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Fetal Thymus Volume as a Marker for Intrauterine Growth Restriction.

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Abstract:

Introduction: The Thymus, is an essential fetal lymphoid organ involved in the development of fetal T-cell lymphocytes. Several studies have suggested a potential correlation between an abnormally small Thymus and unfavorable prenatal and postnatal outcomes.

Aim of the study: To detect an association between fetal growth restriction and Thymus gland volume.

Subjects and methods: The current observational case-control study was conducted in the Obstetric clinic at Fayoum University Hospital, with a total sample size of 110 participants (55 cases and 55 matched controls).

Results: There were non-significant differences between both studied groups regarding maternal age, gravidity, parity and gestational age at the time of study enrolment (p >0.05). Estimated fetal weight was significantly lower among the Intrauterine growth restriction (IUGR) group. A threshold volume of thymus gland ≤3.9 could predict IUGR with a sensitivity of 80.18%% and a specificity of 41.80%.

Conclusion: the study detected an association between IUGR and fetal thymic involution. Accordingly including fetal thymus size measurement in antenatal U/S evaluation improves antenatal fetal surveillance.

Keywords: Thymus; IUGR; Fetal; Pregnancy; Involution.

1. Introduction

The Thymus plays a crucial role in the development of fetal T-cell lymphocytes [1]. As gestational age (GA) increases, the maximal diameters and parameters of the thymus in fetuses as determined by obstetric sonography typically increase under normal circumstances [2]. Several studies have indicated a potential correlation between an

anomalous measure of the fetal thymus and unfavorable outcomes both before and after birth. As an example, in their 2014 study, Aksakal et al. (2014) revealed that from 24 to 37 weeks of gestation, a small fetal thymus (within the fifth percentile) could predict histological chorioamnionitis with 91% sensitivity and 81% specificity among women experiencing preterm premature rupture of membranes (PROM) [3]. Furthermore, 22 out of 27 fetuses with a thymus transverse diameter below the fifth percentile were diagnosed with histological chorioamnionitis. Conversely, in the study by Aksakal et al. (2014), among 23 patients with a thymus diameter above the fifth percentile, only two cases showed a reduction in thymus size associated with chorioamnionitis [3]. Additionally, a study conducted by Eviston et al. (2012) compared 120 healthy pregnancies to 53 preeclamptic pregnancies and found that the fetal thymus was on average 2.1 mm smaller in the preeclamptic group, measuring 16.2 mm compared to 18.2 mm in the control group [4].

As an illustration, Cromi et al. (2009) delineated the correlations between biometric parameters, including the biparietal diameter (BPD) and femur length (FL), and the fetal thymus parameter in Intrauterine growth restriction (IUGR)-affected fetuses [5]. They demonstrated that this ratio is considerably diminished when compared to control fetuses with analogous GA. Similarly, both Olearo et al. (2012) and Ekin et al. (2016) discovered that the thymus size of IUGR fetuses is considerably reduced in comparison to a control group consisting of healthy uncomplicated pregnancies [6,7]. Furthermore, it was documented that IUGR fetuses exhibiting abnormal umbilical artery (UA) and uterine artery Doppler flow had a reduced measure of the thymus in comparison to those with regular flow. Potential mechanisms of thymic involution have been suggested to involve neuroendocrine adaptation in response to malnutrition induced by placental insufficiency or alterations in enzyme expression of syncytiotrophoblasts [7]. Furthermore, it is worth noting that thymocyte depletion and thymus enlargement may result from an intrauterine infection accompanied by an inflammatory response [6]. Inconsistencies exist among the findings of the primary research. To highlight these inconsistencies, they demonstrated that IUGR fetuses had a smaller thymus than the control group with normal growth; however, this was contested in a recent meta-analysis [5, 7]. When IUGR

was defined as a birthweight in the 5th or 10th percentiles, Caissutti et al. (2018) discovered no significant correlation between thymus size and compromised fetal growth [8].

Variations in definitions, methodologies of sonographic examination, and the thymus volume may account for a portion of the discrepancies among the scant publications on this subject. it appears an additional research to complete the body of knowledge regarding fetal thymus size and IUGR. To determine the relationship between IUGR and a diminished fetal thymus size as detected by obstetric sonography, the present study was designed. Furthermore, the objective was to ascertain whether IUGR-affected fetuses exhibited a relation between thymus atrophy and aberrant Doppler flow velocity waveforms.

Ultrasound examinations are conducted utilizing a GE Voluson S10 ultrasound scanner by one of two operators, both of whom possess considerable expertise in obstetric ultrasound. To determine the amniotic fluid volume and fetal biometry (including biparietal diameter (BPD), acromioid centimeter (AC), and femoral length (FL) measurements) while excluding significant structural fetal anomalies, patients underwent a comprehensive sonographic evaluation. Fetal weight estimation (EFW) was determined utilizing the formula that Hadlock et al. (1985) proposed. An assessment was carried out on the flow velocity waveform patterns in the umbilical artery (UA), middle cerebral artery (MCA), and ductus venosus (DV) [9]. Oligohydramnios was defined as amniotic fluid levels with an index below 5 centimeters. Abnormal Doppler indices for the UA and DV were noted when the pulsatility index (PI) surpassed the 95th percentile for a given gestational age. Additionally, brain sparing was indicated by an MCA-PI falling below the fifth percentile relative to the gestational age.

Following this, a precise assessment of the fetal thymus was conducted, along with the determination of its perimeter, as previously detailed. A transverse section of the fetal thorax revealed the thymus positioned posterior to the major vessels of the heart and anterior to the sternum. The thymus perimeter was assessed three times for each patient using the trace function of the ultrasound equipment at maximum magnification. Statistical analysis was conducted using the mean of the three measurements. The precision of the thymus

perimeter measurement has been previously documented.

So, the current study aimed to detect the relationship between fetal growth restriction and Thymus gland volume.

2. Subjects & Methods

2.1.Subjects

The current observational case-control study was carried out in the obstetric clinic at Fayoum University Hospital following approval from the local institutional ethical committee. Eligible participants will sign a detailed informed consent form before recruitment.

Inclusion criteria

All patients were women with singleton pregnancies between 28+0 to 38 +0 weeks gestation and had ages between 18 and 45 years old.

Exclusion Criteria

Patients who had multiple pregnancies, congenital anomalies, or any medical disorders that affect pregnancy were excluded.

Sample Size

The sample size was calculated based on the findings from a 2021 study by Keshavarz et al. (2022), which investigated the link between reduced fetal thymus size and IUGR [10]. This study assessed the association of thymus size with abnormal Doppler indices in the fetal umbilical artery (UA) and middle cerebral artery (MCA). The estimated effect size was 0.5. Using G*Power software version 3.1.9.4, the sample size was determined through an a priori analysis for the difference between two independent means (two groups) using an independent sample t-test. The calculation was based on these specified parameters.

2.2. Methods

A total sample size of 110 participants (55 cases and 55 matched controls) was estimated for 90% power, α-error probability of 0.05 and 10% dropout rate during follow-up. All antenatal women provided informed consent to participate in the study. Accordingly, the studied population was divided into two groups:

- Group (1): A sample of 55 eligible pregnant women between 28 and 38 weeks of gestation IUGR.

- Group (2): An equal number of women with normal pregnancies; 55 in a ratio of 1:1 will be chosen in the (control group), within similar gestational age (28 – 38 weeks).

History taking

The complete histories were taken for the medical disorders that affect pregnancy, obstetric history, and menstrual history.

Ultrasound

The thymus appears homogeneous on ultrasound, with an echo texture comparable to that of the liver but inferior to that of the muscle [11]. Additionally, it exhibits numerous echogenic foci or filaments. These "starry sky"-like hyperechoic foci aid in the identification of thymic tissue. Additionally, the distinctive ultrasound appearance aids in the identification of benign anatomical variations, such as the retrocaval or cervical extension of the thymus. Real-time ultrasound reveals that the thymus's shape fluctuates in response to cardiac and respiratory activity; this characteristic aids in distinguishing it from solid tumors and infiltrative diseases.

Virtual organ computer-aided analysis (VOCAL)

Using three distinct techniques, each employing a 30° rotational step angle:

- Minimal manipulation of the 3-DUS data set, with the fetus rotated along any axis;
- Manipulation of the 3-DUS data set, with the fetus rotated along its anteroposterior axis until the fetus could be observed in a standardized manner [12].
- When manipulating the identical 3-DUS data set, the fetus rotated about its longitudinal axis. The assessment of agreement and reliability among and within observers was conducted by calculating intra-class correlation coefficients and limits of agreement. Furthermore, we evaluated the approach that yielded the highest levels of agreement and reliability by employing rotational step angles of 15° and 9°. The duration of the 3-DUS manipulation and fetal volume determination process was documented. The optimal results in terms of agreement and intra-observer reliability were obtained when the fetus was rotated about its longitudinal axis. Altering the rotational step angle to 9° or 15° had no additional effect.

Reliability/agreement

The method used by the observer to determine fetal volume was relatively quick, taking about 1 minute. Our research suggests that the optimal approach for measuring fetal volume involves rotating the

fetus around its longitudinal axis using a rotational step angle of 30°. This technique is not only speedy but also provides reliable and consistent results in analyzing fetal volume.

2.3.Statistical analysis

The gathered data will be systematically organized, encoded, and examined utilizing SPSS for Windows, version 23. The presentation of continuous variables will consist of mean values accompanied by standard deviation (SD), while categorical variables will be expressed as percentages. To compare qualitative data, the chi-squared test and Fisher test will be applied. Comparisons between groups will be conducted using the independent sample t-test for quantitative data. To conduct further statistical analysis, appropriate tests of significance will be employed. P-values less than 0.05 are deemed to indicate statistical significance.

3. Results

Table 1: baseline characteristics among the studied pregnant women (N= 110).

Characteristics		**Studied Groups**		***p*-value**
		IUGR N= 55	Control N= 55	
Age (years)	**Mean ±SD**	31.5 ±3.0	32.3 ±3.2	0.153
	Range (Mini – Max)	27 - 39	27 - 40	
Gravidity	**Mean ±SD**	3.4 ±1.5	2.8 ±1.4	0.058
	Range (Mini – Max)	1 - 7	1 - 5	
Parity	**Mean ±SD**	2.4 ±1.5	1.8 ±1.4	0.058
	Range (Mini – Max)	0 - 6	0 - 4	
GA (weeks)	**Mean ±SD**	33.7 ±3.9	33.9 ±3.7	0.817
	Range (Mini – Max)	26.0 - 38.0	26.0 - 38.5	
EFW	**Mean ±SD**	1463.5 ±476.0	2252.2 ±627.9	**<0.001***
	Range (Mini – Max)	719.0 - 2335.0	950.0 - 3080.0	

Table 2: Thymus gland volume comparison between the IUGR group and healthy control pregnancies (N= 110).

Characteristics		Studied Groups		p-value
		IUGR N= 55	Control N= 55	
Thymus gland volume	Mean ±SD	4.2 ±1.3	5.3 ±1.7	**<0.001***
	Range (Mini – Max)	1.30 – 7.30	1.82 – 7.52	

Table 3: Correlation analysis between Thymus gland volume and other studied variables (N= 110).

Variables		Thymus gland Volume
Maternal Age (years)	r	0.162
	p-value	0.092
	N	110
Gravidity	r	-0.065
	p-value	0.497
	N	110
Parity	r	-0.065
	p-value	0.497
	N	110
GA (weeks)	r	0.351
	p-value	**<0.001***
	N	110
EFW (gm)	r	0.472
	p-value	**<0.001***
	N	110

** Significant at p <0.05.*

Table 4: results of ROC curve analysis for sensitivity and specificity of thymus gland volume as an indicator and diagnostic predictor for IUGR (N= 110).

	AUC	95% CI of AUC		Cut-off	Sensitivity	Specificity	p-value
		Lower Bound	Upper Bound				
Thymus gland volume	0.683	0.579	0.787	3.9	80.18%	41.80%	<0.001*

AUC: Area under the curve, CI: Asymptotic 95% Confidence Interval of AUC.

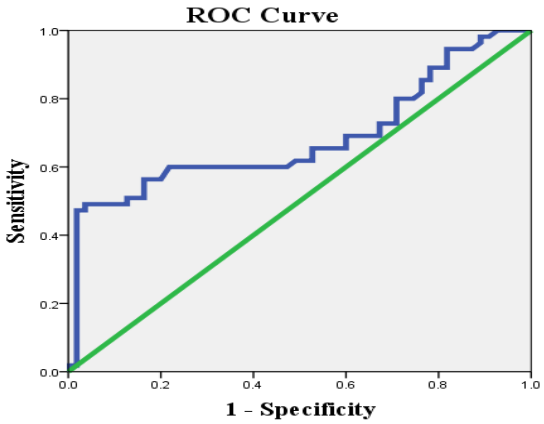

Figure 2: ROC curve for sensitivity and specificity of thymus gland volume as an indicator and diagnostic predictor for IUGR.

Table 5: Unadjusted and adjusted linear regression analysis for predictors of thymus gland volume among our studied population.

	Unadjusted Analysis			Adjusted Analysis		
	Coefficients	**t-test**	**p-value**	**Coefficients**	**t-test**	**p-value**
Maternal Age	0.162	1.701	0.092	0.075	0.851	0.397
Gravidity	-0.065	-0.682	0.497	-0.045	-0.510	0.611
Parity	-0.065	-0.682	0.497	-0.045	-0.510	0.611
GA	0.351	3.898	**<0.001***	0.103	0.934	0.352
EFW	0.472	5.562	**<0.001***	0.389	3.473	**0.001***

Table 6: Association between thymus gland volume and other studied variables (N=110).

Parameters	**Thymus gland volume**		**Test value**	**p-value**
	Range	**Mean±SD**		
Maternal Age (years)				
<30 years	1.43-6.61	4.20±1.52	F:1.911	0.153
30-35 years	1.68-7.52	4.78±1.56		
≥35 years	1.3-7.38	5.15±1.88		
Gravidity				
≤3	1.3-7.52	4.70±1.63	t:0.105	0.917
>3	1.43-7.38	4.74±1.62		
Parity				
<2P	1.3-7.52	4.70±1.67	t:0.137	0.891
≥2P	1.43-7.38	4.74±1.60		
GA (weeks)				
≤32 wks.	1.3-7.52	4.17±1.91	t:2.929	0.004*
>32 wks.	2.28-7.3	5.07±1.31		
EFW (gm)				
≤1500 gm	1.3-7.52	4.06±1.68	t:3.224	0.002*
>1500 gm	2.28-7.3	5.07±1.48		

*Data are expressed as Mean±SD Using: t-Independent Sample t-test & F-One-way Analysis of Variance test p-value >0.05 is insignificant; *p-value <0.05 is significant; **p-value <0.001 is highly significant.*

4. Discussion

In their study involving 60 consecutive IUGR fetuses, Cromi et al. (2009) assessed the thymus perimeter via prenatal ultrasound examination. They discovered that IUGR is associated with a disproportionately small thymus; the ratio of thymus perimeter to BPD, FL, and EFW was significantly lower in IUGR fetuses (>20th gestational week) compared to their control group [5]. The assessment of thymus size to establish its typical range has been conducted; Asghar et al. (2019) published evidence indicating that the diameter and volume of the fetal thymus increase as the weeks of gestation progress [13]. A limited number of studies have conducted direct evaluations of the association between thymic involution and IUGR, according to a limited literature search. To test the hypothesis that IUGR fetuses cause a difference in thymic size from constitutional small for gestational age (SGA) fetuses to intrauterine growth restricted (SGA) fetuses, Olearo et al. (2012) examined 27 SGA and 36 control fetuses [7]. They demonstrated that the fetal thymic volume/AC ratio was greater in the control group compared to IUGR and SGA fetuses 20–37 weeks of gestational age [7]. In a similar vein, Ekin et al. (2016) conducted a study to assess the dimensions of the fetal thymus using sonography in pregnancies characterized by intrauterine growth restriction (IUGR) and to investigate the potential correlation between a diminutive fetal thymus and unfavorable perinatal outcomes [8]. The researchers examined a cohort of 150 healthy fetuses and 143 IUGR fetuses ranging in gestational age from 24 to 40 weeks. Their findings revealed that the transverse diameter of the fetal thymus was noticeably smaller in the IUGR group in comparison to the control fetuses [8].

An additional recent investigation was undertaken by Keshavarz et al. (2022) to assess the correlation between intrauterine growth restriction (IUGR) and diminished fetal thymus size [6]. In a study comparing 46 normal pregnancies within a similar gestational age (GA) range with 46 IUGR pregnancies between 20 and 38 weeks of gestation, adjusted mean thymus diameters were significantly smaller in the IUGR group (mean difference =2.23 mm; *P* =0.02). The researchers concluded that IUGR may be associated with reduced fetal thymus size, particularly when coupled with abnormal Doppler findings.

In contrast to the findings reported in our present study and other comparable research that has been previously referenced, Brandt et al. (2016) examined the correlation between obstetric outcome data and fetal thymus measurements during the second trimester in 520 pregnant women. Their study utilized thymus measurements and obstetric outcome data [16]. Brandt et al. (2016) discovered no correlation between thymus measurements and SGA or pregnancy-related hypertension [14]. The observed incongruity in outcomes may be attributed to the application of an alternative set of inclusion criteria. While Brandt et al. (2016) enrolled expectant women at a gestational age (GA) ranging from 18 to 23 weeks, the current study exclusively recruited women at a GA between 26 and 40 weeks [14]. The size of the fetal thymus during the third trimester is probably more correlated with IUGR and SGA.

The fetal thymus measurements of 70 healthy pregnant patients and 39 pregnant patients with preeclampsia were assessed sonographically in a prospective, comparative cross-sectional study. The findings showed that preeclamptic and small for gestational age (SGA) fetuses had relatively lower thymus measures than the control group. Preeclampsia developed 1–11 weeks later in five fetuses in the control group, as determined by the initial US examination of the small thymus. That study demonstrated that preeclampsia is characterized by a diminutive fetal thymus [15]. It may serve as an early indicator of clinical disease in preeclampsia [4]. Preterm premature rupture of membrane (PPROM) cases involving chorioamnionitis may be significantly correlated with thymus volume loss, according to the findings of two recent studies [16, 17].

Fetal thymus size may play an essential role in the management of pregnancies complicated by a diagnosis of fetal growth restriction, according to the findings of this study. When utilized in conjunction with conventional fetal monitoring techniques like Doppler assessment, it has the potential to influence determinations about the optimal moment of delivery. Clinicians could concentrate on preventive measures, such as hospitalization, maternal corticosteroid administration for fetal lung maturation, and increased surveillance if fetuses with a small thymus are identified. Detection of small fetal thymus intrauterine may also facilitate enhanced and timely interventions for RDS and neonatal sepsis, leading to a reduction in perinatal morbidity and mortality.

Using ROC curve analysis, the sensitivity and specificity of thymus gland volume as an indicator and diagnostic predictor for IUGR was evaluated in the current study, a threshold volume of thymus gland ≤3.9 could predict IUGR with a sensitivity of 80.18%% and a specificity of 41.80%, similar to this finding, a reported in a prospective observational study among 100 women (50 with IUGR and 50 normal pregnancies) with appropriate gestational age, in their analysis thymus size could predict IUGR with a sensitivity of (84%) and a specificity of (84%) [18]. Consistent with the findings presented, Ekin et al. (2016) demonstrated that IUGR was significantly and independently associated with a small fetal thymus in a multiple logistic regression analysis that accounted for oligohydramnios and preeclampsia [8].

Variation in outcomes may arise from manual error in studies conducted in the United States, as it is contingent upon the examiner's level of expertise. To mitigate or eradicate errors, every patient must be evaluated by a single examiner using an identical high-quality, cutting-edge ultrasound scanner equipped with an identical high-frequency transducer and comparable scanning parameters (including gain, electronic focusing, and dynamic range). Nevertheless, none of this is practical in the course of routine clinical practice. It requires sufficient time, high-quality scanners, and the examiner's undivided attention.

The present study is subject to certain limitations. Firstly, the absence of longitudinal sonographic measurements and the comparatively small sample size prevented us from establishing a statistically significant correlation between the extent of compromised thymic growth and neonatal morbidity. Secondly, it was not feasible to monitor the pregnancies beyond delivery to assess post-partum complications and outcomes. Based on the study design, which involved analysing point estimates of various thymus glands, one could contend that the diminutive size of the thymus in fetuses with IUGR is due to its cessation of growth rather than a size reduction.

5. Conclusion

In summary, the findings of this study indicate the presence of a correlation between IUGR and fetal thymic involution. Hence, it can be inferred that fetal thymus size measurement may enhance antenatal fetal surveillance and neonatal management in cases involving IUGR.

Ethical approval and consent to participate: The research was approved by the Fayoum University Faculty of Medicine ethics committee.

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Conflicts of Interest: All authors declare they have no conflicts of interest.

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