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Correlation between Fetal Renal Blood Flow and Fetal Kidney Volume in Normal and Growth Restricted Fetuses

Noura Magdy Sonkor[1*], Diaa Mounir Aglan[1], Amr Mohamed Tawfek[1] and Walid Mamdouh Ataallah[1]

[1]*Department of Obstetrics and Gynecology, Faculty of Medicine, Tanta University, Tanta, Egypt.*

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Some trials have shown decreased weight of fetal kidney in cases of reduced neonatal weight and infants with growth-restriction at birth. In infants with growth-restriction due to poor nutrition, most of the fetal blood supply is directed to vital organs such as fetal heart and brain that leads to deprivation of remaining organs from its nutrients, such as kidney. This work aimed to assess whether the size of fetal kidney in cases of normal and restricted fetal growth patterns after 28 weeks could be affected by reduced fetal renal blood supply or not.
Methods: This case-control trial included 60 patients who were divided into two groups: Each group composed of 30 patients; Study group: fetuses with IUGR and control group: fetuses with normal growth pattern.
Results: There was no significance between both study groups as regard to age, weight, BMI, and gravidity. No significance between the studied groups regarding the clinical findings, gestational age, diabetes, HTN, congenital fetal anomalies, and previous C.S. A high significance was present among both groups as regard to measurements of renal artery Doppler. A correlation of statistical significance was noted as regard Doppler indices and kidney volume in the study group.
Conclusions: The elevated pulsatility index of the renal artery of fetus in fetuses with IUGR showed -ve correlation with the volume of the fetal kidney, resulting in reduced nephron-genesis

**Corresponding author: E-mail: nouramagdy3103@gmail.com;*

and perfusion. Restrictions in intrauterine growth are believed to be associated with a significant reduction in renal volume compared to the normal growth of fetuses. The Doppler of renal artery also reveals significant differences among study groups.

Keywords: Fetal renal blood flow; fetal kidney volume; normal fetus; growth restricted fetus.

1. INTRODUCTION

In order to achieve final functional and structural maturity, the fetal kidneys undergo modifications during pregnancy. In full-term infants, around 1,000,000 nephrons could be seen on the two flanks at birth. Nephro-genesis is affected by maternal nutritional deficiencies, maternal high blood sugar, fetal growth retardation, deficiency of vitamin A, and early exposure to certain medications [1].

Some previous trials have shown decreased renal weight in infants with reduced weight and growth-restriction at birth [2,3].

In humans, authors reported decreased volume of fetal kidney in cases of IUGR compared to fetuses with normal growth patterns at the same gestational age [4,5].

In infants with growth-restriction due to poor nutrition, most of the fetal blood supply is directed to vital organs such as fetal heart and brain that leads to deprivation of remaining organs from its nutrients such as kidney. Fetal kidneys are supplied by about 2-3 percent of the total output of the heart as the renal artery of the fetus has a high resistance at the beginning of pregnancy [6,7].

The renal artery resistance decreases with the progress of the pregnancy, so that fetal renal blood flow increases, represented by end-diastolic and mean velocity elevation. On the other hand, only small adjustments are shown at peak systolic velocity [8]. In fetal hypoxemia, a considerable decrease of the baseline is seen i.e., roughly 25-50 percent. The exact mechanism of which is unknown [6].

Fetal growth is the result of dynamic interactions between the ability of the fetus's genetic growth and the effect of the intrauterine maternal climate. IUGR causes are commonly known as maternal, fetal, or placental. This distinction, however, is somewhat theoretical, since these variables frequently overlap with each other. IUGR is diagnosed when estimated fetal weight (EFW) is below the 10th percentile for gestational age by ultrasound. A diagnosis of IUGR indicates a restriction of pathological growth responsible for low fetal weight [9].

In fetuses with IUGR triggered by placental insufficiency, extensive circulatory changes occur. These changes, called redistribution or (brain-sparing) effect, lead to a decrease in peripheral vascular resistance and, subsequently, an increase in blood flow in survival-critical organs (e.g. brain and heart) and a decrease in blood flow in other parts (e.g. limbs, liver and kidneys) [10].

Maximum kidney growth occurs between 26 and 34 weeks of gestation, and any maternal or fetal factors are likely to cause nephrogenesis during this time, thereby significantly affecting kidney size and volume [11].

After 26 weeks of gestation, this study was done because the time of maximal kidney growth occurs between 26 and 34 weeks of gestation, and growth restriction most likely affects kidney size and volume significantly in this period [12].

This work aimed to assess whether the size of fetal kidney in cases of normal and restricted fetal growth patterns after 28 weeks could be affected by reduced fetal renal blood supply or not.

2. PATIENTS AND METHODS

This case-control trial was conducted in the department of Obstetrics and Gynecology, Sixty patients were included in this study and divided into 2 groups: **Group A:** 30 cases of normally grown fetuses considered as a control group. **Group B:** 30 cases of asymmetric intrauterine growth-restricted fetuses.

Inclusion criteria :

- Age: 18 -35 years old.
- > 28 weeks of gestation.
- Singleton pregnancy.

Exclusion criteria:

- Pregnant women for whom age of gestation had not been proved by earlier ultrasound.

- Renal and non-renal fetal congenital malformations.
- Poorly visualized and/or lack of clarity of margins of fetal kidney.

All patients were subjected to :

- Personal history as age, parity, occupation and special habits, etc.
- Family history.
- Menstrual history as gestational age determined as regard to last menstrual period (If the women aware of der dates and has three regular periods prior to current pregnancy or had a documented first trimester ultrasound).
- Present history [Associated symptoms: (bleeding, abdominal pain) and routine treatment first trimester like folic acid supplement]
- Obstetric history for each previous delivery (number, antepartum period (previous preterm labor or abortion), postpartum and puerperium period, previous history of miscarriage]
- Surgical history [any cervical surgeries, previous cesarean section]
- Routine investigation in first trimester and specific investigations of serum analysis were carried out, and an oral glucose tolerance test
- General Examination:[Vital signs (Blood pressure, pulse, temperature, respiratory rate; body mass index (BMI). and blood pressure), chest and heart examination and limbs examinations.
- Abdominal examination (inspection, superficial palpation and for liver, spleen and loin)

2.1 Methods

In both study groups, 3D ultrasound was used to assess kidney volumes of all fetuses. Also, indices - especially fetal renal artery pulsitility index (PI) - have been measured. Correlations between Doppler indices of fetal renal vessels and volumes were evaluated.

Ultrasound (doppler sonography) scan: Basic sonographic biometry of the fetuses - head circumferences, abdomen circumferences, length of femur and expected fetal weights - has been done. Index of amniotic fluid had been measured for all cases.

Hadlock formula and growth curves were utilized to estimate and analyze expected fetal weights. Expected fetal weights and abdominal circumferences lower than gestational age's 10th percentile had been reported as intra-uterine growth restricted.

Asymmetric IUGR is a form of restriction of intrauterine growth that characterized by certain biometric measurements were unequally smaller than others and fall below the 10th percentile.

3D ultrasonography was used for assessment of kidney volume of the fetuses. during fetal rest times, it was evaluated. When the fetal kidney was visualized in a 2D sagittal plane, the 3D waves were used, and the fetal kidneys were measured in a slowing sweep mode to gain a better scan quality.

This method had been utilized for every fetal kidney to gain a six longitudinal sections sequence around a definite axis each following a rotation of thirty degree from the prior axis. In every one of the six distinctive sections, the renal contour was withdrawn manually.

Before they had been used in analysis, the retrieved 3D volumes were preserved instantly utilizing Sonoview software. Utilizing Virtual Organ Computer-aided Analysis (VOCAL) imaging software, the retrieved volumes datasets were evaluated. Both kidney volumes had been added for the average renal volumes (cm3).

In the longitudinal renal sections, the greatest renal cranio-caudal diameter had been determined (outer to outer). The greatest anteroposterior and transverse renal dimensions had been determined in a transverse section perpendicular to each other, holding the caliper the same as the longitudinal diameter [Volume= length X width thickness X 0.523].

We first used the transabdominal probe to scan one fetal kidney, which was closer to the probe, in each fetus under the quantitative mode of power Doppler at a fixed condition.

Assessment of Doppler of fetal renal arteries was better to be done at transverse view of fetal kidneys. The Doppler gates had been positioned at hilum of the kidney with Doppler in the vessel's lumen to provide optimum renal artery Doppler signal.

The histogram parameters were vascularisation (VI), flow and vascularisation flow (VFI) indices.

The waveform of the renal artery was usually high systolic peak with constant diastolic forward flow. The angle of insonation was held at thirty degrees, because Doppler shifts and waveforms were highly influenced by larger angles. Lower wall filter had been utilized so that diastolic flow of reduced levels could be tested well.

From the sample of 5 equivalent flow velocities waveform, the outline of at least 2 flow velocities waveform had been evaluated. Peak systolic velocity (PSV), End-diastolic velocity (EDV), pulsatility index (PI) and resistive index (RI) were the main Doppler indices of renal artery that had been measured. PI was the most sensitive parameter for evaluating renal artery resistance. PI= PSV - EDV. Doppler indices had been compared with the normal values obtained from previous literatures.

2.2 Statistical Analysis

Statistical analysis was done by SPSS v25 (IBM Inc., Chicago, IL, USA). variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing Student's t- test. Categorical variables were presented as frequency and percentage (%)and were analysed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed P value < 0.05 was considered significant.

3. RESULTS

No difference of statistical significance was observed among study groups as regard to Characteristics of patients (age, weight, BMI, gravidity), clinical findings, gestational age and past history (diabetes, hypertension, fetal congenital anomalies and previous C.S) as in Table 1.

A difference with highly statistical significance was observed among both groups as regard to Rt., Lt. and combined renal volumes. Table 2

A difference with highly statistical significance was observed among both groups as regard to renal artery Doppler measurement. Table 3

A correlation of statistical significance was observed between Doppler indices and fetal kidney volume in the study group I. Table 4 and Fig.1

A difference of statistical significance was observed between asymmetrical IUGR and Group II regarding to renal volume and RI and PI. Table 5.

4. DISCUSSION

In our research, there was no statistically significant difference between the two groups with regard to the length of the right and left kidneys, however a significant difference in

Table 1. Characteristics of patients in both study groups

Variable	Group I (n=30)	Group II (n=30)	P-value*
Characteristics of patients			
Age (years)	27.9 ± 4.7	27.9 ± 4.8	0.975
Weight	72.8 ± 11.9	75.6± 14.5	0.364
BMI	32.4 ± 4.2	30 ± 5	0.064
Gravidity			0.897*
• 1	15	13	
• 2	10	12	
• 3 or more	5	5	
Clinical findings			
Pulse	102.6 ± 9.5	99.8 ± 11.7	0.366#
Systolic blood pressure	110 ± 26.6	113.2 ± 31.2	0.698#
Diastolic blood pressure	69.2 ± 17.5	68.6 ± 21.1	0.913#
Hb	9.7 ± 1.1	9.6 ± 1	0.898#
Gestational age			
Gestational age by date	36.72 ± 1.23	36.79 ± 1.51	0.366#
Gestational age by US	36.70 ± 1.50	36.78 ± 1.40	0.698#
Past history			
Diabetes	0	0	----
Hypertension	0	0	----
Fetal congenital anomalies	0	0	----
C.S	12 (40%)	13 (43.3%)	0.758*

*Data are mean ± standard deviation (SD) or number (percent). *Chi square test, #independent sample t-test* width, which was the same findings as previously reported, is also in line with previous study, which showed that in small-for-gestational age fetuses the length of the kidney remained largely unchanged. In addition, renal duration is a weak measure of the amount of renal parenchyma relative to the volume of the renal parenchyma [13].

Table 2. Comparison between both groups as Right, Left and combined renal volumes

	Group I (n=30)	Group II (n=30)	P value
Right	10.20 ± 0.11	15.14 ± 1.86	0.001**
Left	10.25 ± 0.68	15.85 ± 1.42	0.001*
Combined	20.45 ± 0.79	30.99 ± 3.28	0.001*

**Chi square test, #independent sample t-test*

Table 3. Comparison between both groups as the measurements of renal artery doppler

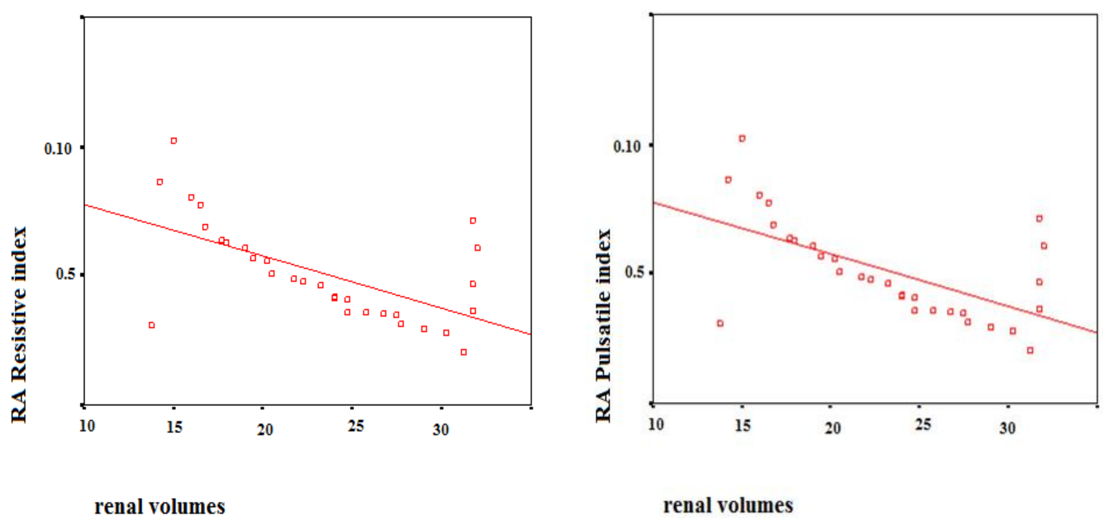
	Group I (n=30)	Group II (n=30)	P value
RA Resistive index	0.93 ± 0.08	0.68 ± 0.01	0.001*
RA Pulsatile index	1.91 ± 0.08	1.48 ± 0.08	0.001*

**Chi square test, #independent sample t-test*

Table 4. Correlation between fetal renal blood flow and combined renal volumes in study group I

		combined renal volumes
RA Resistive index	rs	-0.787
	p	0.001*
RA Pulsatile index	rs	- 0.528
	p	0.005*

rs: Spearman correlation co-efficient



(A) (B)

Fig. 1. A) Correlation between RA Resistive index and combined renal volumes in study group (I). B) Correlation between RA Pulsatile index and combined renal volumes in study group (I)

Table 5. Comparison between asymmetrical IUGR and Group II as the measurements of renal artery Doppler and renal volumes

	Asymmetrical	Group II	P value
RA Resistive index	0.96 ± 0.15	0.68 ± 0.01	0.022
RA Pulsatile index	1.94 ± 0.07	1.48 ± 0.08	0.001
Renal volumes	20.74 ± 0.78	30.99 ± 3.28	0.002

**Chi square test, #independent sample t-test*

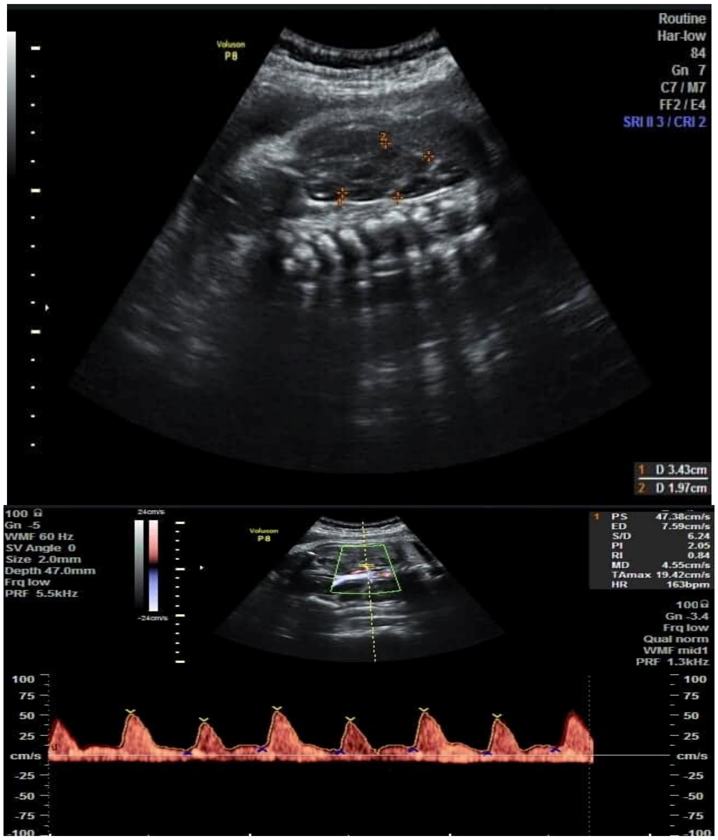


Fig. 2. Ultrasound of normal fetus aged 34 weeks show normal renal measurements and normal renal Doppler

No major difference was observed in the length of both left and right kidneys, which agrees with our findings, which was also noted in previous studies that stayed small for date fetuses in the length of the kidneys [13].

There was no substantial difference in the length of both the left and right kidneys, but there was a significant difference in anteroposterior and transverse diameters, which was also noted in previous studies that the length of the kidneys remained small for date fetuses [1,13]. They concluded that renal length is less precise than renal volume to predict renal parenchymal changes and they took renal volume instead of renal length to combine renal volume as a predictor of renal dysfunction in growth-restricted fetuses.

By applying the ellipsoid formula, several authors used US to calculate fetal or adult kidney volume (15, 16). While one study found that 'theoretical kidney volume' which is (fetal renal volume =0.439 × largest transverse diameter × anteroposterior diameter × longitudinal diameter) was well correlated with the true kidney using the ellipsoid formula [14], Others suggested that the kidney is not a real ellipsoid and found that when two-dimensional US was used, 24% to 32% underestimation of the fetal renal volume [15,16]. The two-dimensional system available in their radiology department was used for calculating renal volume [1]. Three-dimensional ultrasound with the VOCAL method is the most precise method and most generally appropriate [17].

Since it is not cost-effective to conduct three-dimensional ultrasound for kidney volume, the other study prefers to perform two-dimensional ultrasound in its study to measure a more feasible and more or less accurate fetal renal volume [15].

In the present study there was a high significant difference in between the two groups as regard to Right, Left and combined renal volumes which agrees with the study done by El Behery [13] who stated that combined and relative kidney volume was significantly decreased in group 1 than in group 2.

Renal artery PI has been found to be a stronger measure of renal blood flow.

The renal artery resistive index and PI were the Renal Doppler parameters that we used in our analysis. Renal artery PI is a measure of the resistance of the renal artery and hence the flow of renal blood. The resistance of the renal artery is usually high in the first trimester, reflected in the increase in PI. However, with an increase in EDV, renal artery resistance decreases dramatically towards the mid-second and third trimester, with slight improvements in peak systolic velocity. Doppler represents a decrease in resistance as a decrease in PI there by increasing the flow of blood to the kidney.

In our study, there was a highly significant difference between the two groups with regard to renal artery Doppler measurements, which, in line with the El Behery study, showed that renal artery PI was significantly elevated in group 1 compared with group 2 P<0.001[13]. Abd El-Aal also agreed with our findings, which showed that there was a substantial difference between renal artery Doppler parameters in normal and growth-restricted fetuses [18].

We found that the renal artery flow resistance already deviates significantly from the normal range which run with a previous study [19].

This is also in accordance with others who found that in the growth-restricted fetus, the PI of the fetal renal artery was greater than in the normally developed fetus. They also found an inverse association between PI values obtained by cordocentesis in the fetal renal artery and fetal arterial pO2 and the volume of amniotic fluid in growth-restricted fetuses [16,18].

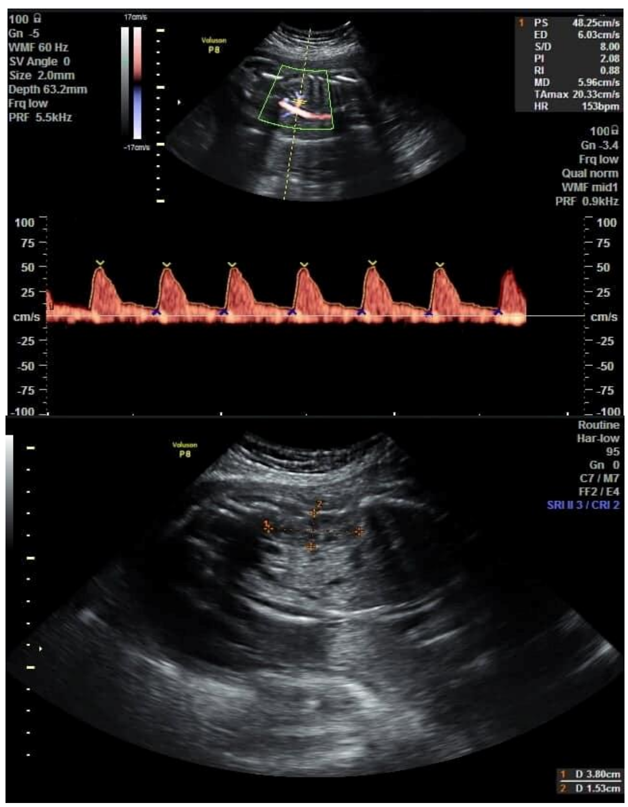


Fig. 3. Ultrasound of IUGR fetus aged 32 weeks show renal measurements and fetal renal Doppler

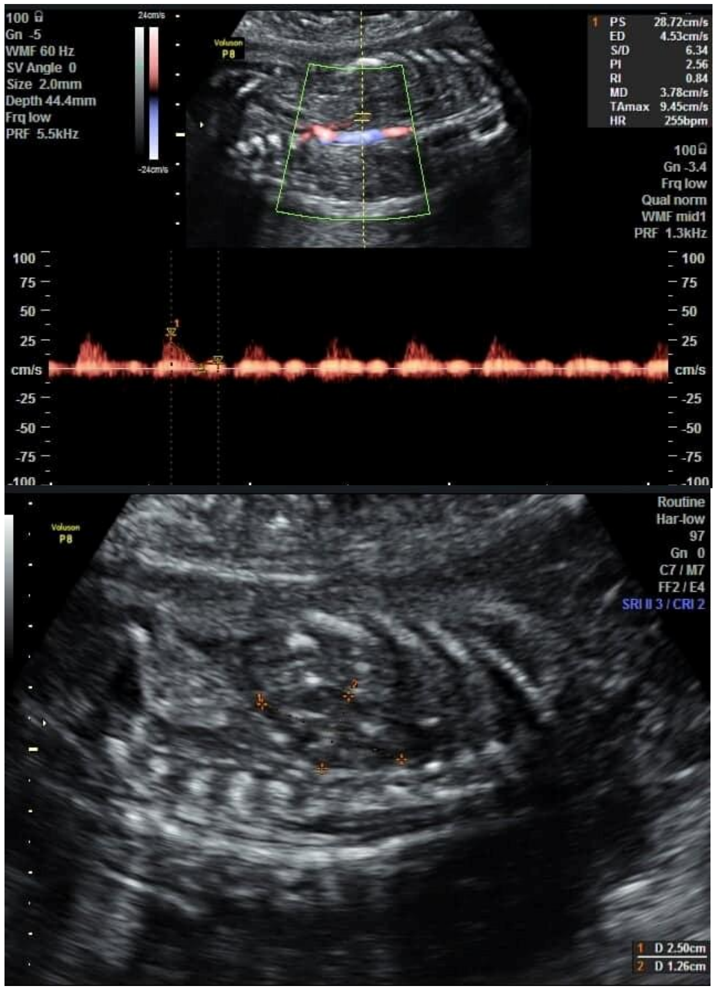


Fig. 4. Ultrasound of IUGR fetus aged 28 weeks show renal measurements and fetal renal Doppler

On the other hand, another study found no improvement in fetal renal artery PI values in severely growth-restricted fetuses with a decrease in renal artery peak systolic velocities over time. In addition, a strong association was found between renal artery peak systolic velocity and both venous cord blood pH values and amniotic fluid quantity.

Abnormal renal artery blood flow resistance patterns represented by an increase in PI were found to be negatively associated with kidney volume, regardless of fetal abdominal circumference at the time of kidney measurement [20].

In the current study there was a significant correlation between Doppler indices and fetal kidney volume in the study group I which agrees with the study done by El Behery [13] who had the same results.

Fetal biometric indices such as femur length, biparietal diameter, head circumference and abdominal circumference were also shown to correlate positively with the volume of the fetal kidney [1].

Positive relations exist between the characteristics of fetal growth in mid-pregnancy and kidney volume in late pregnancy. But these effects are no longer present after adjustment for the same growth parameter in late pregnancy, indicating that the key impact of fetal growth on late pregnancy kidney volume exerts after mid-pregnancy [5].

Both fetal growth features were positively correlated with kidney volume in late pregnancy.

Abdominal circumference and abdominal circumference features were most closely correlated with kidney volume. The positive relation of the abdominal circumference/head circumference ratio indicates that the limitation of asymmetrical fetal growth decreased the volume of the kidney more than the limitation of symmetrical growth, although this impact can only be partly explained by abdominal circumference. The greatest effect of fetal growth on the volume of kidneys during late pregnancy. This is in line with previous research that showed that between 26 and 34 weeks of gestation the duration of maximum kidney growth occurs. Limiting growth most likely affects kidney size and volume dramatically in this time [21].

By reducing the supply of nutrients and oxygen, insufficient placental perfusion contributes to an adverse fetal environment and is one of the most significant causes of fetal growth retardation in Western countries [22]. It is recognized that increased placental vascular resistance and signs of redistribution of blood flow with decreased cerebral resistance are associated with decreased fetal development [21].

Adverse blood flow resistance patterns of the umbilical and uterine arteries were associated with decreased kidney volume in late pregnancy, regardless of fetal abdominal diameter at the time of measurement of the kidney. This means that the volume of the kidney did not depend solely on abdominal diameter and total fetal size, but to some degree directly on placental vascular resistance or redistribution of blood flow. Thus, signs of increased placental resistance and redistribution of fetal blood flow to protect the developing central nervous system are sufficiently detrimental to decrease the volume of the fetal kidney [5].

Changes in renal perfusion caused by preferential blood flow to the brain are a theory for a decrease in renal size in growth-restricted fetuses [23].

A previous study found that in growth-restricted fetuses, renal artery blood flow was not altered [4].
In another study, however, irregular renal artery Doppler flow velocity waveforms were seen in hypoxic growth-restricted fetuses [23].

Fetuses in the lowest percentile of gestational age-adjusted abdominal circumference had a propensity toward greater relative kidney volume, indicating an organ or kidney sparing effect in small for gestational age fetuses [5]. Smaller fetal body size is thus correlated with smaller kidneys, but for that body size, these kidneys are relatively large. Previous studies have shown that the proportion of kidney volume with EFW or abdominal diameter in fetuses of varying size and age is constant [17,24].

The significance of fetal growth and growth characteristics for kidney size determination is underlined in our research. Because the number of nephrons in prenatal life is largely calculated, suboptimal growth of the kidney and growth in fetal life may have lifelong implications [25].

One of the limitations of the study is the small sample size.

5. CONCLUSIONS

The increased pulsatility index of the fetal renal artery in growth-restricted fetuses is negatively associated with the volume of the fetal kidney, resulting in reduced renal perfusion and impaired nephrogenesis. Restrictions in intrauterine development tend to be associated with a statistically significant decrease in renal volume relative to the normal growth of fetuses. The Doppler renal artery also indicates a substantial difference between the two classes, which is consistent with other research.

CONSENT AND ETHICAL APPROVAL

Written signed informed consent was obtained from all participants in this research.

Tanta University Hospitals, from November 2018 to November 2019 after Ethical Committee Approval.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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