Original Research Article

Fetal Renal Volume and Fetal Renal Artery Doppler in Normal and Intrauterine Growth Restricted Fetuses

Abstract

Background: Human fetal kidney undergoes constant changes throughout the pregnancy to attain final maturity in terms of structural and functional aspect. 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. The aim of this study was to evaluate changes in the fetal renal artery Doppler parameter and fetal kidney volume measured by 3D ultrasound system with (VOCAL) method in normally grown and growth restricted fetuses after 26 weeks of gestation.

Methods: This prospective study include 60 pregnant women divided in to two groups, first one (A) contains 30 pregnant women with intrauterine growth restricted fetuses, and the second one (B) contains 30 pregnant women with normally grown fetuses.

Results: There was insignificant differences between two groups as regard gestational age by date but gestational age by US there was significant decrease in group A. There were insignificant differences between two groups as regard length of kidney either right or left. There was significant decrease in kidney width right and left side in group A versus group B. There was significant decrease in kidney depth right and left side in group A versus group B. There was significant decrease in kidney volume right and left side in group A versus group B. There was significant decrease in combined kidney volume in group A versus group B. There was significant increase in renal artery PI, RI in group A versus group B.

Conclusions: 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 compared to normal fetuses.

Keywords: Fetal Renal Volume, Fetal Renal Artery Doppler, Normal Intrauterine Growth, Restricted Intrauterine Growth Fetuses

Introduction:

Intrauterine growth restriction (IUGR), is defined as less than 10 percent of predicted fetal weight for gestational age, may result in significant fetal morbidity and mortality. It is associated with a perinatal mortality rate that is 6 to 10 times higher than that for normally grown fetuses. Human fetal kidney undergoes constant changes throughout the pregnancy to attain final maturity in terms of structural and functional aspect, approximately one million nephrons are seen on either side at birth in term fetuses [1].

Several factors can modulate nephrogenesis including maternal malnutrition, maternal hyperglycemia, Intrauterine Growth Restriction (IUGR), vitamin A deficiency, and fetal exposure to drugs [2]. *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 [3]. As fetal kidney weight cannot be measured in utero. Renal volume measured by ultrasound is a valid substitute [4].

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, 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 [5]. 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.

A direct relationship has been reported between hypoxia and the renal artery pulsatility index (e.g., resistance) [6]. 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 [3].

Renal Doppler parameters which include peak systolic velocity, end diastolic velocity and pulsatility index. Renal artery pulsatility index is a measure of renal artery resistance and

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hence renal blood flow. Normally in the first trimester, the renal artery resistance is high, reflected by increase in the pulsatility index. 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.

With the latest new developments in the field of three-dimensional ultrasonography, accurate assessment of the fetal organ volume has become feasible and this technique has gained widespread application in different medical fields.

The aim of this study was to evaluate changes in the fetal renal artery Doppler parameter and fetal kidney volume measured by 3D ultrasound system with (VOCAL) method in normally grown and growth restricted fetuses after 26 weeks of gestation.

Patients and Methods:

This prospective study include 60 pregnant women Pregnant women with singleton pregnancies, gestational age more than 26 weeks, age of pregnant women from 23 – 35 years and body mass index from 25 -35 kg/m^2 from Obstetrics and Gynecology Department, Tanta University Hospital for estimation of renal volume and renal artery Doppler from September 2018 till May 2020.

An informed written consent was obtained from all pregnant women participating in the study.

Pregnant women with mmultiple gestations, diabetes, preeclampsia or any medical disorder complicating pregnancy, drug intake as Aspirin or ccigarette smoker pregnant women were excluded. And also, Fetuses with structural anomalies, unclear adrenal or renal borders, abnormal renal morphology or poorly visualized kidneys, chromosomal abnormalities and genetic syndromes.

Women were divided in to two groups, first one (A) contains 30 pregnant women with intrauterine growth restricted fetuses, and the second one (B) contains 30 pregnant women with normally grown fetuses.

All patients were evaluated by Complete history taking including:

Personal history as age and age at first marriage. Family history as consanguinity and +ve family history of GDM. Menstrual history as last menstrual period expected date of delivery and gestational age.

Obstetrical history as gravidity, parity, abortion and fetal or neonatal death. Medical history as past history of diseases, operations, allergy and drugs as aspirin. General examination as pulse, blood pressure, respiratory rate and temperature.

Obstetrical examination including Inspection as shape of the abdomen, size of the uterus, scars and stria. Palpation as lie, position, presentation, fundal level and fetal parts.

Auscultation: fetal heart sound. Vaginal examination: to exclude bleeding. Gestational age is based on the first day of the last normal menstrual period and confirmed by ultrasound scan.

Ultrasound examination: All patients were examined by 2D ultrasound to get full obstetric data and 3D ultrasound scan for renal Doppler and renal volume.

All ultrasound measurements were done on SAMSUNG MEDISON HS60, 50/60HZ with transabdominal probe for assessment of: Fetal biometry including: biparietal diameter, abdominal circumference, and femur length were measured. Estimated fetal weight was calculated using the formula by Hadlock using head circumference, abdominal circumference, and femur length [7]. IUGR is diagnosed when the Estimated Fetal Weight (EFW) falls below the10th percentile for gestational age [8].

Method of measurement:

Renal volume: The measurement of the maximum antero-posterior diameter of the kidney was performed using a standard method. The fetal kidneys were identified in a transverse

scan and the greatest APD was searched by scrolling in depth. The APD diameter was measured transverse to the fetal spine. The mean values were used in the analyses, and 3D acquisition of the fetal kidney was recorded in the first session and the volume was calculated using the Virtual Organ Computer-aided Analysis (VOCAL) technique. Right and left kidney volume was calculated individually. Combined kidney volume was calculated by adding right and left kidney volume.

Renal artery Doppler: 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 hilum, 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 [9].

Data analysis: Kidney volume was calculated using formula for ellipsoid i.e., Volume=length X width thickness X 0.523. Right and left kidney volume was calculated individually. Combined kidney volume was calculated by adding right and left kidney volume. Relative kidney volume was calculated as ratio of fetal kidney volume/estimated fetal weight. As fetal kidney weight cannot be measured in utero, so on ultrasound renal volume is considered as equivalent to the weight [10]. For renal artery: the outline of minimum of two flow velocity waveforms was measured from the sample of five identical flow velocity waveforms. 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 [11].

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and interquartile range (IQR). Significance of the obtained results was judged at the 5% level. The used tests were Student t-test: for normally distributed quantitative variables and to compare between two studied groups, Mann Whitney test: for abnormally distributed quantitative variables, to compare between two studied groups.

Results:

There was insignificant differences between two groups as regard maternal age. There was insignificant differences between two groups as regard parity. Table 1

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Table 1: Comparison between the two studied groups according to maternal age and parity.

Maternal age	Group A (n = 30)	Group B (n = 30)	U	p
Min. – Max.	**23.0 – 35.0**	**23.0 – 35.0**	**378.0**	**0.275**
Median (IQR)	**32.0 (32.0 – 34.0)**	**32.0 (30.0 – 33.0)**		
Parity				
Mean ± SD.	**1.30 ± 0.92**	**1.40 ± 0.81**	**423.0**	**0.670**
Median (IQR)	**1.0(1.0 – 2.0)**	**1.0(1.0 – 2.0)**		

There was insignificant differences between two groups as regard gestational age by date but gestational age by US there was significant decrease in group A. there was significant decrease in group A versus group B regarding fetal weight. **[Figure 1]**

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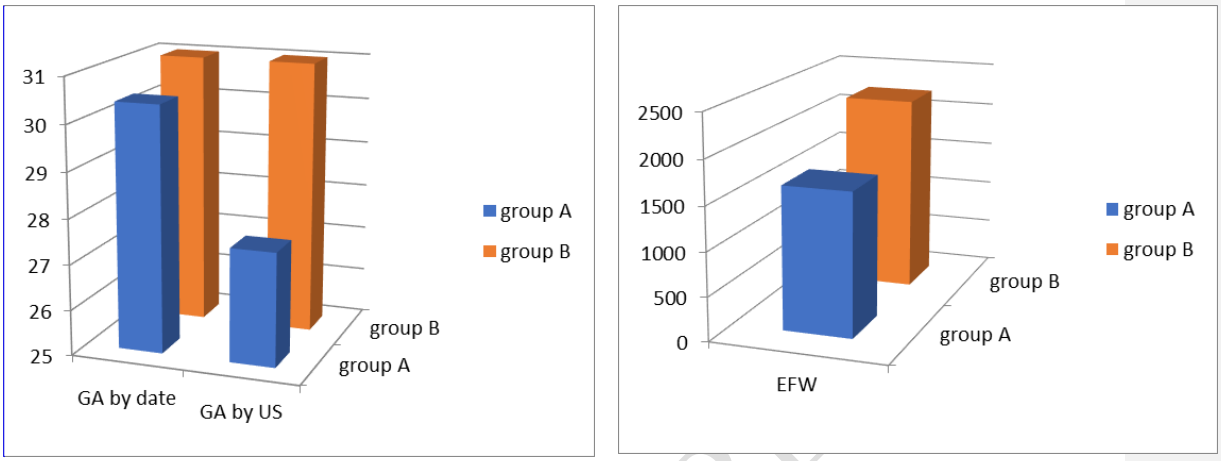

(A) **(B)**

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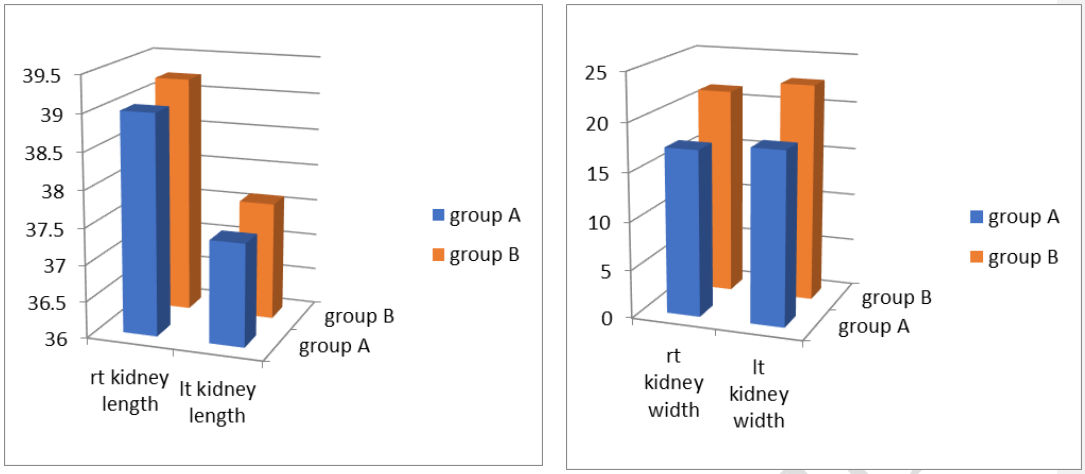
Figure 1: Comparison between the two studied groups according to GA age by date and US (A) and according to EFW (g) (B).

There were insignificant differences between two groups as regard length of kidney either right or left. There was significant decrease in kidney width right and left side in group A versus group B. **[Figure 2]**



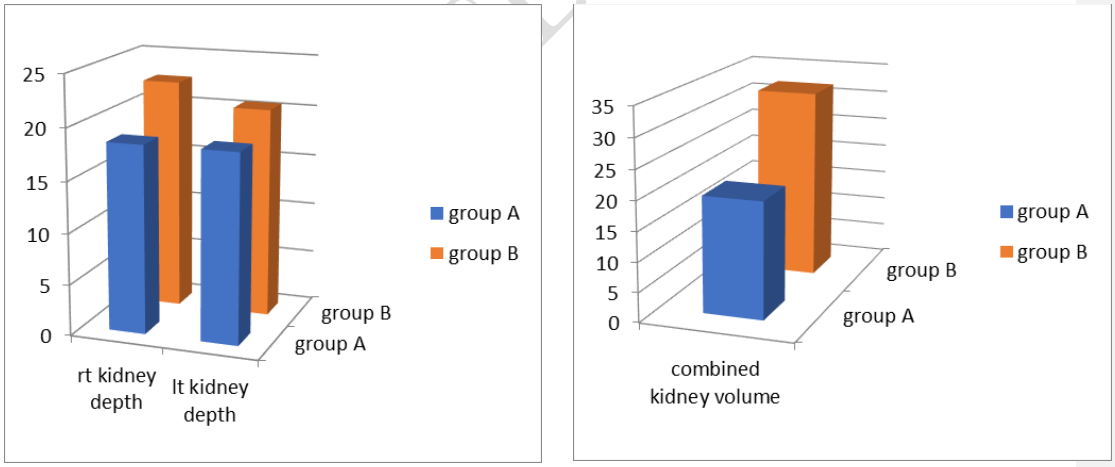
(A) **(B)**

Figure 2: Comparison between the two studied groups according to kidney length (A) and kidney width (B).

There was significant decrease in kidney depth right and left side in group A versus group B.

There was significant decrease in Combined kidney volume in group A versus group B.

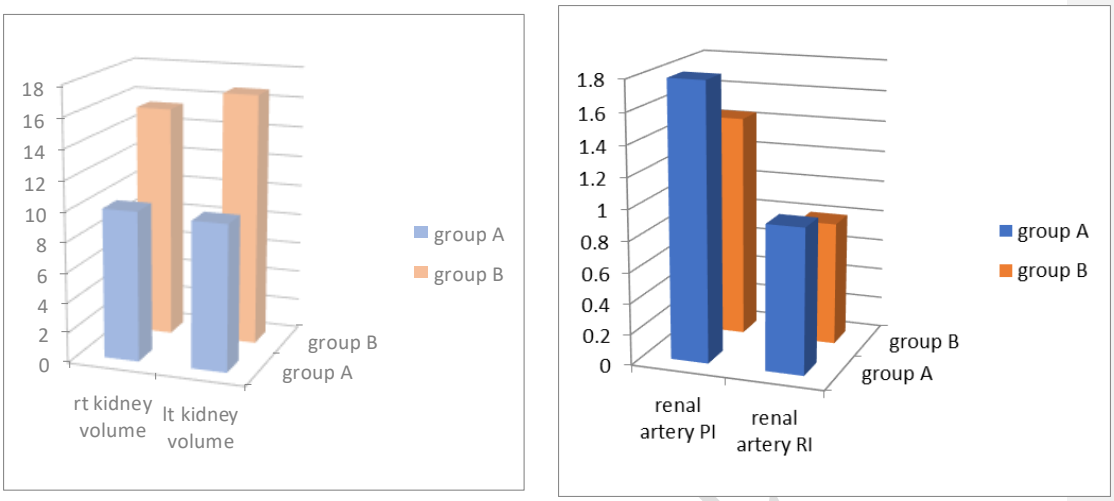
[Figure 3]



(A) **(B)**

Figure 3: Comparison between the two studied groups according to kidney depth (A) and according to Combined kidney volume (B).

There was significant decrease in kidney volume right and left side in group A versus group B. There was significant increase in renal artery PI, RI in group A versus group B. **[Figure 4]**



(A) **(B)**

Figure 4: Comparison between the two studied groups according to renal volume of right and left kidney (A) and between the two studied groups according to renal volume (B).

Discussion

The human kidney develops through three successive embryonic stages. Transient development and regression of the primary (pronephros) and secondary (mesonephros) fetal kidneys occurs between day 23 and day 112. These primitive fetal kidneys have no impact on fetal renal function. The definitive, tertiary fetal kidney is the metanephros and this is the permanent functional kidney. It begins developing on day 30 leading to the formation of nephrons − the functional units within the kidney. Fetal kidneys are unlike most other organs in that the maximum cell proliferation occurs in the third trimester. Nephrogenesis continues up until 34–36 weeks gestation with approximately 60% of nephrons formed in the third trimester [12].

In the current study we found that there were insignificant differences between two groups as regard gestational age by date but gestational age by US there was significant decrease in

group A. In consistent with our result **Abd El-Aal et al** [13] showed that the mean gestational age by date in IUGR group ± SD was 36.72± 1.53 weeks and for normal group was 37.74±1.41 with no difference between the two groups but the mean gestational age by ultrasound was in IUGR 32.5 ±2.02 and in the normal group was 36.72±1.40**.** Another study by **Ratnaparkhi et al** [14] showed that the mean gestational age/SD for normally grown fetuses was 34.15±2.86 and for growth restricted fetuses was 36.1 week ± 2.58. Hence both the groups were comparable.

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In the current study we found that as regard estimated fetal weight **there was** there was significant decrease in group A versus group B regarding fetal weight and this due to group A consisted of intrauterine growth retard fetus. In the current study we found that there were insignificant differences between two groups as regard length of kidney either right or left. This goes with **EI behery et al** [1] as showed that there was no significant difference in right kidney length between normally grown fetuses and those with IUGR. Running in agreement with previous study which showed that the length of the kidney remains largely unchanged in small-for-gestational age fetuses [15]. In addition, the renal length is a poor indicator of the amount of the renal parenchyma than the renal volume. In consistent with our result **Ratnaparkhi et al** [14] showed that 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.

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In the current study we found that there was significant decrease in kidney width right and left side in group A versus group B. In agreement with our result **EI behery et al** [1] showed that there was significant decrease in kidney width right and left side in between normally grown fetuses and those with IUGR. Another study by **Silver et al** [16] showed that intrauterine growth restriction appears to be associated with a decrease in fetal renal volume. Because renal volume is a likely proxy for nephron number, this study supports the

hypothesis that intrauterine growth restriction may be linked to congenital oligonephropathy and potentially to hypertension in later life. The wide range in nephron number between individuals is likely attributed to differences in nephron endowment by the completion of nephrogenesis (which may be due to genetic and/or environmental factors), as well as differences in the exposure to secondary insults throughout life, which lead to loss of nephrons. In this regard, exposure to IUGR and/or preterm birth can negatively impact on nephrogenesis and thus adversely impact on nephron endowment at the beginning of life **(69).** In another study, a linear relationship was reported between the number of glomeruli (and therefore nephrons) and birth weight in full-term neonates; neonates below the 10^{th} percentile of birth weight had 30% fewer glomeruli than the neonates with birth weights above the 10^{th} percentile [17].

In the current study we found that there was significant decrease in kidney depth right and left side in group A versus group B. In agreement with our result **EI behery et al** [1] showed that there was significant decrease in kidney depth right and left side in between normally grown fetuses and those with IUGR**.**

In the current study we found that there was significant decrease in kidney volume right and left side in group A versus group B. In agreement with our result **EI behery et al** [1] showed that there was significant decrease in kidney volume right and left side i**n** between normally grown fetuses and those with IUGR**.** In addition to **Abd El-Aal et al** [13] showed that concerning renal volume found that there was significant difference between the two groups as the IUGR cases had smaller renal volume than normal group. The mean of the right renal volume in IUGR group was (10.35 ± 0.58) and in control group was (15.44 ± 1.76) with significant p value <0.05, in the left side the renal volume in IUGR group was (10.65 ± 0.65) and in normal group was (15.80± 1.62) with significant p value <0.05**. Bakker et al** [18]

showed that compared with children with size appropriate for gestational age, children born small for gestational age had smaller kidney volume (−3.74 cm^3; 95% CI, −6.89 to −0.89)**.**

In the current study we found that there was significant decrease in combined kidney volume in group A versus group B. In agreement with our result **EI behery et al** [1] showed that there was significant decrease in combined kidney volume between normally grown fetuses and those with IUGR**.** Also, **Ratnaparkhi et al** [14] agree with our result as showed that 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**.**

In the current study we found that there was significant increase in renal artery PI, RI in group A versus group B. This goes with **EI behery et al** [1] as showed that renal artery pulsatility index was significantly elevated in fetuses with IUGR, P<0.001**.** In agreement with our 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 [19]**.** Also, **Abd El-Aal et al** [13] agree with our result as showed that as regard renal artery resistive index in IUGR cases was (0.94±0.02) and in control group was (0.79 ± 0.004) and renal artery PI in IUGR was (1.90 ± 0.08) and in normal fetuses was (1.49 ±0.07)**.**

Our results meet with a previous study, which revealed that there was significantly difference was seen between the Doppler parameters of renal artery in normal and growth restricted fetuses. AS compared to the normal fetuses, the renal artery in growth retarded fetuses showed slightly decreased systolic velocities with increase in the pulsatility index [14]**.** 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 [20].

Conclusions:

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 compared to normal fetuses.

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Conflict of Interest: Nil

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References:

1. El Behery MM, Ibrahiem MA, Siam S, Seksaka M. Fetal renal volume and fetal Doppler in normal and growth restricted fetuses: Is there a correlation. Gynecol Obstet. 2012;2:2161-0932.1000118.

2. Merlet-Bénichou C, Gilbert T, Vilar J, Moreau E, Freund N, Lelièvre-Pégorier M. Nephron number: variability is the rule. Causes and consequences. Lab Invest. 1999;79:515-27.

3. Verburg BO, Geelhoed JJ, Steegers EA, Hofman A, Moll HA, Witteman JC, et al. Fetal kidney volume and its association with growth and blood flow in fetal life: The Generation R Study. Kidney Int. 2007;72:754-61.

4. Konje JC, Okaro CI, Bell SC, de Chazal R, Taylor DJ. A cross-sectional study of changes in fetal renal size with gestation in appropriate- and small-for-gestational-age fetuses. Ultrasound Obstet Gynecol. 1997;10:22-6.

5. Arduini D, Rizzo G. Normal values of Pulsatility Index from fetal vessels: a cross-sectional study on 1556 healthy fetuses. J Perinat Med. 1990;18:165-72.

6. Vajda G, Pál A. [Fetal blood flow in the renal artery during the third pregnancy trimester]. Orv Hetil. 1994;135:1751-3.

7. Hadlock FP, Harrist RB, Carpenter RJ, Deter RL, Park SK. Sonographic estimation of fetal weight. The value of femur length in addition to head and abdomen measurements. Radiology. 1984;150:535-40.

8. Goldenberg RL, Cutter GR, Hoffman HJ, Foster JM, Nelson KG, Hauth JC. Intrauterine growth retardation: standards for diagnosis. Am J Obstet Gynecol. 1989;161:271-7.

9. Vyas S, Nicolaides KH, Campbell S. Renal artery flow-velocity waveforms in normal and hypoxemic fetuses. Am J Obstet Gynecol. 1989;161:168-72.

10. Sharma K, Caroli A, Quach LV, Petzold K, Bozzetto M, Serra AL, et al. Kidney volume measurement methods for clinical studies on autosomal dominant polycystic kidney disease. PLoS One. 2017;12:e0178488.

11. Oglat AA, Matjafri MZ, Suardi N, Oqlat MA, Abdelrahman MA, Oqlat AA. A Review of Medical Doppler Ultrasonography of Blood Flow in General and Especially in Common Carotid Artery. J Med Ultrasound. 2018;26:3-13.

12. Brennan S, Watson D, Rudd D, Schneider M, Kandasamy Y. Evaluation of fetal kidney growth using ultrasound: A systematic review. Eur J Radiol. 2017;96:55-64.

13. El-Aal A, Maged H, El-Sheikha KZ, Ragab AMA-E. Fetal renal volume and renal artery doppler in normal and intrauterine growth restricted fetuses. The Egyptian Journal of Hospital Medicine. 2018;73:6238-42.

14. Ratnaparkhi CR, Kurve SA, Mitra KR, Onkar PM, Kulkarni AM, Kant DM. Correlation between fetal renal volume and fetal renal doppler in normal and growth restricted fetuses: An initial experience. Journal of Evolution of Medical and Dental Sciences. 2015;4:10956-67.

15. Bakker J, Olree M, Kaatee R, de Lange EE, Moons KG, Beutler JJ, et al. Renal volume measurements: accuracy and repeatability of US compared with that of MR imaging. Radiology. 1999;211:623-8.

16. Silver LE, Decamps PJ, Korst LM, Platt LD, Castro L. Intrauterine growth restriction is accompanied by decreased renal volume in the human fetus. Am J Obstet Gynecol. 2003;188:1320-5.

17. Merlet-Benichou C, Leroy B, Gilbert T, Lelievre-Pegorier M. Placental insufficiency and its effect on the fetus and adult disease. Lancet. 1993;341:827-8.

18. Bakker H, Gaillard R, Franco OH, Hofman A, van der Heijden AJ, Steegers EA, et al. Fetal and infant growth patterns and kidney function at school age. J Am Soc Nephrol. 2014;25:2607-15.

19. Yu C, Chang C, Chang F, Ko H, Chen H. Fetal renal volume in normal gestation: a three-dimensional ultrasound study. Ultrasound Med Biol. 2000;26:1253-6.

20. Stigter RH, Mulder EJ, Bruinse HW, Visser GH. Doppler studies on the fetal renal artery in the severely growth-restricted fetus. Ultrasound Obstet Gynecol. 2001;18:141-5.