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Diagnostic value of ultrasonographic assessment of fetal thymus gland size in pregnancies associated with the preterm prelabor rupture of membranes

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Abstract
Background: Preterm prelabor rupture of membranes (PPROM) is responsible for approximately one third of preterm deliveries. Prenatal sonographic (US) assessment of the fetal thymus has become available. This research was done to investigate the role of ultrasonographic assessment of fetal thymus size in pregnancy associated with preterm premature rupture of membrane and its relationship with fetal outcome.
Methods: This prospective controlled observational study was carried out on 60 cases with maternal age from 18 to 40 years old, gestational age between 24 and 36 weeks, singleton pregnancy and associated with PROM. Cases were subdivided into two groups Group A: 30 cases with PROM, Group B: 30 normal at the same gestational age. All cases were subjected to history taking, obstetric history, maternal medical history, investigation studies and ultrasound study.
Results: The amniotic fluid index had a significant decrease in group A compared with B, and the gestational diabetes mellitus had a significant increase in group A compared with B. The small fetal thymus size had a significant increase in group A compared with B (p =0.013). The Puerperal endomyometritis had a significant increase in group A (30%) compared with B (0%). The Apgar score at 5 mins (p<0.001) and Apgar score (p= 0.042**)** at 10 mins were significantly decreased in group A compared with B.
Conclusions: In pregnancy associated with preterm premature rupture of membranes, small fetal thymus might be associated with histologic chorioamnionitis, higher rate of perinatal mortality and short- and long-term neonatal morbidity however many cases remained clinically silent.

Keywords: Ultrasonographic assessment, fetal thymus gland, preterm prelabor rupture

Introduction
Preterm prelabor membrane rupture (PPROM) accounts for roughly one-third of preterm births [1]. Approximately 30% of PPROM have been observed to have microbial invasion into the amniotic cavity [2]. The presence of microorganisms in amniotic fluid (AF) initiates a cascade of inflammatory events, followed by neutrophil infiltration of the foetal membrane, placenta, and umbilical cord. This illness, termed as histologic chorioamnionitis (HCA), has two subtypes based on the inflammatory response of the host. It is maternal when the amnion, chorion decidua, and chorionic plate are implicated, and foetal (funisitis) when the umbilical cord is afflicted [3]. Despite the fact that both HCA and funisitis are linked with an increased risk of perinatal death and short- and long-term neonatal morbidity, many cases remain clinically silent [4, 5]. Previous research has shown that the presence of HCA may activate the foetal hypothalamus – pituitary – adrenal gland axis, resulting in foetal adrenal gland growth and an increase in foetal adrenal gland hormone levels [6, 7]. Activation of the hypothalamus – pituitary – adrenal gland axis [8] has also been hypothesised as the cause of stress-related thymus involution. On a postnatal X-ray of the foetal chest, the association between the presence of HCA and the diminution of the foetal thymus was identified for the first time. The thymuses of foetuses from pregnancy affected by HCA were smaller than those of foetuses from pregnancy not associated with HCA [9]. As prenatal sonographic (US) evaluation of the foetal thymus has become feasible, prenatal studies of thymic abnormalities associated with HCA or funisitis have been conducted. In very modest studies [10, 11], the US examination of the foetal thymus has previously been utilised to detect HCA or funisitis in either PPROM or spontaneous premature birth. The presence of a foetal thymus smaller than the fifth percentile for gestational age,

referred to as a tiny thymus, has been hypothesised as a possible predictor of both HCA and funisitis. In each of these experiments, the thymic perimeter will be used to determine the size of the foetal thymus. Under adverse US circumstances, particularly in pregnancy with PPROM, identifying the thymic border might be quite challenging. In PPROM pregnancy, the assessment of the transverse diameter (TD) of the foetal thymus, which is simpler to identify and quantify than the perimeter, might be advantageous [12].

The purpose of this study was to examine the function of ultrasonographic measurement of foetal thymus size in pregnancy affected by preterm premature membrane rupture and its association to foetal fate.

Patients and Methods

This prospective controlled observational study was carried out on 60 cases presented with maternal age from 18 to 40 years old, gestational age between 24 and 36 weeks, singleton pregnancy and Associated with PROM. The study was carried out at Tanta University Hospital, Obstetrics and Gynecology department. from March 2020 to February 2021.

The study was started after being approved from Obstetrics and Gynecology Department, Tanta University Hospitals. Signed consent was obtained from all cases.

Exclusion criteria were fetal growth restriction, fetal malformation, vaginal bleeding, and signs of fetal hypoxia.

All cases in the study were subjected to: History taking, Personal (name, age, duration of marriage, occupation, address, gravidity, parity, special habits, BMI), Obstetric History: (type of conception, gestational age at admission, amniotic fluid index), Maternal Medical History: (maternal illness, preeclampsia or gestational diabetes mellitus, smoking, drug intake, renal disease), Investigation studies and Ultrasound study.

Ultrasound technique: US evaluation of the fetal thymus was performed at the time of admission before the administration of corticosteroids and antibiotics with a convex transabdominal probe. The thymus was observed in a transverse slice of the foetal thorax between the sternum and major blood veins ("three vessels view"). The TD was defined as the largest diameter of the foetal thymus perpendicular to the sternospinal junction. Each foetus was measured three times, and the mean size was utilised for statistical analysis. According to a previously published nomogram, a tiny thymus was described as a thymic TD below the fifth percentile for gestational age [13]. Fetal outcome in cases with PROM in relation to thymus gland size.

Statistical analysis

SPSS v25 performed the statistical analysis (SPSS Inc., Chicago, IL, USA). Quantitative variables were provided as mean and standard deviation (SD) and compared using Student's t-test for unpaired samples (between the two groups). When applicable, qualitative variables were reported as frequency and percentage (%) and compared using the Chi-square test (X2) or Fisher's exact. The selected significance threshold was p0.05.

Results

There was insignificant difference between both groups regarding the demographic data. The amniotic fluid index had a significant decrease in group A compared with B, and the gestational diabetes mellitus had a significant increase in group A compared with B [Table 1].

Table 1: Personal data, obstetric History and Maternal Medical History of both groups

		Group A (n = 30)	Group B (n = 30)	P value
Age (years)	Mean ± SD	31.57±4.78	29.50±5.59	0.129
Duration of marriage (years)	Mean ± SD	7.83±4.14	7.10±4.20	0.499
Residence	Urban	15 (50%)	12 (40%)	0.436
	Rural	15 (50%)	18 (60%)	
Gravidity	Median	2	2	0.386
Parity	Median	1	0	0.290
Weight (kg)	Mean ± SD	74.23±9.45	75.93±9.82	0.497
Height (cm)	Mean ± SD	168.80±5.41	169.97±5.10	0.393
BMI (kg/m²)	Mean ± SD	26.14±3.85	26.28±3.17	0.878
Gestational age at admission (weeks)	Mean ± SD	30.50±3.53	29.43±4.18	0.290
Amniotic fluid index	Mean ± SD	15.50±5.37	18.53±5.15	0.029*
Preeclampsia	N (%)	2 (7%)	0 (0%)	0.150
Gestational diabetes mellitus	N (%)	6 (20%)	1 (3%)	0.044*
Antepartal corticosteroids	Yes	19 (63%)	14 (47%)	0.195

Data was presented as Mean ± SD or frequency and percentage. * Significant as p value < 0.05.

The hemoglobin, platelet, ALT, AST, bilirubin, creatinine and urea levels were insignificantly different between both groups. TLC had a significant increase in group A compared with B [Table 2].

Table 2: Investigation studies in both groups

Mean ± SD	Group A (n = 30)	Group B (n = 30)	P value
Hemoglobin (gm/dl)	12.62±1.10	12.39±1.02	0.399
TLC (*10^3/µL)	10.95±2.67	9.04±2.08	0.003*
Platelet (*10^3/µL)	297.00±82.70	293.17±75.52	0.852
ALT (IU/L)	35.7±5.07	38.2±4.85	0.056
AST (IU/L)	30.07±9.24	29.67±10.38	0.875
Bilirubin (mg/dL)	9.01±4.72	10.22±4.63	0.323
Creatinine (mg/dL)	0.94±1.23	0.94±0.18	0.951
Urea (mg/dl)	25.30±7.24	24.61±7.79	0.726

TLC: Total leucocytic count, ALT: Alanine aminotransferase, AST: aspartate aminotransferase, * significant as P value <0.05

The small fetal thymus size had a significant increase in group A compared with B [Table 3]

Table 3: Ultrasound study of fetal thymus in both groups

		Group A (n = 30)	Group B (n = 30)	P value
Size	Normal	16 (53.3%)	25 (83.3%)	0.013*
	Small	16 (46.7%)	5 (16.7%)	

Data was presented as frequency and percentage. * Significant as P value <0.05.

The spontaneous delivery, mode of delivery and birth weight of newborn were insignificantly indifferent between both groups. The Puerperal endomyometritis had a significant increase in group A compared with B. The Apgar score at 5 mins and Apgar score at 10 mins were significantly decreased in group A compared with B [Table 4].

Table 4: Outcome in both groups

		Group A (n = 30)	Group B (n = 30)	P value
Spontaneous delivery		18 (60%)	11 (37%)	0.071
Mode of delivery	NVD	23 (77%)	23 (77%)	1
	CS	7 (23%)	7 (23%)	
Puerperal endomyometritis		9 (30%)	0 (0%)	0.001*
Birth weight of newborn (grams)	Mean ± SD	2209.97±237.62	2171.27±264.11	0.553
Apgar score (5 mins)	Mean ± SD	5.37±1.10	6.63±1.52	<0.001*
Apgar score (10 mins)	Mean ± SD	5.67±1.45	6.67±2.20	0.042*

Data was presented as mean ± SD or frequency and percentage. * Significant as p value < 0.05.

Discussion

On a postnatal X-ray of the foetal chest, the link between the presence of histologic chorioamnionitis (HCA) and the decrease of foetal thymus was identified for the first time; foetuses from pregnancy associated with HCA had smaller thymuses than those from pregnancy without HCA [14].

Since prenatal sonographic (US) evaluation of the foetal thymus became available, the thymic alterations associated with HCA or funisitis have been analysed prenatally. In PPROM pregnancy, it may be useful to assess the TD of the foetal thymus, which is simpler to identify and quantify than its perimeter [15].

In group A, the amniotic fluid index was substantially lower, gestational diabetes was significantly higher, and TLC was significantly higher than in group B.

Current study concurred with Aksakal *et al.* [16], who included fifty healthy individuals and fifty cases with preterm premature rupture of membranes (PPROM) between 24 and 37 weeks of gestation. Weekly measurements of the foetal thymus were performed until birth. They reported that the mean gestational age of the research groups' participants was comparable (p=0.36). In terms of sedimentation, CRP, and white blood cell values, there was no statistically significant difference between the CA and non-CA groups, however TLC was considerably higher in the CA group compared with the non-CA group.

Concerning the ultrasound research of the foetal thymus and maternal outcomes, statistical analysis of the current data revealed that the foetal thymus size and the incidence of puerperal endo-myometritis were considerably lower in group A than in group B.

Musilova *et al.* [12] found that foetuses from pregnancy associated with HCA had lower transverse thymic widths than foetuses from pregnancy without HCA. The TD of the foetal thymus was smaller in foetuses from pregnancy with funisitis compared with those from pregnancy without funisitis.

Caissutti *et al.* [17] investigated the relationship between an ultrasonographically small foetal thymus and an unfavourable obstetrical outcome. Brandt *et al.* [18] and Di Naro *et al.* [10], including 551 foetuses, investigated the degree of relationship between a small thymus and the incidence of spontaneous PTB 37 weeks of gestation and found no significant difference between the two groups. There was no difference in the risk of PTB before 34 weeks of gestation between foetuses with and those without a small thymus.

Previous research examining the risk of CA in foetuses with a small thymus in comparison to controls concurred with the present findings. All of these trials had high-risk pregnancy for CA, and two included women with PPROM.

El Haieg *et al.* [19] conducted a prospective cohort research in fifty-six women with preterm prelabour rupture of membranes to determine the relationship between sonographic foetal thymus size and the components of foetal inflammatory response syndrome (FIRS) (PPROM). The perimeter of the foetal thymus was assessed sonographically in these mothers. At birth, cord venous plasma interleukin-6 (IL-6) levels were measured and placentas and umbilical cords were examined histopathologically.

Yinon *et al.* [11] investigated whether a smaller foetal thymus is connected with histological or clinical CA in individuals with preterm premature membrane rupture (PROM). Twenty-one individuals with preterm PROM between 24 and 35 weeks of gestation were included. During the latency phase, serial ultrasound exams were done and measures of the foetal thymus size were collected. Using newborn clinical indicators and histological tests of the placenta, CA was diagnosed.

El Haieg *et al.* [19] defined a small thymus by a TD 5th percentile, whereas Yinon *et al.* [11] and Di Naro *et al.* [10] utilised a perimeter 5th percentile. Overall, they agreed with the current study and concluded that the risk of CA was much higher in pregnancy afflicted by PPROM, as shown by a scan revealing a tiny thymus.

According to Aksakal *et al.* [16], fourteen cases in the PPROM group were below the 34th week of gestation; six were between 30 and 34 weeks and eight were below 30 weeks. 28% of cases in the PPROM group (n=14) delivered before the 34th week of gestation, whereas 72% delivered after the 34th week of gestation, which may be attributed to different research sample size and methodologies compared with the present study. In addition, they discovered that histological CA was identified in 48% of cases, which was considerably greater than the non-CA group, and funisitis was identified in 10% of PPROM cases. CA has traditionally been connected with funisitis. Measuring the transverse dimension of the thymus in individuals with PPROM revealed thymic involution in 27 cases (54%) who were considerably smaller. 22 of these individuals were diagnosed with CA.

Regarding ultrasound study of fetal thymus and neonatal outcomes; statistical analysis of current results showed that the fetal thymus size was significantly smaller in group A compared with B. Apgar score at 5 and 10 mins had a significant decrease and neonatal sepsis had a significant increase in group A compared with B but birth weight of newborn was

insignificantly different between both groups.

Caissutti *et al* [17] agreed with current study and stated that three studies Cromi *et al*. [20], Ekin *et al*. [21] and Olearo *et al*. [22] The relationship between a small foetal thymus and the likelihood of IUGR and low birth weight was investigated. All of these studies comprised seemingly straightforward pregnancy and found no greater risk of intrauterine growth restriction in foetuses with a small thymus on ultrasonography compared with those without a small thymus.

Current study found that a small foetal thymus increased the risk of neonatal sepsis and agreed with Cetin *et al*. [23] who evaluated the diagnostic accuracy of foetal thymus TD in predicting foetal infection in preterm premature rupture of membranes (PPROM) and compared its accuracy with cord blood tumour necrosis factor- (TNF-) and interleukin-6 (IL-6). Prospective evaluation of forty consecutive pregnancy associated with PPROM between 26 1/7 and 36 6/7 weeks of gestation. Beginning on the day of admission, serial foetal ultrasonography follow-ups with 3-day intervals were done. In each ultrasonographic examination, the FTTD was recorded. After delivery, cord blood TNF- and IL-6 levels were analysed. In 45% of all PPROM instances, FTTD was reduced to ≤ 5% based on nomograms compared with the original test.

This result concurs with Ekin *et al*. [21], who examined 50 IUGR-affected babies without PROM. In all investigations, the risk of newborn sepsis was greater in foetuses with a small thymus diameter compared with those with a normal thymus diameter.

Current study disagreed with Aksakal *et al*. [16] that birth weights (p50.05), gestational ages at birth (p50.05), and APGAR scores at 1st and 5th min after delivery (p50.05) showed a statistically significant difference between PPROM group and control group (p50.05). This discrepancy could be attributed to different sample size and methods in the current study.

Cromi *et al*. [20] stated that small fetal thymuses were also describer in IUGR fetuses in pregnancy associated with pre-eclampsi and in fetuses with trisomy 21 which disagreed with current study as there was no statistically difference between current study groups as regard fetal weight.

Although the strengths points of current study including complete information in data analysis, performing all clinical assessment, sonographic measurement, deliveries and assessment of study outcomes were done by the same team, there was some limitations including the presence of COVID 19 pandemic, relatively small sample size as regard more outcomes and ultrasound examiners and observers should be unaware of each other's results.

Conclusions

In pregnancy associated with preterm premature rupture of membranes, antenatal ultrasonographic assessment of fetal thymus size had an important role in prediction of fetal outcome. Small fetal thymus might be associated with histologic CA, higher rate of perinatal mortality and short- and long-term neonatal morbidity however many cases remained clinically silent.

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Conflict of Interest: Nil

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