.43	29.45	12.52	2.85	51.65	0.0695
Longitudinal	F	179	26.19	27.50	11.34	4.90	47.35	
Anteroposterior	M	190	15.07	15.88	6.62	1.55	27.85	0.1130
Anteroposterior	F	179	13.97	13.95	6.24	2.45	26.40	
Transverse	M	190	15.93	16.90	7.28	1.45	35.80	0.1224
Transverse	F	179	14.75	14.80	6.66	2.55	27.10	
Volume	M	190	5568.80	4069.50	5314.20	3.34	21,795	0.1010
Volume	F	179	4401.60	2908.20	4242.10	21.00	16,081	

F female, *L* left, *M* male, *R* right

*Mann–Whitney test

^aANOVA for repeated measurements

^bMean of right/left side measurements

age [4–10, 22]. This study assessed fetal kidneys in three dimensions (longitudinal, anteroposterior and transverse), in addition to calculating kidney volume. Knowing that in some situations, such as intrauterine fetal growth restriction, only some renal measurements are likely to suffer alterations [11]. It becomes relevant to assess the three dimensions of the fetal kidney.

Some studies have evaluated renal measurements and calculated only the mean and standard deviation for each gestational age [4–12, 22]. The current study was concerned with the estimation of the 10th, 50th and 90th centiles for each measure and each gestational age. Measurements were stratified into percentiles, allowing for a much more detailed comparative analysis. Stratification also enables the examiner to assess growth progression of a certain measure in serial exams performed at different gestational ages. Furthermore, in practice, there may be a role for the 10th and 90th centiles that may enable cutoff points to become available for suspected diagnoses of abnormality.

Knowing that fetal kidneys are best visualized sonographically starting at 12 weeks and that many pathological conditions may manifest early with alterations in kidney dimensions [3]. We considered it important to build a curve that encompassed virtually the entire period of fetal growth and development. Some previous publications were limited

to specific periods and did not address early or full-term gestational ages, restricting the applicability of those curves. This potential limitation is related to a diagnosis of opportunity, i.e., alterations that may be detected at any gestational phase because they may also appear at distinct time periods of fetal evolution.

The confirmation of similarity between the right and left fetal sides and between male and female fetuses demonstrates that there is no need for curve customization and specific values for each fetal side or gender. The results of other studies are in agreement with this similarity between sides and gender [4, 7, 22, 23, 25].

For this study, a possible limitation was the lack of evaluation of intra- and inter-observer variabilities of fetal kidney measurements. The reason was fundamentally ethical to avoid a prolonged evaluation period by ultrasound. This period was considerably elevated due to all the other measurements that were usually taken for the major study. However, in a similar study where these variabilities were tested, it was demonstrated that fetal kidneys can be measured accurately, with a high level of intra- and inter-observer agreement, ensuring reproducibility of the method [23]. It was also not possible to measure every fetal kidney in all women during all gestational intervals. Nevertheless, a curve could be built.

Table 3 Fitted values for the 10th, 50th and 90th centiles of kidney longitudinal diameter, anteroposterior diameter, transverse diameter and volume from 14 to 40 weeks of gestation (mm and cm³)

Longitudinal diameter (mm)				Anteroposterior diameter (mm)				Transverse diameter (mm)				Volume (cm ³)				N*
Centiles				Centiles				Centiles				Centiles				
GA	10th	50th	90th	GA	10th	50th	90th	GA	10th	50th	90th	GA	10th	50th	90th	
14	10.74	12.81	15.28	14	5.50	6.75	8.55	14	5.70	6.99	8.99	14				66
15	12.00	14.25	16.90	15	6.16	7.52	9.36	15	6.41	7.81	9.88	15				–
16	13.25	15.70	18.53	16	6.82	8.29	10.18	16	7.12	8.63	10.76	16				6
17	14.50	17.14	20.15	17	7.48	9.06	11.00	17	7.83	9.45	11.64	17	0.03	0.27	0.85	38
18	15.75	18.58	21.78	18	8.14	9.83	11.82	18	8.54	10.27	12.53	18	0.41	0.84	1.63	80
19	17.01	20.02	23.40	19	8.80	10.60	12.64	19	9.25	11.09	13.41	19	0.86	1.42	2.41	–
20	18.26	21.47	25.03	20	9.46	11.37	13.45	20	9.96	11.91	14.30	20	1.30	1.99	3.18	–
21	19.51	22.91	26.65	21	10.12	12.14	14.27	21	10.67	12.74	15.18	21	1.74	2.57	3.96	14
22	20.76	24.35	28.28	22	10.78	12.91	15.09	22	11.38	13.56	16.07	22	2.19	3.15	4.74	52
23	22.01	25.79	29.90	23	11.44	13.68	15.91	23	12.09	14.38	16.95	23	2.63	3.72	5.52	68
24	23.27	27.23	31.53	24	12.10	14.45	16.73	24	12.79	15.20	17.84	24	3.08	4.30	6.30	20
25	24.52	28.68	33.15	25	12.76	15.22	17.54	25	13.50	16.02	18.72	25	3.52	4.88	7.08	–
26	25.77	30.12	34.78	26	13.42	15.99	18.36	26	14.21	16.84	19.60	26	3.96	5.45	7.85	–
27	27.02	31.56	36.40	27	14.08	16.76	19.18	27	14.92	17.66	20.49	27	4.41	6.03	8.63	66
28	28.28	33.00	38.03	28	14.74	17.53	20.00	28	15.63	18.48	21.37	28	4.85	6.61	9.41	32
29	29.53	34.45	39.65	29	15.40	18.30	20.82	29	16.34	19.31	22.26	29	5.30	7.18	10.19	–
30	30.78	35.89	41.28	30	16.06	19.07	21.63	30	17.05	20.13	23.14	30	5.74	7.76	10.97	–
31	32.03	37.33	42.90	31	16.72	19.84	22.45	31	17.76	20.95	24.03	31	6.18	8.34	11.74	72
32	33.29	38.77	44.53	32	17.38	20.61	23.27	32	18.47	21.77	24.91	32	6.63	8.91	12.52	48
33	34.54	40.22	46.15	33	18.04	21.38	24.09	33	19.18	22.59	25.79	33	7.07	9.49	13.30	–
34	35.79	41.66	47.78	34	18.70	22.15	24.91	34	19.89	23.41	26.68	34	7.52	10.07	14.08	2
35	37.04	43.10	49.40	35	19.36	22.92	25.72	35	20.60	24.23	27.56	35	7.96	10.64	14.86	38
36	38.29	44.54	51.03	36	20.02	23.69	26.54	36	21.31	25.06	28.45	36	8.40	11.22	15.63	40
37	39.55	45.98	52.65	37	20.68	24.46	27.36	37	22.02	25.88	29.33	37	8.85	11.80	16.41	–
38	40.80	47.43	54.28	38	21.34	25.23	28.18	38	22.73	26.70	30.22	38	9.29	12.37	17.19	2
39	42.05	48.87	55.90	39	22.00	26.00	28.99	39	23.44	27.52	31.10	39	9.774	12.95	17.97	42
40	43.30	50.31	57.53	40	22.66	26.77	29.81	40	24.15	28.34	31.99	40	10.18	13.52	18.75	–

*The ultrasound assessments were performed at intervals of approximately 4–5 weeks and the values for all gestational weeks were estimated with equations generated by quantile regression analysis

Although the amount of measurements was statistically sufficient to construct reference values, it is possible that a still larger number of measurements available for each gestational age could have strengthened the findings, narrowing some variations within the same gestational age. The study was conducted in a sample of low-risk Brazilian women and it has no intention of being representative of all countries. Having a curve in this type of population without fetal growth restrictions is beneficial, since it allows the demonstration of a normality curve that would represent full fetal development potential achieved in a certain population.

Similar multicountry curves are still not available. Therefore, we believe that these curves may and should be used at a national level to monitor the development and growth of fetal kidneys.

Conclusion

By constructing curves of fetal kidney measurements, it was possible to determine standard kidney normality during pregnancy. Values for the 10th, 50th and 90th centiles of different measurements of fetal kidneys (longitudinal, anteroposterior, transverse and volume) were fitted from 14 to 40 weeks of gestation.

Knowledge of this standard and the use of these values are of paramount importance for assessment of normal kidney growth and development in fetal life and its possible alterations, potentially contributing to early diagnosis of kidney abnormalities.

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Authors contributions RMB protocol/project development, data collection or management, data analysis, Manuscript writing/editing; RTS data analysis, Manuscript writing/editing; CS data collection or management, manuscript writing/editing; KCA protocol/project development, data collection or management, Manuscript writing/editing; CMA data collection or management; AGB data collection or management; PFO data analysis, manuscript writing/editing; JGC Protocol/project development, data analysis, manuscript writing/editing

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Compliance with ethical standards

Conflict of interest The authors declare they have no conflicts of interest at all.

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