Evaluation of two-dimensional ultrasound fetal thymus size in correlation to infection parameters in pregnancies complicated with preterm premature rupture of membranes

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Background/aim
The thymus is essential for developing the fetal immune system and may show involution upon exposure to acute stress. Early detection of intrauterine infection is urgently needed to avoid fetal affection and sepsis. The present study aims to correlate the fetal thymus size with the infection parameters in pregnancies complicated with preterm premature rupture of membranes (PPROM).

Subjects and methods
The present study recruited pregnant women who fulfilled the inclusion criteria in a ratio of 1 case to 4 controls according to the study design; Group 1 of twenty cases presenting in PPROM, and Group 2 of eighty cases of women without PPROM. The primary outcome of the study was to measure fetal thymus size by abdominal ultrasound and its correlation with maternal total leukocytic count (TLC) and its differential count, C-reactive protein (CRP), and maternal fever. The secondary outcomes involved the correlation of the fetal thymus size with fetal distress, the occurrence of neonatal infection, Apgar neonatal score, and histological examination of the placenta and membranes for evidence of chorioamnionitis.

Results
Group 1 had a significantly higher CRP level ($P<0.001$), higher TLC level ($P=0.035$), and higher Staff ($P<0.001$). On the contrary, group 2 had significantly higher AFI ($P=0.022$), greater Thymus perimeter ($P<0.001$), and greater thymus transverse diameter ($P<0.001$). In addition, the pathological examination of the placenta revealed positive signs of infection in group 1 in only 65% of cases. Group 1 had a positive correlation between Thymus perimeter and APGAR score of the neonates ($r=0.658$, $P=0.002$), Thymus perimeter and birth weight ($r=0.741$, $P<0.001$), Thymus transverse diameter and APGAR score of the neonates ($r=0.741$, $P<0.001$), and finally Thymus transverse diameter and birth weight ($r=0.734$, $P<0.001$). Group 2 showed a significant positive correlation between the Thymus perimeter and neonatal APGAR score ($r=0.232$, $P=0.039$) and Thymus transverse diameter and birth weight ($r=0.320$, $P=0.004$). In Group 1, Cases with placental signs of infection (n=13) had higher CRP levels ($P=0.046$), higher TLC levels ($P=0.014$), higher Staff ($P<0.001$), but lower AFI ($P=0.032$).

Conclusion
The assessment of the fetal thymus during the routine second- and/or third-trimester scan could be a predictive measure for intra-amniotic infection. However, there is no association between small fetal thymus and adverse perinatal outcomes in uncomplicated pregnancies. Further larger studies with different demographic, maternal characteristics, and different inflammatory processes with and without active management to summarize whether fetal thymus can be used in clinical practice to avoid infection-related fetal morbidities or not.

Keywords:
chorioamnionitis, preterm premature rupture of membranes, thymus gland

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Introduction

Thymus gland nomination is a Latin derivation from the Greek language that means 'warty excrescence.' The thymus gland represented the seat of the soul in ancient Greek civilization [1]. Early in pregnancy, the

third pharyngeal pouch and cleft complex represent the origin of the thymus gland. A fibrous tissue band descends from the capsule to divide the gland into two lobes with a peripheral cortex and a central medulla [2,3]. The thymus is essential for the development of the fetal immune system, and it is the main source of T-cell production and development which is responsible for the fetal inflammatory response. The Thymus gland may show involution upon exposure to acute stress as sepsis, malnutrition, and trauma [4].

In clinical obstetrics, accurate and early detection of intrauterine infection is urgently needed. PPROM is an important condition that needs active investigation [5] to avoid the development of chorioamnionitis (CA). Early diagnosis of chorioamnionitis (CA) in pregnant women with preterm premature rupture of membranes (PPROM) is an important issue that can avoid many neonatal sequelae. Till nowadays, there is a lack of an efficient clinical marker to predict early intrauterine infection in women with PPROM [5]. The thymus gland parameters could be used for early detection of CA [6,7]. It had been reported that intrauterine inflammation led to fetal multisystem affection, failure of tocolysis, as well as adverse fetal morbidities such as sepsis, cardiac dysfunction, cerebral palsy, and bronchopulmonary dysplasia [8].

Ultrasonography and magnetic resonance imaging, to a lesser extent, are the main devices used to assess the thymus gland [9]. Assessment of the thymus by ultrasound is by measuring perimeter, transverse diameter, thymo-thoracic ratio, and thymic index. The fetal thymus is found in the mediastinum anterior to the great arteries and superior vena cava. For many years, the fetal thymus parameters have been used as a marker of heart defects and genetic conditions and as a predictor for intrauterine growth restriction (IUGR) and preeclampsia [10]. Fetal thymus evaluation has become an important diagnostic and predictive tool for obstetricians, neonatologists, and pediatric immunologists that may predict immunodeficiencies and qualify for further vaccination protocol [11]. We also need to clarify the role of the ultrasound of the fetal thymus in inflammatory conditions associated with PPROM.

In our study, we aimed to measure fetal thymus size by abdominal ultrasound and to detect its correlation with maternal total leukocytic count (TLC) and its differential count, C-reactive protein (CRP), and maternal fever. Also, we aimed to study the correlation of the fetal thymus size with fetal distress, the occurrence of neonatal infection, Apgar neonatal score, and histological examination of the placenta and membranes for evidence of CA.

Subjects and methods

Subjects

This prospective controlled study was conducted on a cohort of pregnant women who fulfilled the inclusion criteria (in their antenatal visits) in the Department of Obstetrics and Gynecology, Faculty of Medicine, Beni-Seuf University.

Ethical approval

The study was approved by the scientific committee of the Obstetrics and Gynecology Department, Faculty of Medicine, Beni-Suef University, with approval number 1712-17. All women admitted to the hospital were informed about the nature of the study. Written consent was obtained from all the women prior to their inclusion in the study.

Inclusion criteria

The present study included women with a singleton and gestational age between 24 and 36 weeks who approved to be included in the study after having a consent form. They were followed up every two weeks till delivery. Women were excluded if they had any infectious disease that can affect maternal fever, abnormal amniotic fluid index (AFI) according to gestational age, congenital fetal anomalies, or positive maternal medical history, example, Diabetes, hypertension, SLE. All women that were in active labor or had clinical signs of CA at admission were also excluded from the study.

Study design

The recruited women were divided into two groups according to the ratio of 1 case to 4 controls as in the study design; Group 1 of the first twenty cases presenting in PPROM, and Group 2 of the first eighty cases without PPROM. All women underwent proper history taking, physical examination, and investigations. PPROM was diagnosed by sterile speculum examination and the presence of gross pooling of amniotic fluid in the vaginal vault. Clinical signs of CA were looked for according to RCOG Green-top guidelines; maternal pulse (>100 bpm), maternal pyrexia, uterine tenderness, and fetal tachycardia (>160 bpm). Maternal TLC (including its differential count) and CRP were measured for all cases in both groups.

Using Toshiba ECCO CEE SSA-340A equipment with a 3.5–5 MHz convex probe, all women underwent

a detailed sonographic evaluation to assess fetal biometry and amniotic fluid volume and to exclude major structural fetal anomalies. A targeted sonographic evaluation of the fetal thymus perimeter and transverse diameter was performed (Fig. 1). After identification of the interfaces between the thymus and the lungs, the transverse diameter and perimeter of the thymus were measured. The lateral margins of the thymus were well-defined when they were perpendicular to the ultrasound beam. The perimeter and transverse diameters of the thymus were measured by placing a line cursor perpendicular to the line connecting the sternum and the spine. All cases were examined by the same observer, and a minimum of two measurements of fetal thymus diameters were obtained; then, the average value was calculated, and results were recorded by the principal investigator. The normal thymus parameters during 28–32 weeks and 32–36 weeks are known to be as follows; the transverse diameter is 30–47 mm (42±6.96 mm) and 52–70 mm (64.1±6.46 mm), respectively, while the thymus perimeter is 124–163 mm (143.23±14.8 mm), 196–227 mm (221.9±16 mm), respectively [7].

All enrolled women were receiving the same regimen of treatment in the form of antibiotics (erythromycin) for prophylaxis, and corticosteroids (dexamethasone) if fetal lung maturity was not documented. All women were followed up till delivery. For women in group 1, the placenta, membranes, and umbilical cord were obtained after delivery and washed with saline. Histological evidence of CA, villitis, or funisitis was examined, correlating the findings with fetal thymus size measured by ultrasound. The state of the placenta, membranes, and the umbilical cord, including its vessels, were examined. Histological villitis, CA, and funisitis were diagnosed when any polymorphonuclear leucocytes (PNL) were seen in the placenta, membranes, and umbilical cord, respectively.

Figure 1

Transverse section in the upper mediastinum lateral margins of thymus are well delineated by the difference in echogenicity of both tissue interface (lung-thymus), the three vessel view and the thymus transverse diameter at 34 wks &4 ds GA with PPROM was (2.57 cm).

Outcomes

The primary outcome of the study was to measure fetal thymus size by abdominal ultrasound and its correlation with maternal total leukocytic count (TLC) and its differential count, C-reactive protein (CRP), and maternal fever. The secondary outcomes involved the correlation of the fetal thymus size with fetal distress, the occurrence of neonatal infection, Apgar neonatal score, and histological examination of the placenta and membranes for evidence of CA.

Sample size

We were planning a study of a continuous response variable (thymus perimeter is the primary outcome) from independent control and cases with four controls per case. In previous studies, the response within each subject group was normally distributed with a standard deviation of 0.4 if the true difference in the experimental and control means is 0.6, we will need to study 20 experimental subjects and 80 control subjects to be able to reject the null hypothesis that the population means of the cases and control groups are equal with probability (power) 0.99 the type 1 error probability associated with this test of this null hypothesis is 0.05.

Statistical analysis

Data were analyzed by Statistical Package for the Social Sciences 'SPSS, vs. 25. Normally distributed quantitative variables were expressed in the form of mean±standard deviation (SD), while non-normally distributed variables were expressed in the form of the median and interquartile range (IQR). Qualitative variables were expressed in the form of numbers and percentages. To compare Group 1 with Group 2, we used the independent samples *t*-test in the case of normally distributed variables and the Mann-Whitney test in the case of non-normally distributed variables. Pearson correlation coefficient (r) was used to compare between two values. *P*-value was assumed significant if less than 0.05 and highly significant if less than 0.001.

Results

We assessed the pregnant women who fulfilled the inclusion criteria. Concerning their baseline

characteristics, the mean age in years was 28.58±5.73 (years), and the mean BMI in kg/m^{2}was 28.46±2.94. They were divided into two groups: Group 1 of twenty cases presenting in preterm premature rupture of membranes (PPROM), and Group 2 of eighty cases of women without PPROM. When comparing their baseline characteristics, both groups showed no significant difference regarding age, BMI, parity, frequency of abortions, and mode of delivery. Expectantly, the mean gestational age at delivery was significantly lower in the first group (Table 1).

When comparing both groups regarding the laboratory, ultrasound findings, and placental pathology, we found women with PPROM (group 1) had significantly higher CRP levels (12.9±5.17 vs. 5.27±2.38, $P<0.001$), higher TLC levels (7600±2991 vs. 6493±1782, $P=0.035$), and higher Staff (10.5±4.6 vs. 4.2±1.8, $P<0.001$). On the contrary, women without PPROM (group 2) during ultrasound examination had significantly higher AFI (7.35±1.84 vs. 6.25±2.29, $P=0.022$), greater Thymus perimeter (9.6±1.13 vs. 6.63±1.41, $P<0.001$), and greater Thymus transverse diameter (3.49±0.37 vs. 2.52±0.51, $P<0.001$). In addition, pathological examination of the placenta in both groups revealed positive signs of infection in group 1 only (13 cases [65%], $P<0.001$), as shown in Table 2.

We did a correlation analysis of fetal thymus size in both groups with other parameters (CRP, TLC, Staff, AFI, APGAR score, and birth weight). Regarding women with PPROM (group 1), there was a significant positive correlation between the Thymus perimeter and APGAR score of the neonates ($r=0.658$, $P=0.002$), Thymus perimeter and birth weight ($r=0.741$, $P<0.001$), Thymus transverse diameter and APGAR score of the neonates ($r=0.741$, $P<0.001$), and finally Thymus transverse diameter and birth weight ($r=0.734$, $P<0.001$). Regarding women without PPROM (group 2), there was a significant positive correlation between the Thymus

Table 1 Comparison between both groups regarding the demographic data

	ROM Cases (n=20)	Control (n=80)	P value
Age (years)	29.15±5.34	28.37±5.64	0.580
BMI	27.67±2.10	28.70±2.81	0.131
Parity			
Nullipara	â 8 (40%)â	â 33 (41.3%)â	0.578
Para 1	â 6 (30%)â	â 19 (23.8%)â	
Para 2	â 5 (25%)â	â 13 (16.3%)â	
Para 3	â 1 (5%)â	â 13 (16.3%)â	
Para 4	â 0 (0%)â	â 2 (2.5%)â	
Frequency of abortions			
No abortion	15 (75%)	58 (72.5%)	
Previous 1 Abortion	4 (20%)	17 (21.3%)	0.967
Previous 2 Abortions	1 (5%)	5 (6.3%)	
GA at delivery (weeks)	34.88±2.77	38.59±1.09	<0.001*
Mode of delivery			
NVD	11 (55%)	42 (47.5%)	0.841
CS	9 (45%)	38 (52.5%)	

*: Significant difference at $P<0.05$, using student t-test

Table 2 Comparison between both groups regarding the laboratory, ultrasound findings, and placental pathology

	ROM Cases (n=20)	Control (n=80)	P value
CRP	12.9±5.17	5.27±2.38	<0.001*
TLC	7600±2991	6493±1782	0.035*
Staff	10.5±4.6	4.2±1.8	<0.001*
AFI	6.25±2.29	7.35±1.84	0.022*
Thymus perimeter	6.63±1.41	9.6±1.13	<0.001*
Thymus transverse diameter	2.52±0.51	3.49±0.37	<0.001*
APGAR score	7.85±1.8	7.35±1.7	0.263
Placental pathology			
Positive signs of infection	13 (65%)	0 (0%)	<**0.001****
No sign of infection	7 (35%)	80 (100%)	

*: Significant difference at $P<0.05$, using student t-test. ** Significant difference at $P<0.05$, using Chi-Square test.

Table 3 Correlation of fetal thymus size with other parameters:

	ROM Cases (n=20)		Control (n=80)	
	Thymus perimeter	T. transverse diameter	Thymus perimeter	T. transverse diameter
CRP	−0.269 (P=0.252)	−0.317 (P=0.173)		
TLC	−0.05 (P=0.833)	−0.075 (P=0.752)	0.175 (P=0.121)	0.278 (P=0.112)
Staff	−0.15 (P=0.528)	−0.124 (P=0.604)	−0.044 (P=0.7)	0.016 (P=0.889)
AFI	0.268 (P=0.252)	0.312 (P=0.18)	0.038 (P=0.737)	0.071 (P=0.533)
APGAR score	0.658 (**P=0.002***)	0.741 (**P<0.001***)	0.232 (**P=0.039***)	0.165 (P=0.143)
Birth Weight	0.741 (**P<0.001***)	0.734 (**P<0.001***)	0.161 (P=0.154)	0.32 (**P=0.004***)

*: Significant difference at P<0.05, using Pearson correlation test.

Table 4 Relation between the pathology of the placenta and other parameters among cases with PROM

	Cases with signs of placental infection (n=13)	Cases without signs of placental infection (n=7)	P value
CRP	16±12.2	7.14±2.3	0.046*
TLC	8692.3±3010.7	5571.4±1682.9	0.014*
Staff	12.77±6.3	6.14±1.35	<0.001*
AFI	5.5±2.4	7.7±1.25	0.032*
Thymus perimeter	6.4±1.6	7.04±1.03	0.358
Thymus transverse diameter	2.4±0.55	2.72±0.35	0.209
APGAR score	6.9±1.41	8.3±1.8	0.063
Birth Weight	2334.6±500.9	2992.9±372.4	0.007*

*: Significant difference at P<0.05, using student t-test.

perimeter and APGAR score of the neonates (r=0.232, P=0.039), and Thymus transverse diameter and birth weight (r=0.320, P=0.004), as shown in Table 3.

The relation between the pathology of the placenta and other parameters among women with PROM (group 1) was studied in Table 4. Cases with placental signs of infection (n=13), when compared with cases without placental signs of infection (n=7), had higher CRP levels (16±12.2 vs. 7.14±2.3, P=0.046), higher TLC levels (8692.3±3010.7 vs. 5571.4±1682.9, P=0.014), higher Staff (12.77±6.3 vs. 6.14±1.35, P<0.001), but lower AFI (5.5±2.4 vs. 7.7±1.25, P=0.032).

Discussion

The thymus gland is a very sensitive organ that is affected by many factors as environmental, nutritional, and immunological factors. The thymus gland involution upon exposure to stress is not been fully studied till nowadays. Our study aimed to determine the perimeter and transverse diameter of the fetal thymus in preterm fetuses between 24 and 36 weeks of pregnancy (with and without PPROM) and correlate them with maternal features of infection as well as placental signs of infection. Secondarily we observed if there is a relation between thymic gland size at this gestational age and perinatal morbidity.

We found a significant decrease in both thymic perimeter and transverse diameter in fetuses of pregnant women with PPROM with laboratory features of infection and placental infection. The thymus gland of fetuses of 145 women with PPROM between 24 to 36 weeks of pregnancy was also studied by Kacerovsky and Musilova. They defined the small fetal thymus when the transverse diameter was below the 5th percentile for gestational age. Histological examination of the placenta, the fetal membranes, and the umbilical cord was done to detect CA and funisitis. They were found in 58% of the women. The small fetal thymus had 63% sensitivity and 54% specificity. The positive versus negative predictive value for intrauterine inflammation was 49% vs. 67%, respectively (P=0.04). In agreement with our results, intrauterine inflammation in PPROM women, as well as CA, is associated small transverse diameter of the fetal thymus [12].

Kacerovsky and Musilova, later in the same year, performed Amniocentesis in 140 PPROM women between 24 and 36 weeks of pregnancy in order to examine the microbial status of amniotic fluid and correlate this with the thymus gland transverse diameter. They found Positive bacterial culture in the amniotic fluid of 37% of the women. After examining the microbial status of the amnion, they concluded that the small transverse diameter of the fetal thymus is a weak tool for early detection of intrauterine infection in PPROM women and, in turn, pregnancy complications [13]. These controversial results urged us to study the placental

histopathology after delivery to identify features of intra-amniotic inflammation. Villitis, CA, and funisitis were diagnosed when any PNL was seen in the placenta, membranes, and umbilical cord, respectively.

We found that the small thymus gland perimeter and transverse diameter are associated with intra-amniotic inflammation features. Bopegamage and his coworkers studied 216 fetuses' thymus transverse diameters of PPROM women. The placenta, the fetal membranes, and the umbilical cord were examined as well to detect any inflammatory features. 69% of fetuses presented with a small thymus gland with 79% sensitivity and 47% specificity. Although they concluded that the small thymus is a good indicator for diagnosing CA and\or funisitis, they excluded it from being of clinical value due to low specificity [14,15].

A Turkish study group found that 45% of fetal thymus transverse diameters measured were below the 5th percentile for gestational age compared to the initial measurement in PPROM women. They concluded that the involution of fetal thymus transverse diameter had a 100% sensitivity and 73% specificity. The positive versus negative predictive value was 55% vs. 100% to predict early intra- amniotic sepsis. They also concluded that Fetal thymus transverse diameter is a more valuable diagnostic tool than Cord blood TNF-α and IL-6 which had a lower sensitivity and specificity in predicting early intra-amniotic sepsis [16]. A systematic review in 2018 showed that pregnant women complicated with PPROM have an increased risk of preterm labor, CA, neonatal morbidity, and mortality. Although they also found that this condition is associated with small fetal thymus with good diagnostic accuracy in only complicated pregnancies, the small fetal thymus was of no value in uncomplicated pregnancies [17].

In 2021, An English team used the MRI to build the normal ranges for fetal thymus and thymus: body volume ratios between the 20th and 32nd weeks of pregnancy. They found that the thymus gland volume of fetuses delivered very preterm was reduced when compared to the fetal size. They recommended that the reduction in thymus volume can help predict preterm delivery and be a tool to diagnose early fetal and intra-amniotic inflammation [18]. The correlation between the thymus gland involution and intra-amniotic inflammation needs a mega study with a large number of pregnant women, races, and different pregnancy-associated inflammatory processes to reach a relation between them accurately.

Thymus size was shown to be correlated with birth weight and not different between male and female fetuses [19]. In our study, we found a significant difference in fetal birth weight in correlation with both the perimeter and Transverse diameter of the thymus gland, but on the contrary, only the transverse diameter showed a significant difference regarding fetal birth weight. From this observation, we can assume that the perimeter measurement is more accurate than the transverse diameter. Further research is needed to address this issue. Obstetricians could suggest strategies to prevent preterm delivery by assessing the fetal thymus parameters as a predictive tool for preterm delivery. Low birth weight fetuses, as well as fetal mortality/morbidity, could be reduced in case we could avoid preterm delivery.

A group of researchers found a small thymus gland in the fetuses of women who got pregnant via Artificial Reproductive Techniques (ART). A less homogeneous tissue was observed on ultrasonographic examination of the fetal thymuses compared to those whose mothers got pregnant naturally. Poor pregnancy outcome was also a finding that could be due to some sort of inflammatory process in ART embryos. Further investigations are needed to evaluate whether the fetal thymus gland parameters could be used as a valuable method to evaluate the long-term impact of ART later on in fetal life [20]. Another research group found a similar observation regarding twin pregnancy and thymus gland size and the incidence of preterm delivery and fetal mortality\morbidity [21].

The strength of this study is the evaluation of TLC, CRP, and maternal fever as other diagnostic features of intra-amniotic infection. The placental pathology is a confirmatory step for intra-amniotic infection. Another point of strength of this study is that we measured both the transverse diameter as well as the perimeter of the fetal thymus.

The limitation of our study is studying a small number of women with a specific condition (PPROM), and all women were studied in the same institution and race. The active management of PPROM women in our institute is another limitation of our study. Also, in some cases, a short interval between PPROM to delivery did not allow the inflammatory process to occur. Therefore, we assume that placental histopathology, as well as thymus measurement in most women, could be missed.

Conclusion

We concluded from our study that assessing the fetal thymus during the routine second- and/or third-trimester scan could be a predictive measure for intra-amniotic infection. Still, there is no association between small fetal thymus and adverse perinatal outcomes in uncomplicated pregnancies. Further larger studies with different demographic, maternal characteristics, and different inflammatory processes with and without active management to summarize whether fetal thymus can be used in clinical practice to avoid infection-related fetal morbidities or not.

Author's contribution: All authors have read and approved the final manuscript. Amal Abdallah: study design, data collection, manuscript writing. Mohamed Mohesen: data collection, manuscript writing. Nagwan Kamal: data collection, manuscript writing. Sahar Abd Elsalam: data collection, manuscript writing. Sondos Salem: data analysis, manuscript writing. Ehab Salama: data analysis, manuscript writing. Mazen Abdel-Rasheed: data analysis, manuscript writing. Mohamed Eweis: data collection, manuscript writing.

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Conflicts of interest

There are no conflicts of interest.

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