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Diagnostic Value of Fetal Thymus Size in Intrauterine Growth Restriction

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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: Changes in thymus size and histopathology have been observed both in animal models of intrauterine growth restriction (IUGR). The aim of the present study was to evaluate the size of the fetal thymus by sonography in pregnancies with IUGR and to search for a possible relationship between a fetal thymus size and adverse perinatal outcomes.
Methods: This prospective observational study was carried out on 100 participants who were divided into two groups. Group A: Study group which include 50 patients with IUGR. Group B: Control group which Include 50 normal patients with appropriate gestational age. All patients were subjected to: History taking: (Personal, Obstetric History, Maternal Medical History) and trans-abdominal ultrasound.
Results: IUGR group show statistically significant decrease in the estimate of fetal weight (EFW) compared to the control group ($P<0.05$). Doppler study of umbilical artery shows significant increase of (pulsatility index (PI), resistance index (RI) and systolic/diastolic (S/D) in IUGR group when compared to control group. Doppler study of middle cerebral artery (MCA) shows significant increase in (RI, SD) in IUGR group when compared to control group while PI doesn't show significant difference between two groups. Thymus size decrease in IUGR group when compared to the control group. IUGR group had low survival and lower APGR Score when compared to the

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control group. Correlation between thymus size with the studied doppler parameters and pregnancy outcome in the current study. Umbilical Doppler RI, PI and SD showed statistically significance in this study (P<0.05) and this means that the blood flow in the umbilical arterial (UA) is important for the fetus. As regard the MCA RI and SD Doppler, they show statistically significance in this study (P<0.05) while the MCA PI Doppler did not show any statistically significance in this study (P>0.05).

Conclusions: IUGR is associated with small thymus and small fetal thymus may be an early indicator of adverse perinatal outcomes in pregnancies complicated by IUGR.

Keywords: Fetal; size; thymus; intrauterine growth restriction; diagnosis.

1. INTRODUCTION

Intrauterine growth restriction (IUGR) refers to a fetus who is unable to reach the genetically determined potential size and carries an increased risk of perinatal morbidity and mortality. Although the causes of IUGR are very diverse, abnormal placental implantation plays an important role in the pathogenesis. According to this process, insufficient trophoblastic invasion of the spiral arteries results in the reduction of uteroplacental blood flow [1].

Assessment of the uteroplacental and fetal circulation by Doppler sonography has been used to identify fetuses at risk of hypoxemia and acidemia. Also, Doppler sonography is generally accepted as the primary tool in the surveillance and management of IUGR. Nevertheless, there is a need for additional prognostic factors for predicting perinatal outcomes of pregnancies with IUGR [2].

In recent years, the fetal thymus size has been suggested as another sensitive parameter related to pregnancy complications. It has been proposed that thymic involution in pregnancy is a stress related condition consequent to activation of the hypothalamic pituitary adrenal gland axis suggested that fetal thymic involution in patients with preterm labor is strongly associated with the fetal inflammatory response syndrome [3].

It was shown that fetal thymus size was reduced in chorioamnionitis after preterm premature rupture of membranes (PPROM), that preeclamptic women had substantially smaller fetal thymuses than healthy control women, and that IUGR was linked to a considerable reduction in fetal thymus size [4].

The aim of the current study was to evaluate the size of the fetal thymus by sonography in pregnancies with IUGR and to search for a possible relationship between a fetal thymus size and adverse perinatal outcomes.

2. PATIENTS AND METHODS

This is a prospective observational study performed on 100 pregnant women aged from about 18 to 35 years old, Singleton pregnancy, during the third trimester at department of obstetrics and gynecology at Tanta university hospital from February 2020 till February 2021.

The inclusion criteria**:** Fifty pregnant women with IUGR and 50 pregnant women with appropriate gestational age diagnosed by ultrasound (u/s), maternal age from 18 to 35 years old, singleton pregnancy, during third trimester**.**

The exclusion criteria: patient with known maternal infections, fetal structural or chromosomal malformations, fetal demise or maternal complications (hypertension, maternal diabetes, preeclampsia, or maternal obesity).

Patients were divided into 2 groups: Group A: 50 patients with IUGR. Group B: 50 normal patients with appropriate gestational age.

All patients in this study were subjected to the following: a) personal, obstetric and maternal medical history b) clinical examination c) investigation studies: Imaging trans-abdominal ultrasound.

Every woman in this study was evaluated by ultrasound as following:

Healthy controls were women with appropriate gestational age who were referred to an outpatient clinic for routine sonographic evaluations. The control group included pregnant women with an estimated fetal weight between the 10th and 90th percentiles. The diagnosis of IUGR was made in the presence of an estimated fetal weight that was below the 10th percentile

for gestational age. All patients underwent a detailed sonographic examination by ultrasound machine with a 5-MHz transabdominal transducer before administration of any medication (including steroids).

Fetal biometric parameters and the amniotic fluid volume were measured. The calculation of estimated fetal weight for the IUGR and control groups was done by using the formula proposed by Hadlock et al. In all pregnancies complicated by IUGR, Doppler flow velocity waveforms of the umbilical and middle cerebral arteries were evaluated.

The thymus was visualized on a transverse section of the fetal chest posterior to the sternum and anterior to the great vessels of the heart. The maximum transverse diameter was measured by placing the calipers.

2.1 Statistical Analysis

Statistical analysis was done by SPSS v25 (IBM Inc., Chicago, IL, USA). Normality of data was checked with Shapiro-Wilks test and histograms. Numerical 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 analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed P value < 0.05 was considered significant.

3. RESULTS

IUGR group show statistically significant decrease in the EFW compared to the control group (P<0.05) Table 2.

Doppler study of umbilical artery shows significant increase of (PI, RI, SD) in IUGR group when compared to control group Fig. 1.

Doppler study of MCA artery shows significant increase in (RI, SD) in IUGR group when compared to control group while PI doesn't show significant difference between two groups. Fig. 2

Thymus size decrease in IUGR group when compared to the control group Fig. 3.

IUGR group had low survival and lower APGR score when compared to the control group Table 3.

Correlation between thymus size with the studied doppler parameters and pregnancy outcome in the current study. Umbilical Doppler RI, PI and SD showed statistically significance in this study (P<0.05) and this means that the blood flow in the UA is important for the fetus. As regard the MCA RI and SD Doppler, they show statistically significance in this study (P<0.05) while the MCA PI Doppler did not show any statistically significance in this study (P>0.05) Table 4.

Diagnostic profile of thymus size in diagnosis of IUGR are shown in Table 5 and Fig. 4.

Table 1. No significant difference was found as regard age, Body mass index (BMI), occupation residency, gestational age and parity, between cases and control

		IUGR group (n= 50)	Control group (n= 50)	95% CI	P
Age (years)		24.90 ± 3.394	25.02 ± 3.449	-1.48, 1.24	0.861
BMI (kg/m^2)		23.28 ± 3.913	22.72 ± 3.687	-0.94, 2.06	0.463
Occupation	Housewife	64.0% (32)	58.0% (29)		0.539
	Worker	36.0% (18)	42.0% (21)		
Residency	Urban	30.0% (15)	28.0% (14)		0.826
	Rural	70.0% (35)	72.0% (36)		

Data is expressed as mean and standard deviation or as percentage and frequency. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05.

Table 2. Obstetric history of the studied groups

	IUGR group (n= 50)	Control group (n= 50)	95% CI	P
Parity	1.56 ± 0.884	1.70 ± 1.129	-0.54, 0.26	0.492
Gestational age	31.76 ± 2.181	32.60 ± 2.312	- 1.73, 0.05	0.065
EFW (gm)	1491.58 ± 242.906	1721.90 ± 259.281	-330, -130	< 0.001***
History of PIH	26.0% (13	18.0% (9		0.334
History of Pre-eclampsia	24.0% (12)	32.0% (16)		0.373
Oligohydramnios	20.0% (10)	84.0% (2)		0.028***
Gestational diabetes	4.0% (2)	2.0% (1		0.558

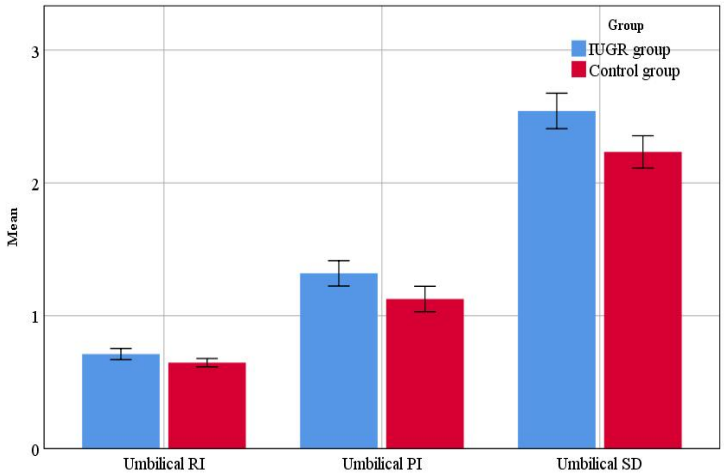

Fig. 1. Doppler study of umbilical artery of the studied groups

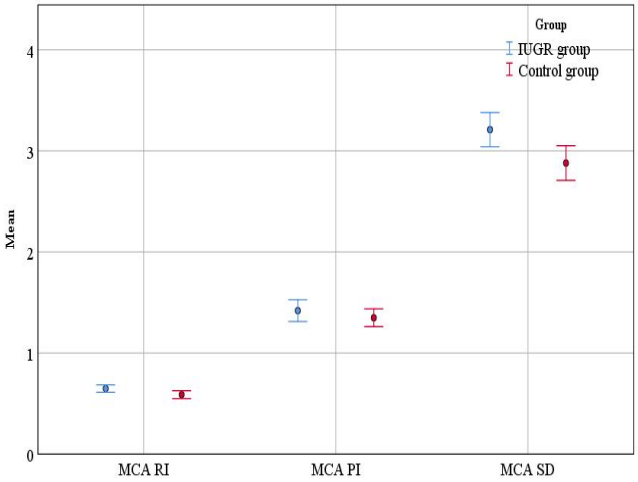

Fig. 2. Doppler study of MCS of the studied groups

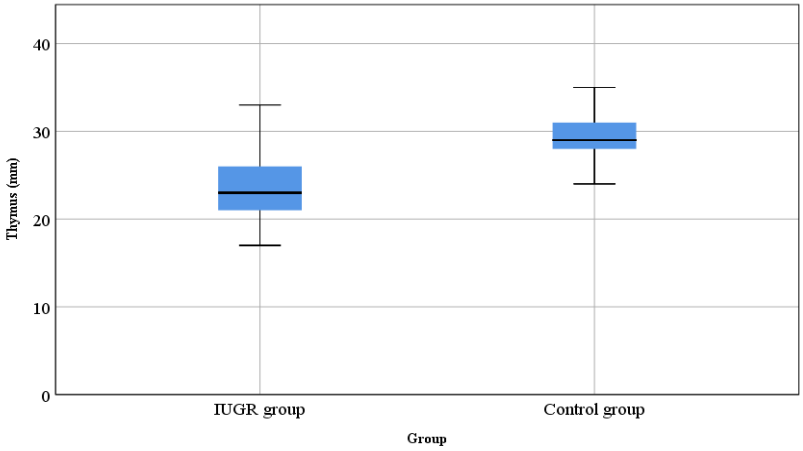

Fig. 3. Thymus size in centimeters as measured by US of the studied groups

Table 3. Outcome of pregnancy in the studied groups:

		IUGR group (n= 50)	Control group (n= 50)	95% CI	p
GA of termination (weeks)		36.76 ± 1.205	37.10 ± 1.329	-0.84, 0.16	0.183
Outcome	Survival	92.0% (46)	100.0% (50)	0.01, 0.16	0.041
	Demise	8.0% (4)	0.0% (0)		
Apgar score	5 minutes	7.30 ± 0.963	7.80 ± 1.385	-0.98, - 0.01	0.043
	10 minutes	7.50 ± 1.150	8.12 ± 1.206	-1.1, -0.14	0.012
NICU admission		28.3% (13)	18.0% (9)	-0.21, 0.33	0.331

Data is expressed as mean and standard deviation. 95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05

Table 4. Correlation between thymus size with the studied doppler parameters and pregnancy outcome in the current study:

		Correlation coefficient	P
Umbilical artery	RI	-0.287	0.004
	PI	-0.227	0.023
	SD	-0.280	0.005
MCA	RI	-0.240	0.016
	PI	-0.129	0.201
	SD	-0.220	0.028
Fetal demise		-0.135	0.181

Table 5. Diagnostic profile of thymus size in diagnosis of IUGR in the current study:

	Thymus size (mm)
AUC	0.896
95% AUC	0.834, 0.959
P	< 0.001
Cut off point (Length of the thymus by cm)	26.50
Sensitivity	84.0%
Specificity	84.0%
PPV	84.0%
NPV	84.0%
Accuracy	84.0%

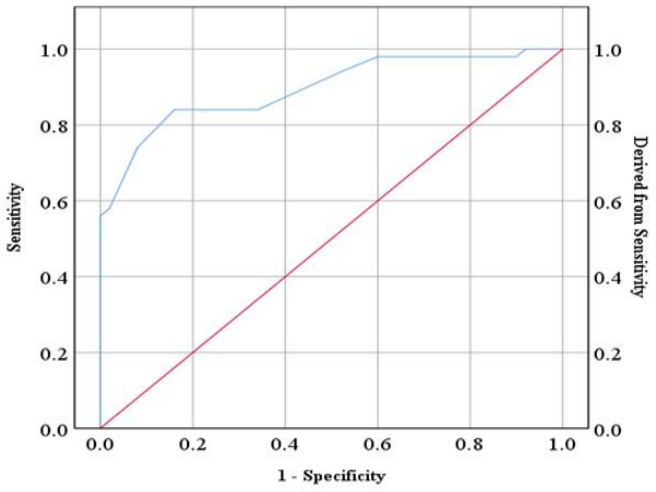

Fig. 4. ROC curve for diagnostic profile of thymus size in diagnosis of IUGR in the study. Examples of ultrasonic pictures are shown in Fig. 5

Fig. 5. Examples of ultrasonic pictures

4. DISCUSSION

In the present study we found statistically significant decrease in the EFW in IUGR group when compared to the control group (P<0.05).

Doppler study of umbilical artery shows significant increase of (PI, RI, SD) in IUGR group when compared to control group. Umbilical artery was the main vessel used for monitoring high risk pregnancies. This is because umbilical artery represents fetoplacental system and primarily reflects placental resistance.

In agreement with our results, Yang et al [5] Conducted Prospective observational study from 2017 to 2019. The study included 50 singleton pregnancies with suspected IUGR and 50 healthy uncomplicated pregnant women as control cases. In umbilical artery, S/D ratio, PI and RI of IUGR fetuses were significantly higher than that of normal fetuses.

Also, Sattar and Wahed [6] Studied 100 pregnant females at 3rd trimester were submitted to full clinical examination, laboratory assessment and Color Flow Doppler (CFD) examination. 58 cases had normal CFD findings and fetal outcome. The remainder 42 cases had IUGR. They found that umbilical artery Doppler PI is significantly higher in-patient group than control group.

Doppler study of MCA artery shows significant increase in (RI, SD) in IUGR group when compared to control group while PI doesn't show significant difference between two groups.

Hussein and Elshikh [7] stated that there is a linear decline in MCA (PI and RI) values according to advancing gestational age, whereas elevated PI and RI values are observed in IUGR.

In contrary to our results, Khanduri et al [8] studied thirty-nine (62.9%) deliveries were IUGR. On all the three visits MCA PI, RI and SD values were significantly lower in IUGR as compared to non-IUGR cases. This might be because of the dynamic behavior of MCA RI as reported by Kurmanavicius et al.[9].They observed a parabolic pattern of change in MCA RI with increasing age; this implies that a single cut-off value should not be employed for the prediction of IUGR.

As regard thymus size we found significant decrease in thymus size in IUGR group when compared to the control group.

In agreement with our results, Cromi et al. [10] studied 63 consecutive patients with growth-restricted fetuses met the inclusion criteria and the control group consisted of 60 appropriate for-gestational age fetuses, thymus perimeter was successfully measured in all cases. They suggest that IUGR is associated with a significant decrease in fetal thymic size compared with that in controls.

Also, Olearo et al. [11] studied 27 SGA and 36 control fetuses. Controls presented a significantly higher TV/AC compared with IUGR with normal umbilical artery FVW and IUGR with abnormal umbilical artery.

Yang et al. [5] studied 53 patients with suspected fetal IUGR were selected into the observation group while another 53 cases as the control group corresponding to the former group's gestational week (GA). The transverse and anteroposterior diameters were measured in the three-vessel view by 2D-ultrasound in IUGR, fetal thymus transverse diameter, is less than those of the same GA fetal thymus.

IUGR group had low survival and lower APGR score when compared to the control group [12]. Increased adverse perinatal outcomes in IUGR pregnancies with a small fetal thymus could partly be explained by the fact that pregnancies with small thymuses are associated with more severe placental disorders compared to normal thymuses. Another contributing factor may be explained by effects of the accompanying intrauterine inflammation in the form of histologic chorioamnionitis and funisitis. Fetal thymic involution has been documented in histologic chorioamnionitis and funisitis, which are usually subclinical and present no overt signs or symptoms [12].

In agreement with our results, Ekin et al. [13] studied the transverse diameter of the fetal thymus in 150 healthy and 143 IUGR fetuses between 24- and 40-weeks' gestation. Small thymus in IUGR fetuses was independently associated with early delivery, respiratory distress syndrome, early neonatal sepsis, and a longer stay in the neonatal intensive care unit.

De Felice et al. [14] observed a significant correlation between a small thymus at birth and adverse neonatal outcomes, such as RDS and sepsis, in a regression analysis after adjusting for gestational age and birth weigh.

Correlation between thymus size with the studied doppler parameters and pregnancy outcome in the current study. Umbilical Doppler RI, PI and SD showed statistically significance in this study ($P<0.05$) and this means that the blood flow in the UA is important for the fetus.

As regard the MCA RI and SD Doppler, they show statistically significance in this study ($P<0.05$) while the MCA PI Doppler did not show any statistically significance in this study ($P>0.05$).

In agreement with our results, Olearo et al. [11] found that all IUGR with abnormal umbilical artery FVW presented with worsening umbilical artery Doppler and compromise of fetal wellbeing before 30 weeks of GA.

Also, we found statically significance of the thymus size in the outcome of this study ($P<0.05$). The sensitivity and the Specificity of this maneuver was 84 % and 84% respectively.
In agreement with our results, Ekin et al. [13] showed that small fetal thymus size showed a significant independent association with IUGR in the multiple logistic regression analysis adjusted for preeclampsia and oligohydramnios.

Disparity in result may be due to manual variation in US studies as it depends on experience of the examiner. In order to eliminate or reduce errors all patients should examined on the same high-quality state-of-art ultrasound scanner with the same, high quality high-frequency transducer, with similar settings and scanning parameters (gain, electronic focusing, and dynamic range) by a single examiner. However, all this is not feasible in daily clinical practice. It requires time, high quality scanners, and maximum concentration of the examiner.

5. CONCLUSIONS

IUGR is associated with small thymus and small fetal thymus may be an early indicator of adverse perinatal outcomes in pregnancies complicated by IUGR.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

This study was approved by the Ethical Committee of Faculty of Medicine, Tanta University. Written informed consent was obtained from all participants,

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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