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Fetal Renal Volume and Fetal Doppler in Normal and Growth Restricted Fetuses: Is there a Correlation?

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Abstract

Objective: To evaluate if umbilical, middle cerebral and fetal renal artery Doppler could affect fetal kidney volume in healthy and growth restricted fetuses after 26 weeks of gestation.

Design: A prospective cross sectional study.

Setting: Obstetrics& Gynecology department, Zagazig University, Egypt.

Sample: One hundred ten pregnant women, 77 with normal fetal growth parameter, and 43 with IUGR fetuses.

Methods: Fetal renal volume, combined and relative kidney volume were measured using 2-dimensional ultrasound. Umbilical, middle cerebral artery and fetal renal artery Doppler indices were examined.

Main outcome measures: Correlation of Doppler parameter to fetal kidney volume, and association of fetal biometric indices to combined fetal kidney volume.

Results: Combined and relative fetal kidney volume was significantly reduced in growth restricted fetuses than in normally grown fetuses 29% (95% CI, 18%-37%), for the former and 18% (95% CI, 3%-22) for the latter. All fetal biometric indices were positively associated with combined kidney volume. The largest effects were found for estimated fetal weight and abdominal circumference after adjustment for gestational age. No correlation exists between umbilical or middle cerebral artery Doppler and fetal renal volume. A significant negative correlation was found between fetal renal artery pulsatility index and fetal renal volume after adjustment for abdominal circumference.

Conclusion: Increased fetal renal artery pulsatility index in growth restricted fetuses is negatively correlated with fetal kidney volume with resultant decreased renal perfusion and impaired nephrogensis.

Keywords: Fetal kidney volume; Fetal renal artery doppler; Intrauterine growth restriction

Introduction

Human fetal kidney development passes through a series of continuous and dependent changes to reach both morphological and functional maturity. The final number of nephron, on average 1 million per kidney, is defined at birth, in term newborn. Several factors can modulate nephrogensis including maternal malnutrition, maternal hyperglycemia, Intrauterine Growth Restriction (IUGR), vitamin A deficiency, and fetal exposure to drugs [1].

Human studies showed a lower kidney weight with a reduced number of nephrons in low birth weight infants and growth restricted fetuses at birth [2,3]. *In vivo* studies of kidney size in human fetuses of known gestational age have shown that intrauterine growth restriction is accompanied by decreased kidney volume compared to fetuses with appropriate weight for gestational age [4,5].

As fetal kidney weight cannot be measured in utero. Renal volume measured by ultrasound is a valid substitute [6].

In response to general fetal malnutrition there is a preferential fetal blood flow to the brain and heart, depriving other organs, including the kidneys, from oxygen and nutrients [7].

Under physiological conditions the fetal renal blood flow represents 2-3% of the cardiac output because of the very high resistance in the human fetal renal artery [7]. During the third trimester of pregnancy, fetal renal arterial resistance decreases moderately, with increase in the End-Diastolic Velocity (EDV) and mean velocity and only minor changes seen in the Peak Systolic Velocity (PSV) possibly related to the increased blood flow of the renal circulation. During hypoxemia, the renal blood flow fell by 25–50% as compared to the baseline values,

but the exact mechanism of this reduction has not been elucidated [7]. A direct relationship has been reported between hypoxia and the renal artery pulsatility index (e.g., resistance) [8].

The aim of this study was to evaluate if the umbilical, middle cerebral or fetal renal artery Doppler parameter could affect fetal kidney volume in normally grown and growth restricted fetuses after 26 weeks of gestation.

Methods

This prospective, cross-sectional study was conducted from March 2009 to April 2010. All women attending the antenatal care clinic of Obstetrics and Gynecology Department, Zagazig University Hospital were invited to participate after taking an informed consent. Inclusion criterions were singleton pregnancy more than 26 weeks of gestation. Patients with multiple gestations, diabetes, preeclampsia, or any medical disorder complicating pregnancy were excluded. Fetuses with structural anomalies, unclear adrenal or renal borders, abnormal renal morphology or poorly visualized kidneys due to gross maternal obesity were also excluded. One hundred ten women were included, 76 were from uncomplicated pregnancies and 43 with intrauterine growth

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restriction (IUGR). The study was approved by the local hospital ethics committee.

Gestational age was based on the first day of the last normal menstrual period and confirmed by either first or early second-trimester ultrasound scan. Fetal biometry including head circumference, abdominal circumference, and femur length was measured. Estimated fetal weight was calculated using the formula by Hadlock using head circumference, abdominal circumference, and femur length [9]. IUGR is diagnosed when the Estimated Fetal Weight (EFW) falls below the 10th percentile for gestational age [10].

The maximum longitudinal kidney length was measured in a sagittal plane by placing the calipers on the outer edges of the caudal and cranial side. Antero-posterior and transverse kidney diameter were measured perpendicular to each other, outer to outer, in an axial plane as described previously [11]. The cross-sectional area in which the kidney appeared symmetrically round and at its maximum width was used. The images were sufficiently magnified to ensure optimal measurements. Kidney volume was calculated using the approximation of an ellipsoid: Volume = length x width x thickness x 0.523 [12]. The left and right kidney was measured. Combined kidney volume in cm^3 is calculated as the sum of left and right kidney volume [2]. Relative kidney volume was also calculated as the ratio of fetal kidney volume/estimated fetal weigh [13]. All ultrasound examinations were performed using (GE Healthcare, Voluson 730 pro V, Austria) Medical System, equipped with a 3.75-MHz abdominal transducer. One qualified examiner performed all ultrasonographic examinations to avoid inter observer errors.

Umbilical artery Doppler flow velocity waveform was assessed as a proxy of placental function .Umbilical artery Pulsatility Index (PI) was measured in a free-floating loop of the umbilical cord. The middle cerebral artery Doppler was performed with color Doppler visualization of the circle of Willis in the fetal brain and the flow velocity wave forms were obtained in the proximal part of the middle cerebral artery. A reduction in middle cerebral artery (PI) is an indicator of 'brain sparing effect' due to fetal redistribution [14].

For fetal renal artery examination an axial view of the fetus was obtained at the level of the kidneys. The Doppler gate was placed at the renal hilus, keeping the Doppler sample within the lumen of the vessel so that the maximum signal from the renal artery was obtained. The renal artery Doppler waveform has a characteristically high peak forwarded velocity and low but continuous forwarded flow during diastole that is easily differentiated from the abdominal aorta. There is no significant difference between the two sides of the renal artery [15], thus fetal renal arterial blood flow was determined on only one side. Angle of Insonation was kept at < 30°, as Doppler angle >30 could

significantly affect the Doppler shift and thus the Doppler waveform signal. Low wall filter 50 Hz was used, as high pass filter may obscure low level of end diastolic flow. Measurements were made during the absence of fetal breathing movements, since fetal breathing movements are known to exert marked effects on blood flow. For peak velocities (V max) measurement PI-values were calculated on-line by the built-in computer software of the ultrasound equipment by tracing the outer envelope of the Flow velocity Waveforms (FVW). The outline of at least two FVWs was measured from a sample of at least five identical FVWs obtained. The most uniform frozen waveform was used for calculation of the resistance index, defined as the difference between the peak systolic and end-diastolic frequency shifts divided by the peak systolic frequency shift [16].

Flow measurements were interpreted with respect to the normal ranges taken from literature data on the umbilical artery and the renal artery [8,15].

Data analysis

All statistical analyses were performed using the Statistical Package of Social Sciences version 11.0 for Windows (SPSS Inc., Chicago, IL, USA).

Data are expressed as mean ± SD (Standard Deviation). The associations of fetal biometric indices (head circumference, abdominal circumference, and femur length) with combined kidney volume were assessed using gestational age adjusted (Standard Deviation Score) SDSs multiple linear regression models. Furthermore, the effect of gestational age-adjusted abdominal circumference on relative kidney volume (kidney volume/estimated fetal weight) was examined.\

Results

The mean gestational ± SD was 20.3 ± 5.2 weeks. Table 1 showed no significant difference in right kidney length between normally grown fetuses and those with IUGR, however there was a significant width difference 0.42 mm, depth difference 0.30 mm, and volume difference 0.29 cm^3 between the two groups. Also, combined and relative kidney volume was significantly increased in group 1 than in group2. Regarding left kidney measurements Table 2 showed no significant differences in kidney length between the two groups, however there was a significant width difference 0.33 mm, depth difference 0.34 mm, and volume difference 0.25 cm^3 between normally grown fetuses and fetuses with IUGR.

The 5th and 95th centiles of the combined kidney volume were 13.7 cm^3 and 21.8 cm^3 respectively in normally grown fetuses. For IUGR fetuses these figures were 10.1 cm^3 and 16.5 cm^3 respectively as shown in Table 3.

Right kidney parameter	Gestational age (Mean ± SD)	Group 1 Normal fetuses (N=76)	Group2 IUGR fetuses (N=33)
Length (mm)		38.9 ± 3.9	38.2 (3.5)
Width (mm)	29.3 ± 5.4	22.3 ± 2.9	17.1 ± 2.7*
Depth (mm)		21.6 ± 2.8	17.6 ± 3.4*
Volume (cm^3)		11.2 ± 3.0	8.3 ± 4.3
Combined kidney volume (cm^3)		21.6 ± 4.9	15.2 ± 5.0**
Relative kidney volume (cm^3)		4.2 ± 1.3	2.9 ± 2.04**

Data are expressed as mean ± SD unless otherwise indicated, IUGR: intrauterine growth restriction
*P< 0.05, **P< 0.001

Table 1: Right fetal kidney measurements in normal and IUGR fetuses after 25 weeks of gestation.

The Spearman rho correlation between the right kidney and gestational age was 0.93. For the left kidney the figure was 0.90. The results of $\chi2$ analyses of the right/left kidney and gestational age indicated a statistically significant and strong association between right/left kidney and gestational age. ($\chi2$ = 218.37, p = 0.000, Cramer's V = 0.726). The regression equation for the fetal kidney volume (y) according to the Fetal renal artery blood flow resistance expresses as Pulsatility Index PI (x) was: y = + 0.0602 −0.0028 x. A significant correlation was found between Fetal renal artery PI and the fetal kidney volume (r = 0.74, P < 0.05).

Table 4 presents the associations of fetal biometric indices with combined kidney volume after 26 weeks of gestation. All fetal biometric indices were positively associated with combined kidney volume. Estimated fetal weight and abdominal circumference showed the largest effects on combined kidney volume as combined kidney volume increased 1.77 cm^3 and 1.76 cm^3 for each Standard Deviation Score (SDS) increase in estimated fetal weight and abdominal circumference, respectively. Also, combined kidney volume was negatively associated with renal artery PI.

Table 5 showed Doppler parameters in the two studied groups. Umbilical and middle cerebral artery PI showed no significant differences between normally grown fetuses and those with IUGR. On the other hand, renal artery pulsatility index was significantly elevated in group 2 than in group1 P<0.001.

Left kidney parameter	Gestational age (Mean ± SD)	Group 1 Normal fetuses (N=76)	Group2 IUGR fetuses (N=33)
Length (mm)	29.3 ± 5.4	38.1 ± 4.4	37.8 ± 4.2)
Width (mm)		22.6 ± 3.6	18.3 ± 1.8*
Depth (mm)		23.1 ± 2.4	17.8 ± 3.1*
Volume (cm³)		10.4 ± 3.3	7.9 ± 5.6*
Combined kidney volume (cm³)		21.6 ± 4.9	15.2 ± 5.0**
Relative kidney volume (cm³)		3.8 ± 1.6	2.3 ± 1.3**

*P< 0.05, **P< 0.001

Table 2: Left fetal kidney measurements in normal and IUGR fetuses after 25 weeks of gestation.

Gestational Age(weeks))	Number of patients	5th centile		Mean		95th centile	
		Normal Fetuses	IUGR	Normal fetuses	IUGR	Normal fetuses	IUGR
26	8	12.0 ± .98	8.97 ± .79	11.98 ± .13	6.1 ± .34	20.5 ± .51	15.2 ± .61
27	6	12.6 ± .19	9.2 ± .37	12.0 ± 46	74 ± .00	21.2 ± .97	15.9 ± .80
28	10	13.7 ± .46	10.1 ± .60	12.8 ± 87	7.6 ± 56	21.8 ± 52	16.5 ± 24
29	10	14.7 ± .81	10.5 ± 11	13.1 ± .35	7.9 ± .55	22.4 ± 16	16.9 ± .60
30	5	15.1 ± 23	11.7 ± .40	13.4 ± .92	10.1 ± 85	23.8 ± 89	17.0 ± 91
31	4	15.7 ± 74	11.9 ± 16	13.9 ± 58	114 ± .78	24.7 ± 72	17.2 ± 70
32	6	16.3 ± 33	12.6 ± 69	14.6 ± .34	12.8 ± 74	25.5 ± .65	18.7 ± .55
33	7	**17**.9 ± .01	13.0 ± 34	15.1 ± 19	12.8 ± 54	26.7 ± 70	19.3 ± .64
34	8	18.2 ± 79	13.8 ± 59	15.6 ± 16	13.3 ± .69	27.3 ± 87	20.2 ± 72
35	6	19.8 ± .68	14.4 ± .69	15.8 ± 23	13.5 ± 11	27.6 ± .15	21.4 ± .45
36	9	205 ± 67	14.9 ± .79	16.8 ± 43	139 ± 43	28.4 ± 57	21.7 ± 67
37	8	21.8 ± .77	16.2 ± 37	17.2 ± 75	14.6 ± .75	28.7 ± .13	23.2 ± 67
38	10	22.1 ± 00	16.9 ± 40	18.3 ± 20	14.8 ± 60	29.8 ± 84	24.1 ± 91
39	9	23.3 ± 65	17.0 ± 95	18.8 ± .96	14.5 ± 19	30.6 ± 24	26.8 ± .33
40	5	24.2 ± 15	18.6 ± 75	19.6 ± .46	15.5 ± 11	32.16 ± 14	27.5 ± 59

Table 3: Normal range (mean, 5th and 95th centile) for combined fetal kidney volume in cm³ relative to gestational age (weeks).

Parameter	Difference in combined kidney volume (cm³) (95% CI)	
	Normal fetuses	IUGR fetuses
Fetal biometric indices		
Head circumference (SDS)	0.63 (0.7, 0.98)	0.91 (0.57, 1.23)*
Abdominal circumference (SDS)	1.06 (0.91, 1.56)	1.76 (1.47, 2.05)*
Femur length (SDS)	1.15 (1, 1.67)	1.03 (0.71, 1.35)*
head circumference/ abdominal circumference (SDS	0.78 (0.34, 1.67)	1.71 (1.34, 2.09)*
Estimated fetal weight (SDS)	0.71 (0.12, 1.68)	1.77 (1.46, 2.08)*
Doppler indices		
Umbilical artery, PI	-3.17 (-5.5, -0.39)	-2.74 (-4.55, -0.92)
Middle cerebral artery (PI)	-0.64 (-0.18, 1.09)	0.46 (-0.41, 1.33)
Renal artery (PI)	0.91 (0.29, 1.11)	0.87 (0.22, 1.51)*
Renal artery V max	-3.04 (-2.87,-1.16)	-2.14 (-355,-0.68)

PI, pulsatility index; V max, peak systolic velocities with time. SDS, standard deviation score. Values are regression coefficients (95% CI) and reflect the difference in kidney volume per unit increase in fetal growth and fetal blood flow characteristic

Table 4: Associations of fetal biometric indices and Doppler indices with combined fetal kidney volume in both groups after 26 weeks of gestation.

Parameter	Group 1 Normal fetuses n=77	Group 2 IUGR fetuses n=33
Umbilical artery, PI	0.66 ± 0.14	0.71 ± 0.05
Middle cerebral artery (PI)	0.81 ± 0.47	074 ± 0.38
Renal artery (PI)	0.79 ± 0.44	1.75 ± 0.76**
Renal artery V max	124 ± 13cm/sec	110 ± 26cm/sec

**P< 0.001 .Values are mean ± SD

Table 5: Doppler parameters in the two studied groups.

Discussion

We performed this cross sectional study after 26 weeks of gestation because the period of maximum kidney growth occurs between 26 and 34 weeks of gestation, and growth restriction in this period most probably affects kidney size and volume considerably [5].

All fetal biometric indices were positively associated with kidney volume in our study. Furthermore, the combined kidney volume in the growth-restricted fetuses was 29% less than that in the group of normally grown fetuses after adjustment for gestational age running in agreement with a previous study [4].

We suggest that asymmetrical fetal growth restriction could reduce kidney volume more than symmetrical growth restriction. This is supported by the positive association for the ratio of abdominal circumference/head circumference and kidney volume

In this study we did not detect any significant differences in kidney length between normal and growth restricted fetuses running in agreement with previous study which showed that the length of the kidney remains largely unchanged in small-for-gestational age fetuses [19]. In addition, the renal length is a poor indicator of the amount of the renal parenchyma than the renal volume.

Using three-dimensional US systems with VOCAL method gives a good agreement with true kidney volumes [20, 21]. However, 3-dimensional US for kidney volume estimation are limited by high cost of the equipment. For this reason, we suggest that two dimensional US, which is more practical and still preferable to the three-dimensional US for measuring the fetal renal size.

Many authors used US to measure fetal or adult kidney volume by applying the ellipsoid formula [3,11,18]. While one study found that 'theoretical kidney volume' was well correlated with the true kidney using the ellipsoid formula [18], others stated that the kidney is not a true ellipsoid and found 24% to 32% underestimation of the fetal renal volume when two dimensional US was used [20,22].

In this study, we did not find any association with umbilical, or middle cerebral artery PI and kidney volume in agreement with a previous study that showed no association between umbilical, and middle cerebral artery PI and kidney volume. However, in their study the authors found cerebro-umbilical ratio to be negatively associated with renal volume [5].

A direct measure of renal blood flow would be renal artery PI. In this study renal artery flow resistance changes appears earlier than change in umbilical arterial flow. Running in agreement with a previous study which showed that the renal artery flow resistance already deviates significantly from the normal range, while that for the umbilical artery is in the normal field [22]. Likewise we showed that adverse blood flow resistance patterns of the renal artery expressed as increased PI was negatively correlated to kidney volume, independent of fetal abdominal circumference at the time of the kidney measurement. This implies that kidney volume did not solely depend on abdominal circumference or overall fetal size but to some extent directly on blood flow redistribution with resultant increased intra renal resistance.

In our study Doppler ultrasonography of the renal artery revealed a significant difference between normal fetuses and fetuses with intrauterine growth retardation. As compared with the normal picture, the renal arterial blood flow velocities showed decreased systolic flow with increased resistant index. This runs in agreement with others who observed that the PI of the fetal renal artery was higher in the growth-restricted fetus than in the normally grown fetus. In addition they found an inverse relationship between PI-values in the fetal renal artery and the fetal arterial pO2 obtained by cordocentesis, and the quantity of amniotic fluid in growth restricted fetuses [15,22,23]. On the other hand another study found no change in PI-values of the fetal renal artery in severely growth restricted fetuses with reduction in renal artery peak systolic velocities with time .Furthermore, they detect a significant correlation between renal artery peak systolic velocity and both pH values in venous cord blood and quantity of amniotic fluid [24].

We concluded that reduction in the percentage of cardiac output directed towards the kidneys in cases of fetal hypoxemia leads to increased fetal renal artery pulsatility index with decreased renal perfusion .This decreased renal perfusion could be responsible for impaired nephrogensis and decreased kidney volume in fetuses with intrauterine growth restriction.

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