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

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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: 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.

1. 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 [1]. 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 [2].

Several factors can modulate nephrogenesis including maternal malnutrition, maternal
hyperglycemia, Intrauterine Growth Restriction (IUGR), vitamin A deficiency, and fetal exposure
to drugs [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] As fetal kidney weight cannot
be measured in utero. Renal volume measured by ultrasound is a valid substitute [5]

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 [6]. 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) [7]. 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 [4].

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 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
foetal kidney volume measured by 3D ultrasound system with (VOCAL) method in normally grown
and growth restricted fetuses after 26 weeks of gestation.

2. 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.

Pregnant women with multiple gestations, diabetes, preeclampsia or any medical disorder complicating pregnancy, drug intake as Aspirin or cigarette 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 foetuses, and the second one (B) contains 30 pregnant women with normally grown foetuses.

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 [8]. IUGR is diagnosed when the Estimated Fetal Weight (EFW) falls below the10th percentile for gestational age [9].

2.1 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 [10].

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 [11]. 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 [12].

### 2.2 Statistical Analysis

Data were fed to the computer and analysed 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.

### 3. RESULTS

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

There was insignificant difference 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 [Fig. 1].

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. [Fig. 2]

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. [Fig. 3]

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. [Fig. 4]

### 4. 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 [13].

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 results Abd El-Aal et al. [14] 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. [15] 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.

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

<table>
<thead>
<tr>
<th>Maternal age</th>
<th>Group A (n = 30)</th>
<th>Group B (n = 30)</th>
<th>U</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min. – Max.</td>
<td>23.0 – 35.0</td>
<td>23.0 – 35.0</td>
<td>378.0</td>
<td>0.275</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>32.0 (32.0 – 34.0)</td>
<td>32.0 (30.0 – 33.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td>1.30 ± 0.92</td>
<td>1.40 ± 0.81</td>
<td>423.0</td>
<td>0.670</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.0(1.0 – 2.0)</td>
<td>1.0(1.0 – 2.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fig. 1. Comparison between the two studied groups according to GA age by date and US (A) and according to EFW (g) (B)
Fig. 2. Comparison between the two studied groups according to kidney length (A) and kidney width (B)
Fig. 3. Comparison between the two studied groups according to kidney depth (A) and according to Combined kidney volume (B)
Fig. 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)
In the current study we found that as regard estimated fetal weight there was significant decrease in 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. [2] 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 (16). 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. [15] 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.

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. [2] 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. [17] 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 10th percentile of birth weight had 30% fewer glomeruli than the neonates with birth weights above the 10th percentile [18].
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 [15]. 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 [21].

5. CONCLUSION

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.

here are some limitations of the study relating to blood urinary nitrogen. We were not able to correlate the Doppler findings with the neonatal period blood urinary nitrogen, and follow up the neonatal infants for urinary system infection.

CONSENT

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

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES


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