

CORRELATION BETWEEN FETAL RENAL VOLUME AND FETAL RENAL DOPPLER IN NORMAL AND GROWTH RESTRICTED FETUSES: AN INITIAL EXPERIENCE

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ABSTRACT: One of the major factors affecting nephrogenesis in utero is intrauterine growth restriction (IUGR). Few studies showed reduced weight of the fetal kidney in IUGR fetuses as compared to normally grown fetuses. Reduced blood flow to the kidneys due to fetal hypoxemia in IUGR foetus leads to increased pulsatility index which is likely to be responsible for impaired nephrogenesis and decreased kidney volume. **AIMS AND OBJECTIVE:** To estimate if fetal renal artery Doppler could affect fetal renal volume in healthy and growth restricted fetuses after 26 weeks of gestation. **STUDY DESIGN AND SETTING:** Cross sectional study carried out in the Department radio diagnosis, Lata Mangeshkar hospital, Nagpur, Maharashtra, India. **MATERIAL AND METHODS:** Total 336 patients, which consisted of 309 normally grown fetuses and 27 intrauterine growth restricted fetuses were included in the study. Fetal renal volume of individual kidney, combined renal volume and relative renal volumes were calculated using 2 dimensional ultrasound for normal and IUGR fetuses. Fetal renal artery parameters particularly renal arterial pulsatility index were calculated for both the groups. Correlation of fetal renal Doppler parameters with renal volume was estimated for respective groups. **RESULTS:** Combined kidney volume was significantly reduced in growth restricted fetuses than normal fetuses i.e. mean combined kidney volume for growth restricted fetuses was 12.6cc and for normal fetuses was 19.29cc. Most of the fetal biometric indices were positively correlated with the combined kidney volume. Increased pulsatility index was seen in growth restricted fetuses i.e. on right side 1.37 ± 0.35 and on left 1.40 ± 0.35 i.e. >1 while for normal fetuses was 0.88 ± 0.08 on either side i.e. <1 . Considerable negative correlation was found between fetal renal artery pulsatility index and renal volume. **CONCLUSION:** Increased fetal renal artery pulsatility index in intrauterine growth restricted fetuses is negatively correlated with renal volume resulting in reduced renal perfusion and impaired nephrogenesis.

KEYWORDS: Intrauterine growth restriction (IUGR), Foetal renal volume, Foetal renal artery Doppler, Pulsatility index.

INTRODUCTION: Human fetal kidney undergoes constant changes throughout the pregnancy to attain final maturity in terms of structural and functional aspect.⁽¹⁾ Approximately one million nephrons are seen on either side at birth in term fetuses.

Many factors both maternal and fetal affect nephrogenesis viz. maternal malnutrition, maternal hyperglycemia, Intrauterine Growth Restriction (IUGR), vitamin A deficiency, and fetal exposure to some drugs.⁽²⁾

Few studies showed reduced weight of the kidney in low birth weight infants and growth restricted fetuses at birth.^(3,4) The studies carried out in human fetuses showed reduced kidney

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volume in intrauterine growth restricted fetuses as compared to normally grown fetuses for that gestational age.^(5,6)

In cases of fetal malnutrition resulting in intrauterine growth restriction more blood flow is directed to the organs like brain and heart depriving other organs like kidney from its nutrition.⁽⁷⁾ Normally kidney receives approximately 2-3% of cardiac output as fetal renal artery shows increased resistance in early trimester.⁽⁷⁾ Towards the term, the resistance in the renal artery falls thus directing more blood towards the kidneys which is reflected by increase in end diastolic velocity and mean velocity. However peak systolic velocity shows only minor changes.⁽¹⁾ In fetal hypoxemia, significant reduction i.e. by approximately 25-50% of baseline values is seen. The exact mechanism of which is unknown.⁽⁷⁾ In these cases, fetal renal Doppler shows increased resistance in the form of raised pulsatility and resistivity index. Thus stating direct relationship between fetal hypoxia and renal artery resistance.⁽⁸⁾

The aim of our study is to estimate whether fetal renal artery Doppler parameter could affect fetal kidney volume in normally grown and growth restricted fetuses after 26 weeks of gestation.

MATERIAL AND METHODS: A cross sectional study was conducted over a period of one year from September 2013 to August 2014 in the department of radiodiagnosis of Lata mangeshkar Hospital, Nagpur, Maharashtra, India. Women attending the antenatal care clinic with pregnancy of more than 26 weeks of gestation referred for ultrasonography were invited to participate after acquiring all the necessary formalities as per pre- conception & pre-natal diagnostic technique act (PCPNDT act).

Women with first or early second trimester ultrasound which had confirmed gestational age were included in the study. Pregnant ladies whose gestational age was not confirmed by previous ultrasound were excluded from the study. Pregnant ladies with multiple gestations, gestational diabetes, preeclampsia and any medical or surgical condition complicating the pregnancy were also excluded from the study. Patients with polyhydramnios and oligohydramnios were excluded from the study. Fetuses with structural anomalies both renal and non-renal, unclear renal margins and poorly visualized kidneys were excluded.

The study was approved by the Institutional ethics committee and all the patients were included after prior written consent explained in their own language.

Total 336 women were included in the study. Out of which 306 had normally grown fetuses and 27 had intrauterine growth restricted fetuses.

Gestational age was calculated from first day of last menstrual period and confirmed by first or early second trimester ultrasound scan. All ultrasound measurements were done on Esaote My Lab 50 ultrasound machine which was registered under PC/PNDT act using 3.5MHZ convex abdominal transducer. Fetal biometric measurements include biparietal diameter, head circumference, abdominal circumference and femur length. Estimated fetal weight was calculated using the formula by Hadlock using head circumference, biparietal diameter, abdominal circumference, and femur length.⁽⁹⁾ IUGR was labeled if estimated fetal weight falls below 10th percentile for particular gestational age.⁽¹⁰⁾

The maximum craniocaudal dimension of the kidney was measured in longitudinal sections of the kidney by keeping the caliper at outer edges. The maximum Antero-posterior and transverse diameters of the kidney were measured perpendicular to each other in transverse plane with keeping the caliper same as for longitudinal dimension.⁽¹¹⁾ The cross-sectional area where kidney appeared round and at its maximum width was used.⁽¹⁾

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Kidney volume was calculated using formula for ellipsoid i.e., Volume=length X width thickness X 0.523.⁽¹²⁾ Right and left kidney volume was calculated individually .Combined kidney volume was calculated by adding right and left kidney volume.⁽³⁾ Relative kidney volume was calculated as ratio of fetal kidney volume/estimated fetal weight.⁽¹³⁾ As fetal kidney weight cannot be measured in utero, so on ultrasound renal volume is considered as equivalent to the weight.⁽¹⁴⁾

Amniotic fluid index is calculated. Only patients with normal amniotic index for gestational age were included.

Fetal renal artery Doppler examination can be done in longitudinal or transverse section. However preferable is transverse section of the kidney. The Doppler gate was placed at renal hilum with Doppler sample within the lumen of the vessel so as to yield maximum Doppler signal from the renal artery.⁽¹⁾ The renal artery waveform is typically high systolic peak with continuous forward diastolic flow. Angle of insonation was kept at 30 degree, as more angle significantly affect Doppler shift and Doppler waveform.⁽¹⁾ Low wall filter was used, so that low level diastolic flow can be well sampled. No significant difference was found in the Doppler parameters of renal arteries so only one renal artery was sampled. Measurements were taken in the absence of fetal breathing movements so as to minimize aliasing.

The outline of minimum of two flow velocity waveforms was measured from the sample of five identical flow velocity waveforms.⁽¹⁾ The renal artery Doppler parameters which were calculated include Peak Systolic Velocity (PSV), End Diastolic Velocity (EDV), Pulsatility Index (PI) and resistivity Index (RI). Out of these parameters, the most sensitive to determine resistance in the renal artery is pulsatility index. Pulsatility index is calculated in the uniform flow velocity waveforms as difference between the peak systolic velocity and end diastolic velocity frequency shift divided by the peak systolic frequency shift.⁽¹⁵⁾

Doppler measurements were interpreted on comparison with the normal ranges taken from the published literature on renal artery.⁽¹⁶⁾

Ethical Aspect: The study was approved from Institutional Ethics Committee. Pregnant ladies were included in the study after acquiring informed written consent from them in a language which they understand best. Patients referred from the Department of obstetrics and Gynecology for ultrasound were subjected to the ultrasonography after acquiring all the necessary formalities as per pre-conception and pre- natal diagnostic technique act (PC PNDT act).

Statistical Method: All statistical analyses were performed using the EPI Info Ver. 6. All the data was stated as mean +/- SD (Standard Deviation). The relationship 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 ⁽¹⁾. Association of fetal renal artery pulsatility index with fetal renal volume for that gestational age was calculated. Also the association of gestational age-adjusted abdominal circumference on relative kidney volume (kidney volume/estimated fetal weight) was assessed.

RESULTS: The mean gestational age+/-SD for normally grown fetuses was 34.15+/-2.86 and for growth restricted fetuses was 36.1week +/- 2.58. Hence both the groups were comparable.

Table 1 shows number of normal and growth restricted fetuses according to gestational age. Maximum numbers of normal fetuses were seen in 36 weeks followed by 35weeks and 32weeks. In growth restricted fetuses maximum number was seen at 37, 38 and 39 weeks i.e. five in each group.

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Gestational Age in weeks	No. of Normal Fetuses	No. of iugr Fetuses
27	5	-
28	15	-
29	5	-
30	7	1
31	17	-
32	39	1
33	29	1
34	34	2
35	44	3
36	46	1
37	37	5
38	23	5
39	5	5
40	3	3

Table 1

Table 2 and 3 show combined kidney volume as per the gestational age in normal and growth restricted fetuses respectively. Both the group showed significant difference in the combined kidney volume with growth restricted fetuses showing significantly lower values as compare to the normally grown fetuses.

Gestational Age wks.	No. of Patients	Mean with sd
27	5	11.1 +/- 1.90
28	15	11.2 +/-2.17
29	5	14 +/- 2.27
30	7	15.75 +/-0.96
31	17	16.4 +/-3
32	39	17.16 +/-2.3
33	29	18.13 +/-1.97
34	34	19.3 +/-2.53
35	44	20.3 +/-2.61
36	46	21.5 +/-3
37	37	22.4+/-2.5
38	23	22.9 +/-2.29
39	5	22.9 +/-2
40	3	22.9 +/-1.6

Table 2

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Gestational Age in Weeks	No	Mean and sd
30	1	11.5
31	0	
32	1	10
33	1	10.5
34	2	10.5 +/- 3.5
35	3	11.8 +/-1.54
36	2	12 +/-0.15
37	4	12.25 +/-2.5
38	4	13.4 +/-1.59
39	6	15.1 +/-2.6
40	3	17.2 +/-0.5

Table 3

The mean combined kidney volume for normal fetuses was 19.29+/-3.9cc i.e. 5th and 95th percentile of combined kidney volume for normally grown fetuses is 11.49cc and 27.09cc respectively. However the mean combined kidney volume for growth restricted fetuses was 12.6+/-2.8cc i.e. 5th and 95th percentile of combined kidney volume for IUGR fetuses were 7cc and 17.8cc respectively.

Figure 1A and 1B show kidney volume in normal fetuses and Fig 2 A and 2B show kidney volume in growth restricted fetuses. There was no significant difference in the length of the kidneys in both the groups on either side, however antero-posterior diameter and transverse diameter showed significant difference. When we compared the combined kidney volume with fetal biometric indices after 26 weeks of gestation strong positive correlation has been found between them.

Relative kidney volume i.e. Ratio of combined kidney volume to estimated fetal weight was significantly less in intrauterine growth restricted fetuses as compared to normal fetuses. The mean relative kidney volume+/-SD for IUGR fetuses was 0.006+/-0.0058 and for normal fetuses was 0.0081+/-0.0015 which was significantly less for IUGR fetuses. Thus postulating that fetal weight has positive correlation with fetal kidney volume.

Table 4 shows renal artery pulsatility index in normally grown and intrauterine growth restricted fetuses. There was significant increase in the renal artery pulsatility index in growth retarded fetuses as compared to the normally grown fetuses reflecting increase in the renal artery resistance.

Study Population n=336	Renal Artery pi +/- 2sd	
	Rt Renal Artery	lt Renal Artery
Normal N= 306	0.87 +/- 0.085	0.87 +/- 0.080
IUGR N=27	1.37 +/-0.35	1.40 +/-0.35

Table 4

Fig. 3A and Fig. 3B show renal artery Doppler in the normal and IUGR fetus.

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Table 5 shows significant correlation between fetal renal artery pulsatility index (PI) and fetal renal volume ($P < 0.001$).

	NORMAL		IUGR		T VALUE	P VALUE
	Mean	Std. Deviation	Mean	Std. Deviation		
GA(LMP)	34.15	2.86	36.85	2.63	-4.73	<0.0001
Renal Volume	9.625	2.09	6.45	1.77	7.65	<0.0001
Renal Doppler	0.88	0.08	1.37	0.359	-19.34	<0.0001

Table 5

Pearson correlation showed moderate association between renal artery volume and renal artery pulsatility index in normal fetuses (Table 6).

Correlations (NORMAL)				
		GA (LMP)	Renal Volume	Renal Doppler
GA(LMP)	Pearson Correlation		0.729**	-0.329**
	Sig. (2-tailed)		0.000	0.000
	N		309	309
Renal Volume	Pearson Correlation	0.729**		-0.191**
	Sig. (2-tailed)	0.000		0.001
	N	309		309
Renal Doppler	Pearson Correlation	-0.329**	-0.191**	
	Sig. (2-tailed)	0.000	0.001	
	N	309	309	

**. Correlation is significant at the 0.01 level (2-tailed).

Table 6

Pearson correlation showed significant association between renal artery volume and renal artery pulsatility index (Table 7).

Correlations(IUGR)				
		GA(LMP)	Renal Volume	Renal Doppler
GA(LMP)	Pearson Correlation		0.429*	-0.003
	Sig. (2-tailed)		0.026	0.987
	N		27	27
Renal Volume	Pearson Correlation	0.429*		-0.437*
	Sig. (2-tailed)	0.026		0.023
	N	27		27
Renal Doppler	Pearson Correlation	-0.003	-0.437*	
	Sig. (2-tailed)	0.987	0.023	
	N	27	27	

*. Correlation is significant at the 0.05 level (2-tailed).

Table 7

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DISCUSSION: Maximum kidney growth occurs between 26 to 34 weeks of gestation and growth restriction by any maternal or fetal factors during this period is likely to affect nephrogenesis and thereby kidney size and volume significantly.⁽⁶⁾ So we included pregnant ladies more than 26 weeks of gestation in our study.

In our study, only those patients whose gestational age was confirmed by first or early second trimester ultrasound were included so as to avoid inter observer variation. And it helped in following up the growth restricted fetuses.

Fetal biometric indices viz. femur length, biparietal diameter, head circumference and abdominal circumference were positively correlated with fetal kidney volume in our study. Combined kidney volume in growth restricted fetuses was approximately 35% less as compare to the normally grown fetuses in our study group in consensus with studies previously published in the literature.⁽⁵⁾

In a study done by Manal Mohamed El Behery et al asymmetrical fetal growth restriction was found to be more responsible for reduction in kidney volume than symmetrical growth restriction.⁽¹⁾ They found positive association for the ratio of abdominal circumference /head circumference and kidney volume. However in our study both symmetrical and asymmetrical IUGR fetuses showed reduction in the renal volume to the same extent.

In our study, no significant difference was seen in the length of both kidneys, however antero-posterior and transverse diameters showed considerable difference which was also noted in the previous studies which mentioned that length of the kidneys remain unchanged in small for date fetuses.^(1,17) So we concluded that renal length is less accurate parameter to predict renal parenchymal changes than renal volume.⁽¹⁾ And hence instead of renal length we took renal volume that to combined renal volume as a predictor of renal impairment in growth restricted fetuses.

For measurement of renal volume we used two dimensional technique which was available in our radiology department. Most accurate method is by three dimensional ultrasound with VOCAL method and most widely acceptable.^(18,19) However doing three- dimensional ultrasound for kidney volume is not cost effective and hence we preferred doing two dimensional ultrasound in our study to calculate fetal renal volume which was more feasible and more or less precise.

Few authors considered kidney as an ellipsoid and calculated renal volume on ultrasound by applying ellipsoid formula.^(4,11,20) In one study 'theoretical kidney volume' was well correlated with the true kidney volume by using the ellipsoid formula.⁽²⁰⁾ However others did not agree as they considered that kidney is not true ellipsoid and found that 24% to 32% underestimation of the fetal renal volume while using two dimensional ultrasound.^(18,21)

Renal Doppler parameters which we included in our study were peak systolic velocity, end diastolic velocity and pulsatility index. Renal artery pulsatility index is a measure of renal artery resistance and hence renal blood flow. Normally in the first trimester, the renal artery resistance is high, reflected by increase in the PI. However towards the mid second and third trimester renal artery resistance decreases significantly with increase in the end diastolic velocity with minor changes in the peak systolic velocity. Decrease in the resistance is reflected on Doppler as reduction in the pulsatility index there by increasing the blood flow directed to the kidney. So we concluded that renal artery PI is better indicator of renal blood flow.

In our study abnormal blood flow resistance patterns of the renal artery reflected by increase in PI was negatively correlated to kidney volume, independent of fetal abdominal circumference at the time of the kidney measurement.

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This suggests that kidney volume not only depends on abdominal circumference or overall fetal size but also on blood flow redistribution with resultant increased intra renal resistance which is running in consensus with previous study.⁽¹⁾

As in previous study,⁽¹⁾ significant difference was seen between the Doppler parameters of renal artery in normal and growth restricted fetuses. In our study, as compared to the normal fetuses, the renal artery in growth retarded fetuses showed slightly decreased systolic velocities with increase in the pulsatility index. Similar findings were also seen in the previous published study.⁽¹⁾ In addition few observers 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.^(21,22,23) On the other hand another study found no change in PI-values of the fetal renal artery in 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⁾

Previously published study did not find any association between umbilical artery, middle cerebral artery pulsatility index and renal volume ⁽¹⁾. One study showed an inverse relation between cerebro/umbilical ratios to the renal volume.⁽⁶⁾

Thus we concluded that fetal hypoxemia which occurs in growth restricted fetuses leads to reduction in the percentage of the cardiac output reaching the kidneys which was reflected on Doppler as increase in the renal artery pulsatility index causing reduced renal perfusion. This reduction in the renal perfusion was responsible for impaired nephrogenesis and thus decreased kidney volume in growth restricted fetuses as compare to normal fetuses.

Fig. 1A and Fig. 1B: Shows measurement of renal volume in two different normal fetuses.

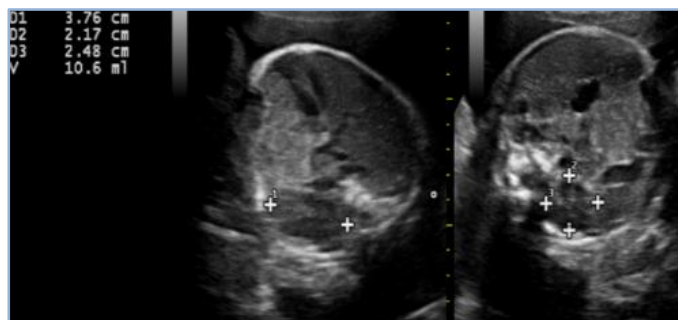


Fig. 1A



Fig. 1B

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Fig 2 A and Fig 2 B: Shows measurement of renal volume in two different growth restricted fetuses.



Fig. 2A

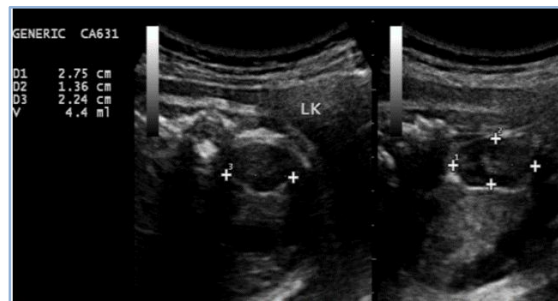


Fig. 2B

Fig 3 A and Fig 3 B: Shows renal Doppler in normal and growth restricted fetuses.

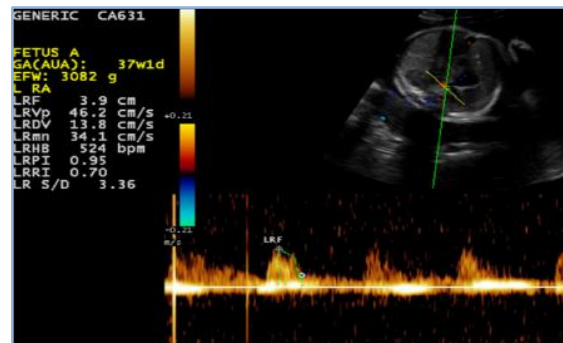


Fig. 3A

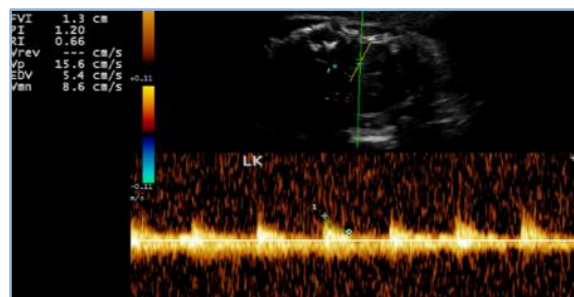


Fig. 3B

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