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ORIGINAL ARTICLE

Fetal Thymus Measurement as a Sonographic Marker of Subclinical Chorioamnionitis in Preterm Premature Rupture of Membranes.

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ABSTRACT

Background: Preterm premature rupture of membranes (PPROM) increases risk for early neonatal sepsis causing neonatal morbidity and mortality. This study was carried out to assess fetal thymus measure by ultrasound as a predictor of subclinical chorioamnionitis in PROM.

Methods: This prospective analytical study included 206 pregnant women who fulfilled the inclusion criteria in emergency obstetric hospital and outpatient antenatal care unit faculty of medicine Zagazig University. Patients were divided into 2 groups; Control group formed of 103 cases of uncomplicated pregnancy between 24-36 weeks gestational age, and Study group formed of 103 cases of preterm premature rupture of membrane between 24-36 weeks gestational age. All patients had a detailed sonographic assessment to evaluate fetal biometry, fetal thymus measurement, amniotic fluid volume and major structural fetal anomalies.

Results: 68.9% of studied cases had positive histological examination for chorioamnionitis versus 0% of their controls. The ability of small thymus transverse diameter to detect subclinical chorioamnionitis occurrence among PROM females was 100%, while it could exclude 91.5% negative cases among truly negatives examined. With accuracy as a predictor tool of 94.2%.

Conclusion: Assessment of the decrease in fetal thymus diameter by serial ultrasonographic examinations is a promising prenatal method in the prediction of intra-amniotic infection and subclinical chorioamnionitis in cases of PPROM.

Key words: Fetal Thymus, Chorioamnionitis, Preterm PROM

INTRODUCTION

For decades intrauterine infection had been established as one of the main causes of premature rupture of membranes (PROM) and preterm birth, and a risk factor of fetal morbidity and mortality after birth by causing several complications such as, neonatal sepsis, pneumonia, respiratory distress syndrome (RDS), and others [1,2]. The thymus is a primary lymphoepithelial gland plays a vital role in adaptive immunity during both intrauterine and extra uterine life [3].

Around the ninth gestational week the thymus increases in size because of migration of lymphocytes and hematopoietic cells from fetal blood vessels to locate between thymus epithelial cells. By the 12th gestational week, the thymus descends into the anterior mediastinum and becomes encapsulated organ formed of lobules. The cortex contains densely populated lymphocytes while the inner medulla appears less dense because of a relatively small number of lymphoid cells. The thymus size increases continuously throughout fetal life[4].

The Thymus has a major role in T-lymphocyte formation and maturation till puberty after that it decrease in size in a process called involution. Involution can also occur in some stress conditions like acute infection, trauma and malnutrition [4].

The thymus gland size was evaluated sonographically during various gestational ages. It was concluded that; there is progressive increase in thymus gland size with progressing gestational age[5].

Some authors studied the value of estimating fetal thymus size during various pregnancy complications e.g. Fetal thymus size in IUGR fetuses Cromi et al. [6] while, Others have shown a strong correlation between fetal thymus involution and the presence of funisitis in preterm

labor with intact membranes Di Naro et al., [7], or in preterm PROM and chorioamnionitis [8].

Another study reported that measurement of fetal thymus diameter had a good predictive value for identification of Fetal Inflammatory Response Syndrome (FIRS), respectively [9]. So, in recent years, fetal thymus size has been suggested as another sensitive parameter related to pregnancy complications. It has been proposed that thymic involution in pregnancy is an infection-related condition as chorioamnionitis and even subclinical cases[10]. The aim of this study was to assess the role of ultrasound measurement of fetal thymus measures as a predictor of subclinical chorioamnionitis in preterm premature rupture of membranes.

METHODS

A prospective analytical study which included 206 pregnant women who fulfilled the inclusion criteria in emergency obstetric hospital and outpatient antenatal care unit faculty of medicine Zagazig University in the period from October 2017 to February 2020. A verbal and written consent was obtained from all participants and the study was approved by the Research Ethics Committee of the Faculty of Medicine, Zagazig University accepted the study (IRB#534) (TEC No. IEC/07.02.2008 and 46/RIMS & R/2015-16) and performed as per the ethical standards laid down in 1964 (Declaration of Helsinki and its later amendments).

Inclusion criteria: Pregnant women between 24-36 weeks gestational age (control group). Pregnant women with preterm premature rupture of membrane between 24-36 weeks gestational age (study group). Singleton pregnancy. Exclusion criteria: Presence of fetal congenital anomalies. Positive maternal medical history e.g. Diabetes, hypertension, SLE etc. Abnormal AFI according to gestational age (< 5^{th} centile or > 95^{th} centile for gestational age) (for group 1 only). A patient during active labor or presented with clinical signs of chorioamnionitis at time of admission.

Patients were divided into 2 groups: Control group (group 1): 103 cases of uncomplicated pregnancy between 24-36 weeks gestational age undergoing ultrasonographic fetal anomaly scan to exclude fetal anomalies at the time of presentation and fetal thymus measurement. Study group (group 2): 103 cases presented to hospital or outpatient clinic by preterm premature rupture of membrane between 24-36 weeks gestational age. All patients underwent detailed history taking regarding personal, menstrual, and obstetric data including past and family history. Clinical examination had been done including general, abdominal and pelvic examination. Clinical signs of chorioamnionitis were looked for according to Royal College of obstetricians and gynecologists[11]. Clinical chorioamnionitis was considered when there is fever 38.0C (100.4 F) and two signs of the following: uterine tenderness, maternal or fetal tachycardia, and foul/purulent amniotic fluid [12, 13].

Examination for group 2; PPROM was diagnosed by sterile speculum examination and the presence of gross pooling of amniotic fluid in the vaginal vault. The diagnosis of preterm labor was considered when there are regular uterine contractions (at least 3 in 20 min) accompanied by cervical changes (dilatation and effacement) at less than 37 weeks' gestation [14]. Uterine contractions were monitored clinically and / or by CTG.

Laboratory investigations:

Maternal total leucocytic count (TLC) and its differential count including neutrophil % were measured in all patients in the two groups. Normal leucocyte count varies considerably during pregnancy usually ranging from 5000 to 12000/ ml [15]. C-reactive protein was also measured (CRP normal reference range < 6).Two injections 24h apart of betamethasone 12 mg was given to all pregnant women < 34 gestational weeks. All patients received intravenous ampicillin sulbactam 1 g, qid for the first 48h, as a prophylaxis of infection followed by oral ampicillin-sulbactam 375 mg, qid for 5 days. Patients diagnosed as clinical chorioamnionitis received clindamycin at the time of umbilical cord clamping.

UltraSonography and Doppler:

After hospital admission, the fetal thymus measurements were assessed. The fetal thymus in patients of control group were assessed at the same week of gestation of the patients in PPROM group. The measurements were repeated and recorded each week until delivery [16,17]. The assessment of thymus measurements was done by a C1–5MHz abdominal convex probe with Voluson E6 (GE USA) ultrasound machine. A detailed sonographic evaluation including fetal biometry, amniotic fluid volume and exclusion of major structural fetal anomalies. A targeted sonographic evaluation of the fetal thymus perimeter (as previously prescribed by *Zalel et al.*, [5] and fetal thymus transverse diameter (as previously prescribed by Cho et al., [16] was performed. Thymus diameters were measured every week till delivery and the mean of the measures for each case was included in the statistical analysis.

All subjects underwent examination by expert ultrasonographer. The transverse diameter and perimeter of the thymus gland were measured twice for each patient, once with the previously prescribed method by Zalel (an oval homogenous structure in the anterior mediastinum, formed of

two connected lobes which was visualized in the transverse section of the fetal chest between the sternum and the great vessels of the heart ('the three vessels view') and between both lungs) and Cho (the maximum transverse diameter of the thymus by placing a line cursor perpendicular to the line connecting the sternum and the spine) and once using the *thy-box* (where the internal mammary arteries that course laterally to the thymus were located by using color or power Doppler ultrasonography with a low pulse repetition frequency of these vessels as described by Paladini et al [18] to facilitate visualization of the thymus gland(figure 1,2)

In the patients of two groups, the placenta, membranes and umbilical cord were obtained after delivery, washed with saline, preserved in 10% buffered formalin with ratio 10:1 of fixative to tissue and sent to pathology department where an expert pathologist evaluated them for histological evidence of chorioamnionitis, villitis or funisitis. Each specimen was subjected to serial sections of 2cm thickness fixed in normal saline. Acute chorioamnionitis defined as presence of any polymorphonuclear leukocytes in the chorion, amnion or umbilical cord, or in significant amounts in the subchorionic space[19]. Funisitis was diagnosed by the presence of neutrophil infiltration into the wall of 1or more umbilical vessel or Wharton's jelly[20].

STATISTICAL ANALYSIS

Data were analyzed using IBM SPSS 23.0 for windows (SPSS Inc., Chicago, IL, USA) and NCSS 11 for windows (NCSS LCC., Kaysville, UT, USA). P-value <0.05 was considered significant, P-value <0.001 was considered as highly significant.

RESULTS

Table (1), showed a high significant decrease in gestational age at ROM and at delivery among studied cases with significant decrease in birth weight too than their controls. More than half of the studied cases (57.3%) had neonates admitted to NCU (mean GA at delivery 34.5wks) versus 2.9% (GA at delivery 36.2wks) among their controls, showed high statistical significant difference between the two groups, with increased prevalence of complications

Table (1): Basic data and neonatal complications of the studied groups

Variables	Studied groups Mean SD					P value
	Studied cases (N=103)		Controls (N=103)			
Mother age Range	26.1 ± 4.92 19 - 33		25.7 ± 6.57 17 - 37		0.36	0.72 NS
Gestational age at ROM/week Range	33.2 ± 2.42 28 - 36		38.4 ± 0.92 37 – 40		20.5	<0.001 HS
Gestational age at delivery Range	35.6 ± 3.25 30 –36		38.4 ± 0.92 37 – 40		8.31	<0.001 HS
ROM latency period/day Range	19.1 ± 18.8 7 – 90 (14)		1.67 ± 0.76 1 – 3 (1.5)		8.95*	<0.001 HS
Birth weight Range	1835.7± 234.3 1500-2230		2790.7± 519.9 1990 – 3700		16.99	<0.001 HS
	N	%	N	%		
Mode of delivery CS NVD	 84 19	 81.6 18.4	 85 18	 82.5 17.5	 0.03	 0.86 NS
Parity Nullipara ≥2	 46 57	 44.7 55.3	 47 56	 45.6 54.4	 0.02	 0.89 NS
Admission to NCU	59	57.3	3	2.9	Fisher	<0.001 HS
Neonatal complications Neonatal sepsis Respiratory distress Pneumonia IVH (>grade II) Broncho-pulmonary dysplasia Necrotizing enterocolitis	 6 27 13 15 3 4	 5.8 26.2 12.6 14.6 2.9 3.9	 1 3 2 0 0 0	 1 2.9 1.9 0 0 0	81.96	 <0.001 HS

SD:standered deviation *ROM : rupture of membrane* *IVH : intra-ventricular hemorrhage*
NCU: neonatal care unit *CS : cesarean section* *HS :highly significant*

NVD: normal vaginal delivary NS :non significant

Table (2), showed that significant difference among both groups regarding all laboratory data (WBCs, total, differential and C-reactive protein values).

Table (2): Laboratory data of the studied group.

Variables	Studied groups Mean SD		MW	P value
	Studied cases (N=103)	Controls (N=103)		
WBCs Median Range	12.7 ± 3.32 12.5 7 – 18.5	10.6 ± 3.97 10.6 4.5 – 18.9	3.48	<0.001 HS
Neutrophils Median Range	9.88 ± 3.37 9.6 5.3 – 15.8	7.5 ± 3.62 7.1 2.5 – 17.2	4.92	<0.001 HS
Monocytes Median Range	1.47 ± 0.68 1.2 0.1 – 3	1.9 ± 1.02 1.8 0.5 – 3.8	2.13	0.03 S
Lymphocyte Median Range	1.31 ± 0.85 0.9 0.4 – 2.7	0.98 ± 0.65 0.9 0.2 – 3	2.1	0.04 S
CRP Median Range	8.16 ± 5.13 7 3 – 22.8	4.81 ± 2.1 4 3 – 10	6.1	<0.001 HS

SD: standered deviation WBCs: white blood cells
CRP: c-reactive protein HS: highly significant

Table (3), showed that 68.9% of studied cases had positive histological examination for chorioamnionitis versus 0% of their controls. There was a high statistically significant difference among both groups regarding transverse thymus diameter and its perimeter, which is significantly decreased among studied cases than controls.

Table (3): Histological chorioamnionitis, thymus transvers diameter and perimeter among both studied groups.

Variables	Studied groups			P value
	Studied cases (n=103)	Controls (n=103)		
Positive Negative	71 (68.9%) 32 (31.1%)	0 (0.0%) 103 (100%)	Fisher	<0.001 HS
Thymus transverse diameter (cm) Range	1.98 ± 0.54 1.16 – 2.98	2.42 ± 0.17 2.11 – 3.25	7.8	<0.001 HS
Perimeter (cm) Range	5.77 ± 1.5 2.96 – 8.34	7.64 ± 0.64 5.62 – 8.81	11.9	<0.001 HS

HS: highly significant

Table (4), showed that significant association between histological (subclinical) chorioamnionitis and GA at ROM and delivery, CS and multipara and occurrence of complications and admission to NCU.

Table (4): Association of histological chorioamnionitis and basic data and neonatal complications of the studied cases.

Variables	Studied cases Mean SD			P value
	Positive (N=71)	Negative (N=32)		
Mother age Range	25.4 ± 4.72 19 – 33	27.4 ± 5.13 20 – 33	1.98	0.05 NS
Gestational age at ROM/ week Range	32.3 ± 2.1 28 - 35	33.6 ± 2.46 30 – 36	2.65	0.009 S

Variables	Studied cases Mean SD					P value
	Positive (N=71)		Negative (N=32)			
Gestational age at delivery Range	34.5 ± 1.88 30 – 36		36.2 ± 3.6 32– 37		2.52	0.01 S
ROM latency period/ day Range	17.2 ± 3.2 7 – 90 (10)		19.99 ± 22.5 13 – 23 (17)		2.36*	0.02 S
Birth weight Range	1813.4± 247.8 1500-2230		1845.8± 228.6 1990 – 3700		0.65	0.52 NS
	N	%				
Mode of delivery CS NVD	 64 7	 90.1 9.9	 20 12	 62.5 37.5	11.3	0.001 S
Parity Nullipara ≥2	 20 51	 28.2 71.8	 26 6	 81.2 18.8	25.1	<0.001 HS
Admission to NCU	59	83.1	0	0.0	Fisher	<0.001 HS
Neonatal complications Congenital sepsis Respiratory distress Pneumonia IVH (>grade II) Broncho-pulmonary dysplasia Necrotizing enterocolitis	 6 26 13 15 3 4	 8.5 36.6 18.3 21.1 4.2 5.6	 0 1 0 0 0 0	 0.0 3.1 0.0 0.0 0.0 0.0	81.96	<0.001 HS

SD: Standered Deviation ROM :rupture of membrane IVH : Intra-Ventricular Hemorrhage NCU: neonatal care unit CS : cesarean section NVD: normal vaginal delivery HS :highly significant NS :non significant

Table (5), showed that significant association between histological (subclinical) chorioamnionitis and laboratory data, small thymus and perimeter diameter.

Table (6), showed that the ability of small thymus diameter to detect histological (subclinical) chorioamnionitis occurrence among PROM females was 100%, while it could exclude 91.5% negative cases among truly negatives examined. With accuracy as a predictor tool of 94.2%.

Table (5): Association of histological chorioamnionitis with laboratory data, thymus transvers diameter and perimeter of the studied cases.

Variables	Studied cases Mean SD		t-test MW*\	P value
	Positive (N=71)	Negative (N=32)		
WBCs Median Range	13.7 ± 3.36 13.5 7 – 18.5	10.4 ± 1.73 10.2 8.5 – 12.5	6.85	<0.001 HS
Neutrophils Median Range	10.99 ± 3.39 9.8 5.3 – 15.8	7.42 ± 1.53 7.6 5.6 – 9.1	7.35	<0.001 HS
Monocytes Median Range	1.53 ± 0.64 1.3 0.5 – 3	1.37 ± 0.78 1.2 0.1 – 2.4	0.101*	0.92 NS
Lymphocyte Median Range	1.22 ± 0.83 0.8 0.4 – 2.7	1.52 ± 0.85 1 0.5 – 2.5	2.81*	0.005 S
CRP Median Range	9.38 ± 5.7 9 3 – 22.8	5.44 ± 1.4 5 4 – 7	3.74*	<0.001 HS

Variables	Studied cases Mean SD		t-test MW*\	P value
	Positive (N=71)	Negative (N=32)		
Thymus transverse diameter(cm) Range	1.72 ± 0.42 1.16 – 2.45	2.56 ± 0.27 1.88 – 2.98	12.1	<0.001 HS
Perimeter(cm) Range	5.1 ± 1.1 2.96 – 6.32	7.24 ± 1.1 5.49 – 8.34	9.39	<0.001 HS

SD: Standered Deviation WBCs: white blood cells CRP: c-reactive protein
HS: highly significant S:significant NS :non significant

Table (6): Reliability data of thymus diameter as a predictor of histological chorioamnionitis occurrence among studied cases of PROM.

Cut off	AUC	P-value	PPV	NPV	sensitivity	specificity	accuracy
<1.86 cm	0.998	<0.001	84.2%	100%	100%	91.5%	94.2%

AUC: area under the curve PPV: positive predictive value
NPV: negative predictive value
Fisher's exact test, P < 0.05 is significant, NS: Non-significant

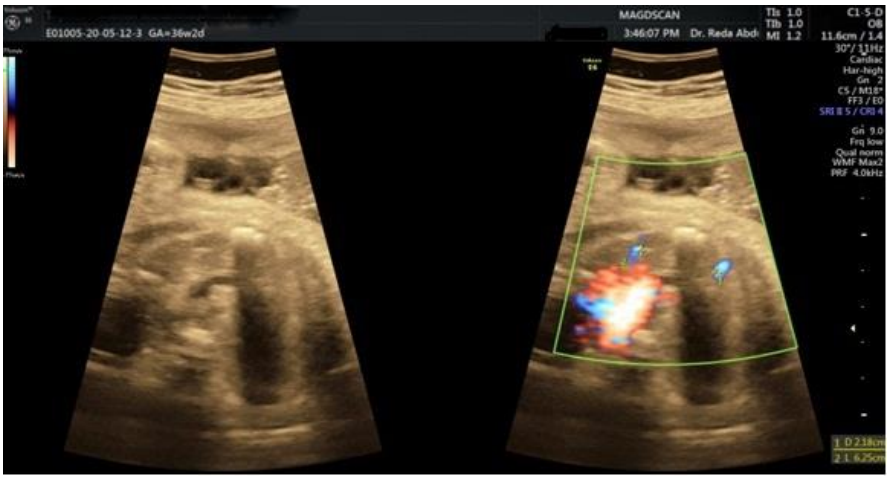

Figure 1: Appearance and measurement of fetal thymus of a patient at the 36 wk+2d of gestation. Using power Doppler ultrasonography with a low pulse repetition frequency of these vessels as described by Paladini et al. 1:trans. diameter 2:perimeter diameter.

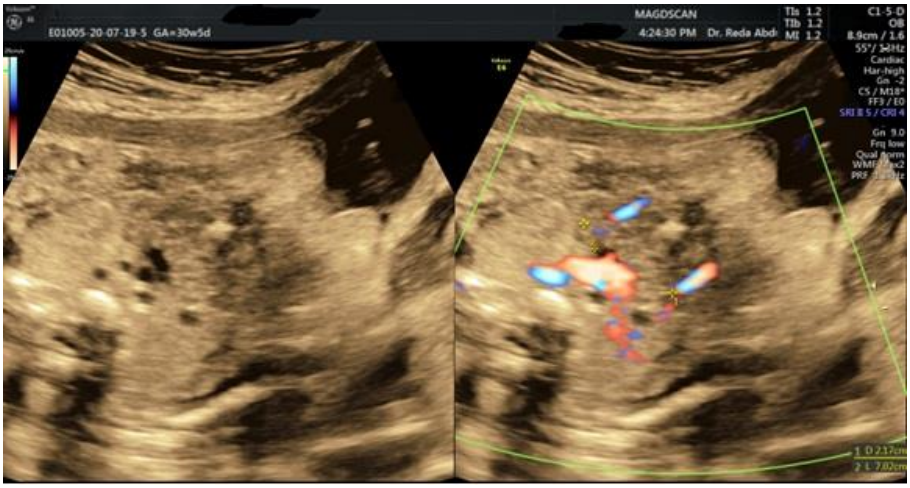

Figure 2: Appearance and measurement of fetal thymus of a patient at the 30wks+5d of gestation. using color Doppler ultrasonography with a low pulse repetition frequency of these vessels as described by Paladini et al.1:trans.diameter 2:perimeter diameter.

The mean for both measurements was then used for statistical analysis. Thymus diameters were measured every week till delivery and the mean of the measures was included in the statistical analysis. A small thymus in the study group was defined as a thymus perimeter and transverse diameter < 5th percentile according to the control in control group. Thymus tissue was identified in the fetal thorax as a quadrangular shape located at mid-sternum level in front of the pulmonary artery, aorta, superior vena cava (Three vessel sign) (Figure 3).

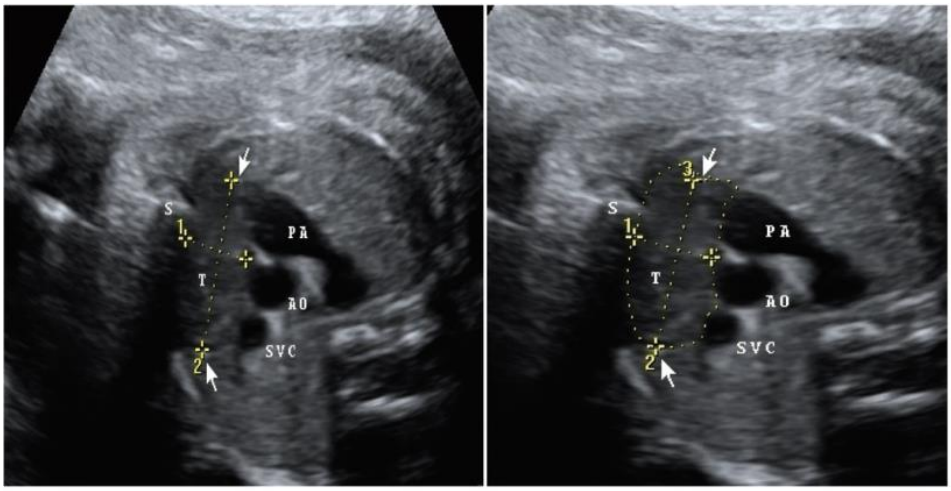

Figure (3): Appearance and measurement of fetal thymus of a patient at the 30th week of gestation. Fetal thymus and 3-vessel sign on a transverse section taken on midsternal line in fetal thorax. 1 – Thymus anteroposterior diameter, 2 – Thymus transverse diameter, 3 – Thymus perimeter measurement. (P, pulmonary artery; Ao, aorta; SVC, superior vena cava; S, sternum; T, thymus)

DISCUSSION

In the present study, there was a high statistically significant decrease in gestational age at ROM and at delivery among studied cases with significant decrease in birth weight too when compared with the results of control group.

These findings agree with those of Aksakal et al. [21] who found that the patients of PPROM group who delivered earlier than 34th week of gestation were 28%, while 72% delivered after the 34th – 36th week and there was a statistically significant difference between PPROM group and control group regarding birth weights ($p < 0.05$), while the mean gestational age of the patients were similar in both groups ($p = 0.36$).

In the present study, there was a statistically significant difference among the two groups regarding total and differential leukocytic count and CRP which disagrees with Aksakal et al. [21] who found no statistically significant difference as regards CRP and white blood cell values between cases of chorioamnionitis and those without chorioamnionitis.

Also, Vizcaíno et al. [22] found that chorioamnionitis is associated with an elevated maternal white blood cell count (>15 000 cells/mm3), while Tita and Andrews, [23] reported that leukocytosis and high levels of C-reactive protein were found in approximately 70% to 90% of cases of clinical chorioamnionitis.

In the present study, more than two thirds of the study group had positive histological examination for chorioamnionitis (presence of any polymorphonuclear leukocytes in the chorion, amnion or umbilical cord, or in significant amounts in the subchorionic space [19]. versus 0% of their controls.

This came in agreement with Aksakal et al. [21] results as in the PPROM group the histological chorioamnionitis was detected in about half of patients and funisitis (presence of neutrophil infiltration into the wall of 1or more umbilical vessel or Wharton's jelly) [20]. was detected in only 10% and cases of Funisitis were always associated with histological chorioamnionitis. Tita and Andrews, [23] found that the prevalence of histological chorioamnionitis (HCA) was >50%.

In the present study, there was a high statistically significant difference among both studied groups regarding transverse thymus diameter and perimeter, which decreased more among studied cases than controls and there was a statistically significant association between histological chorioamnionitis and thymus transverse diameter and perimeter diameter. Which were decreased in positive cases with histological chorioamnionitis.

This came in agreement with Cetin et al. [24] who found that fetal thymus transverse diameter was found decreased in all fetuses suffered from neonatal sepsis. Also, Musilova et al. [25] evaluated the fetal thymus transverse diameter in 216 fetuses from pregnancies associated with PROM by a single measurement at admission and observed that a small fetal thymus transverse diameter below 5% (according to the normograms from their previous study Musilova et al., [17] was

detected in 80% (106/133) and 88% (36/41) of patients with histologic chorioamnionitis and funisitis, respectively.

Gantert et al. [26] found acute thymic involution occurred in very low birth weight preterm infants of cases of chorioamnionitis as a significant decrease in thymic size was found in cases of chorioamnionitis. Moreover, the measurement of the fetal thymus using ultrasound not only decreased in women with PPROM and chorioamnionitis, but also might indicate presence of subclinical cases [8,26,27].

Furthermore, Toti et al. [28] revealed even in cases of subclinical CA the involution of the fetal/neonatal thymus has been observed. The involuted thymuses presented with extensive lympho-depletion of the cortex and a decreased corticomedullary ratio. These findings made the authors conclude that histological CA is associated with thymus changes and shrinkage, which overlap with those found in neonates with proven sepsis and suggested that the process of thymic involution can be an integral part of the fetal inflammatory response syndrome.

This came in disagreement with Aksakal et al. [21] who reported that there was no statistically significant difference between study groups regarding mean thymus area measurement values ($p = 0.65$).

Hamamoto et al.[29] suggested that a decrease in thymus size may be sign of chorioamnionitis and preterm labor. Also, the study of Yinon et al. [8] revealed that there was a negative correlation between fetal thymus size with chorioamnionitis and with the resulting PROM.

Moreover, a correlation with infection was also noticed significantly only in the first 24h of life as clinical signs of infection are yet to develop. The prove of an association between thymic size and infection is further provided by a pathology study of Galvina-Durov et al. [30] who investigated post-mortem 100 premature neonates and results indicated that advanced thymic involution was associated with infection as a cause of death ($p < 0.001$).

In the present study, the ability of small thymus diameter to detect chorioamnionitis occurrence among PROM females was 100% with area under the curve (AUC) 0.998, while it could exclude 91.5% negative cases among truly negatives examined. With accuracy as a predictor tool of 94.2%.

This came in agreement with Aksakal et al. [21] who reported that thymus measurements had sensitivity of 75%, specificity of 81%, PPV of 78%, NPV of78% in detecting CA in PPROM patients. Also, the receiver operating characteristics (ROC) analysis of Cetin et al. [24] showed that the area under the curve was 0.867 (95% CI: 0.758–0.976) for decreased fetal thymus transverse diameter. This decrease in fetal thymus transverse diameter can predict neonatal sepsis with a sensitivity of 100% (95% CI: 68–100), specificity of 73% (95% CI: 54–87), PPV of 55%, and NPV of 100%.

Musilova et al. [25] found that the presence of a small fetal thymus transverse diameter can identify chorioamnionitis with a sensitivity of 79%, specificity of 47%, PPV of 71%, and NPV of 59%, $p < 0.0001$; odds ratio 3.5. Whereas, it can detect funisitis with a sensitivity of 88%, specificity of 35%, PPV of 24%, and NPV of 92%, $p = 0.004$; odds ratio 4.4.

Aksakal et al. [21] found that in PPROM patients fetal thymus transverse diameter can predict histological chorioamnionitis with 91% sensitivity, 81% specificity, 82% PPV, and 91% NPV. They denote that among several methods for measuring thymus size, fetal thymus transverse diameter is the easiest method.

Yinon et al. [8] revealed that fetal thymus perimeter if below the 5th percentile can adentify chorioamnionitis with a sensitivity of 100%, specificity of 66.7%, a PPV of 69% and a NPV of 100%. In other words a normal thymus size in preterm PROM patient could be a reassuring sign that there is a minimal risk for CA. Depending on their results, a small thymus has a positive predictive value of 69% and the possibility of infection, should be confirmed or rulled out by further tests, such as clinical findings and amniotic fluid tests.

El-Haieg et al. [9] found that a small thymus had an accuracy of 84%, sensitivity of 87.5% (14/16), specificity of 67% (2/3), positive predictive value of 93% (14/15) and negative predictive value of 50% (2/4) in the identification of fetal inflamatory response syndrome which reflect intra-amniotic infection and/or chorioamnionitis even the subclinical one. Li et al. [31] found that ultrasound measurements of fetal thymus may have prediction value for subclinical chorioamnionitis. A finding which completely agrees with our results.However our results differs in that,we concluded a cutoff point for prediction of subclinical chorioamnionitis.

The weaknesses of our study could be the low number of cases and inability to assess the interpersonal variability between different sonographers in measuring fetal thymus transverse diameter [because the examinations were all performed by the same expert ultra-sonographer].

Obtaining a good measurement of the thymus was limited by anterior placement of the placenta,

decreased amniotic fluid volume or a fetus facing the mother's back. In our study, 103 women had PPROM, and hence decreased amniotic fluid, which constituted a major difficulty for the visualization of the thymus, especially during measurement of thymus perimeter and determining its boundaries for accurate measurement (which takes time) and inadequate measurement in some cases. In the case of an inappropriate positioning of fetus, waiting for a while for the fetus to move may be an option for better visualization; however, oligohydramnios restricts the movement of the fetus; therefore, it has a dual impact on fetal thymus visualization.

CONCLUSION

Assessment of the decrease in fetal thymus diameter by serial ultrasonographic examinations is a promising prenatal method in the prediction of intra-amniotic infection and subclinical chorioamnionitis in cases of PPROM. Normal thymic measures could be a sign of a very small risk of neonatal sepsis, and a small thymus should lead to additional tests for decision-making. The decrease in fetal thymus diameter gives a better prediction of intra-amniotic infection and subclinical chorioamnionitis compared to the prenatal maternal CRP and WBC count, and has a predictive value.

REFERENCE

1. **Goldenberg, R.L., Andrews, W.W., Mercer, B.M., Moawad, A.H., Meis ,P.J., Iams, J.D., et al.** The preterm prediction study: granulocyte colony-stimulating factor and spontaneous preterm birth. Am J Obstet Gynecol. 2000,(182) 625-30.
2. **Henríquez, G.M., & Rodrigo, F.G.** Chorioamnionitis and neonatal morbidity: current perspectives. Res Rep Neonatol. 2017,(7)41.
3. **Rodewald, H.R.** Thymus organogenesis. Annu. Rev. Immunol. 2008,(26)355-88.
4. **Gordon, J., & Manley, N.R.** Mechanisms of thymus organogenesis and morphogenesis. Development. 2011,(138) 3865-78.
5. **Zalel, Y., Gamzu, R., Mashiach, S., & Achiron, R.** The development of the fetal thymus: an in utero sonographic evaluation. Prenat Diagn. 2002; 22: 114–7.
6. **Cromi, A., Ghezzi, F., Raffaelli, R., Bergamini, V., Siesto, G., & Bolis, P.** Ultrasonographic measurement of thymus size in IUGR fetuses: a marker of the fetal immunoendocrine response to malnutrition. Ultrasound Obstet Gynecol. 2009, (33) 421-6.
7. **Di Naro, E., Cromi, A., Ghezzi, F., Raio, L., Uccella, S., D'Addario, V., et al.** Fetal thymic involution: a sonographic marker of the fetal inflammatory response syndrome. Am J Obstet Gynecol. 2006,(194)153-59.
8. **Yinon, Y., Zalel , Y., Weisz, B., Mazaki-Tovi, S., Sivan, E., Schiff, E., et al.** Fetal thymus size as a predictor of chorioamnionitis in women with preterm premature rupture of membranes. Ultrasound Obstet Gynecol: J Int Soci Ultrasound Obstet Gynecol. 2007, (29) 639-43.
9. **El-Haieg, D.O., Zidan, A.A., & El-Nemr ,M.M.** The relationship between sonographic fetal thymus size and the components of the systemic fetal inflammatory response syndrome in women with preterm prelabor rupture of membranes. BJOG: Int J Gynaecol Obstet. 2008,(115) 836-41.
10. **Caissutti, C., Familiari, A., Khalil, A., Flacco, M.E., Manzoli, L., Scambia, G., et al.** Small fetal thymus and adverse obstetrical outcome: a systematic review and a meta-analysis. Acta Obstet Gynecol Scand. 2018,(97)111-121.
11. **No, RGTG.** Antenatal corticosteroids to reduce neonatal morbidity and mortality. London, RCOG.(2010),No 44.
12. **Gibbs, RS., & Duff, P.** Progress in pathogenesis and management of clinical intra amniotic infection. Am J Obstet Gynecol. 1991, (164) 1317–26.
13. **Newton, E.R.** Chorioamnionitis and intraamniotic infection. Clin Obstet Gynecol. 1993, (36)795–808.
14. **Goldenberg, R.L., Culhane, J.F., Iams, J.D., & Romero, R.** Epidemiology and causes of preterm birth. The lancet. 2008, 371(9606): 75-84.
15. **Taylor, D.G., Phillips, P., & Lind, T.** Puerperal hematological indices. Br J Obstet Gynaecol. 1981, (88)601-6.
16. **Cho, J., Min, J.Y., Lee, Y.H., McCrindle, B., Hornberger , L.K, & Yoo SJ.** Diameter of the normal fetal thymus on ultrasound. Ultrasound in Obstetrics and Gynecology: Ultrasound Obstet Gynecol. 2007,(29)634-8.
17. **Musilova, I., Kacerovsky, M., Reslova, T., & Tosner, J.** Ultrasound measurements of the transverse diameter of the fetal thymus in uncomplicated singleton pregnancies. Neuro Endocrinol Lett. 2010,(31) 766.
18. **Paladini, D.** How to identify the thymus in the fetus: the thy-box? Ultrasound Obstet Gynecol. 2011, (37)488-492.
19. **Redline, R.W., Faye-Petersen, O., Helle, D., Qureshi, F., Savell, V., & Vogler, C.** Amniotic infection syndrome: nosology and reproducibility of placental reaction patterns. Pediatr Dev Pathol, 2003, (6)435–48.

20. **Toti, P., De Felice, C., Stumpo, M., Schürfeld, K., Di Leo, L., Vatti, R., et al.** Acute thymic involution in fetuses and neonates with chorioamnionitis. Hum Pathol. 2000,31(9) 1121-8.
21. **Aksakal, S.E., Kandemir, O., Altınbas, S., Esin, S., & Muftuoglu ,K.H.** Fetal tyhmus size as a predictor of histological chorioamnionitis in preterm premature rupture of membranes. J Maternal Fetal & Neonatal Medicine. 2014, (27) 1118-22.
22. **Vizcaíno, L.T., Herrera, D.C., & Torriente, M.C.** Chorioamnionitis: review of the literature. World Journal of Advanced Research and Reviews. 2020, (7) 238-46.
23. **Tita, A.T., & Andrews,W.W.** Diagnosis and management of clinical chorioamnionitis. Clin Perinatol. 2010, 37(2) 339-54.
24. **Cetin, O., Cetin, I.D., Uludag, S., Sen, C., Verit, F.F., & Guralp, O.** Serial ultrasonographic examination of the fetal thymus in the prediction of early neonatal sepsis in preterm premature rupture of membranes. Gynecol Obstet Invest. 2014, (78) 201-7.
25. **Musilova, I., Hornychova, H., Kostal, M., Jacobsson, B., & Kacerovsky, M.** Ultrasound measurement of the transverse diameter of the fetal thymus in pregnancies complicated by the preterm prelabor rupture of membranes. J Clin Ultrasound. 2013,(41)283–9.
26. **Gantert, M., Been, J.V., Gavilanes ,A.W., Garnier, Y., Zimmermann, L.J., & Kramer, B.W.** Chorioamnionitis: a multiorgan disease of the fetus. J Perinatol. 2010, (30) 21-30.
27. **Zuckerwise, L.C., Li, L., & Copel, J.A**. Thymus. In Obstetric Imaging: Fetal Diagnosis and Care. 2018,(20) 25-8.
28. **Toti, P., De Felice, C., Stumpo, M., Schürfeld, K., Di Leo, L., Vatti, R., et al.** Acute thymic involution in fetuses and neonates with chorioamnionitis. Human pathology. 2000,31(9) 1121-8.
29. **Hamamoto, T.E., Hatanaka, A.R., & Franca, M.S.** Ultrasonographic measurements of fetal thymus size and preterm birth predictors. Available at: https://fetalmedicine. org/abstracts/ 2015/var/pdf/abstracts/1102.pdf. (2015).
30. **Galvina-Durdov, M., Springer, O., Ćapkun, V., Saratlija-Novaković, Ž., Rozić , D., & Barle, M.** The grade of acute thymus involution in neonates correlates with the duration of acute illness and with the percentage of lymphocytes in peripheral blood smear. Biol Neonate. 2003, (83) 229-34.
31. **Li, ZH. O.U.,&Yong-hong, W.A.** Advances in the Prediction of Premature Rupture of Membranes with Chorioamnionitis by IL-1β, MMP-8 and Fetal Thymus. Journal of International Obstetrics and Gynecology. 2019, (46) 44.

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