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Fetal Thymus Size in Pregnancies Complicated by Preterm Premature Rupture of the Membranes: A Case-Control Study

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ABSTRACT

The aim of this study was to investigate the fetal thymus size in pregnancies complicated by preterm premature rupture of membranes.

This prospective case-control study comprised 50 pregnant women aged 18-40 years with active amniotic fluid leakage between 24 and 37 gestational weeks and 60 healthy pregnant women as controls. Anteroposterior diameter of the thymus, transverse thymic diameter, and thymic-thoracic ratio were compared between the study and control groups. Correlations between the thymic-thoracic ratio and maternal and fetal serum inflammation parameters were determined in the case group.

The thymic-thoracic ratio was found to be 0.30±0.06 in pregnancies complicated by preterm premature rupture of the membranes and 0.39 ± 0.08 in the control group ($p<0.001$). In the case group, the transverse thymic diameter was statistically significantly lower than in the control group (26±7.06 and 35.1±11.9, respectively; $p<0.001$). There was a statistically significant moderate negative correlation between maternal white blood cell count and fetal thymic-thoracic ratio ($r=-0.318$, $p=0.010$).

In pregnancies complicated by preterm premature rupture of the membranes, the fetal thymic-thoracic ratio and fetal transverse thymic diameter were reduced.

Keywords: thymus, thymo-thoracic ratio, preterm, fetal inflammation

Introduction

Preterm premature rupture of the membranes affects 3% of pregnancies and is responsible for one-third of preterm births (Thomson, 2019). Preterm premature rupture of the membranes (PPROM), which complicates pregnancy through the rupture of the membranes before the onset of labor and the 37th week of gestation, is associated with high mortality and morbidity in newborns. Conditions such as chronic inflammation, infection, and maternal stress contribute to PPROM by altering the structure and integrity of membranes through the stimulation of cytokines and the endocrine system. Conditions such as chronic inflammation, infection, and maternal stress, which are among the causes of PPROM, stimulate the cytokines and endocrine system, affecting the structure of the membranes and causing their integrity to deteriorate (Garg & Jaiswal, 2023). Existing factors in this process have been shown to affect the fetus by impacting both the hypothalamus-pituitary-adrenal (HPA) axis and inflammatory parameters. Given the crucial role of the thymus in the immune system during the prenatal period and early life, thymic size may be affected in PPROM-complicated pregnancies.

The thymus, situated in the upper mediastinum, constitutes a fundamental component of the immune system, pivotal in the developmental process of T cells (Thapa & Farber, 2019). In human anatomy, the thymus comprises two

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principal lobes, each containing the cortex and medulla regions. Functioning as a primary lymphoid organ, the thymus exhibits a dynamic nature, susceptible to alterations in size influenced by factors including age, infections, and stress (Rezzani, Nardo, Favero, Peroni, & Rodella, 2014). It is composed of a dynamic tissue that plays a pivotal role in the specific development and differentiation of T cells. The development of specific thymic epithelial cells in the cortical and medullar regions is particularly crucial for thymic organogenesis in intrauterine life (Thapa & Farber, 2019). The age-related and puberty-induced decrease in thymic epithelial cells results in the reduction and involution of thymic size. Research indicates that stress, mediated via the HPA axis, contributes to thymic involution, instigating apoptosis during the early stages (Chen, Liu, Yan, Wu, & Ping, 2016). Previous investigations have revealed a reduction in thymus size in various pathological conditions, including infections, chorioamnionitis, and maternal autoimmune disorders. The current study aimed to explore the relationship between PPROM, an inflammatory process, and changes in fetal thymus size.

Materials and Methods

This prospective case-control study received approval from the Ethics Committee of the Turkish Ministry of Health (date: September 27, 2023, number: E2-23-4879). The study cohort comprised 50 pregnant women aged 18 to 40 who presented to the perinatology unit between October 1, 2023 and April 1, 2024, with active amniotic flow and were diagnosed with PPROM at 24-37 gestational weeks, as well as 60 healthy pregnant women. The inclusion of the case group in the ultrasound evaluation occurred on the day of membrane rupture. The control group comprises pregnant women who randomly want to participate in the research and who do not have any inflammatory process. The participants in the control group were selected to be compatible with the gestational week in which the study group was diagnosed with PPROM. The exclusion criteria of the study were fetal chromosomal and structural anomalies, pregnant women with high risk in combined screening tests, multiple pregnancies, body mass index (BMI) > 35 kg/m^2, smoking, antenatal steroid administration, use of assisted reproductive techniques, intrauterine growth restriction, and maternal chronic diseases, such as diabetes and hypertension. Written consent was obtained from all participants. Data on the patients' age, BMI, nulliparity, the gestational week and pregnancy outcomes during the ultrasound examination, and maternal blood serum inflammation parameters were recorded. As the control group comprised healthy pregnant women, obstetric outcomes and inflammatory parameters were determined by establishing subgroups within the case group. Gestational age was confirmed based on the measurement of the crown-rump length during the first trimester.

To eliminate inter-observer variability, the patients' ultrasound scans were evaluated by a single individual (Betül Akgün Aktaş). Ultrasonographic measurements were performed using a convex transducer C1-5-RS (1.75-4.95 MHz) and GE Voluson S10 Ultrasound (GE Healthcare Ultrasound, USA) during fetal apnea and immobility. The thymus was visualized in the three-vessel trachea section following fetal biometric measurements and fetal echocardiography. The distinct echogenicity of thymic tissue and surrounding vessels allowed clear delineation of the thymus, as described by Chaoui et al. (Chaoui, Heling, Lopez, Thiel, & Karl, 2011). The anteroposterior diameter of the thymus was measured as the distance between the posterior edge of the sternum, distinguished by hyperechogenic tissue, and the aortic arch. The thymic-thoracic ratio (TTR) was calculated by dividing the measured distance by the sternum-vertebrae anterior distance (Figure 1). The transverse thymic diameter was measured as the widest part between the sternum and spine at their junction point using ultrasonic calipers (Zalel, Gamzu, Mashiach, & Achiron, 2002) (Figure 2). In the PPROM group, correlations between TTR and maternal and fetal blood parameters were determined.

Statistical analysis was undertaken using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). The normality of the variables was tested with both Shapiro–Wilk and Kolmogorov–Smirnov tests. Groups were compared with the Student t-test. P-values < 0.05 were considered statistically significant. Correlation analysis was conducted using Pearson's test and confidence interval was determined as 95%. Sample size was determined as required for each group, at least 29 patients based on a similar study (8), considering 5% margin of error and 90% power.

Results

The study included 50 pregnant women diagnosed with PPROM and 60 healthy pregnant

Fig. 1. The fetal thymic-thoracic ratio (Number 1. The anteroposterior diameter of the thymus)

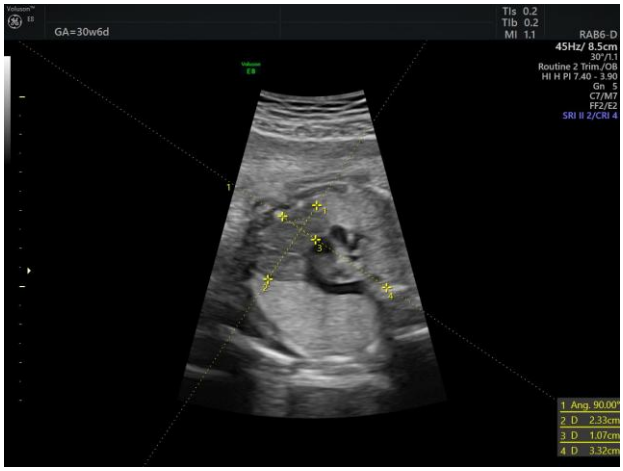

Fig. 2. Fetal thymus transverse measurement (Number 2. The transverse thymic diameter)

women. The baseline data of study population are shown in Table 1. There was no significant difference in maternal age or BMI between the two groups. The mean gestational week during ultrasound examination was 30.9 in the PPROM group and 31.9 in the control group ($p = 0.077$). In the PPROM group, pathogenic microorganisms were detected in the rectovaginal swab cultures of 10 patients, with a mean umbilical cord blood gas pH of 7.28±0.1 (range: 6.9-7.4), a mean C-reactive protein (CRP) value of 4.97±12.6 mg/dL (range 0.5-75.5), and a mean interleukin (IL)-6 value of 389±1045.7 pg/mL (range 2.7-5500) for neonates. The emergency cesarean section rate in the PPROM group was 20%. Four neonates in the PPROM group died in the early period. Since it was inevitable for patients diagnosed with PPROM to have preterm birth compared to the control group Table 2 presents the obstetric and neonatal outcomes by dividing the case group into two subgroups, below and above the 32th week of gestation, in order to avoid any bias.

The mean TTR was 0.30 ± 0.06 in pregnancies complicated by PPROM and 0.39 ± 0.08 in the control group ($p < 0.001$). The transverse thymic diameter of the PPROM group was statistically significantly lower compared to that of the control group (26 ± 7.06 and 35.1 ± 11.9, respectively; $p < 0.001$) (Table 3). There was no statistically significant difference in the fetal TTR values between the patients diagnosed with PPROM under and over 32 weeks of gestation (0.31 ± 0.06 and 0.29 ± 0.07, respectively; $p = 0.470$).

A correlation analysis was performed between the fetal TTR ratio and maternal serum inflammation markers, such as white blood cell count, neutrophil-to-lymphocyte ratio, and CRP, at the time of diagnosis (Table 4). There was a statistically significant moderate negative correlation between the fetal TTR and maternal white blood cell count ($r = -0.318$, $p = 0.010$) (Table 4). Although there was a negative correlation between the fetal TTR and neonatal CRP and IL-6 levels, this was not statistically significant (Table 5).

Discussion

In this study, we found that the fetal TTR and the transverse thymic diameter were decreased in pregnancies complicated by PPROM. The measurement of the fetal TTR is an optimal method for the evaluation of thymus size because it is not affected by gestational age or fetal sex (4, 6). Decreased fetal thymus size has been shown in the presence of obstetric complications such as preeclampsia and intrauterine growth restriction, as well as in maternal diseases. The fetal TTR has been shown to be reduced in diseases that may cause increased inflammation and cortisol levels in the mother. In addition, fetal thymus size is decreased in pregnancies with gestational diabetes and poor glucose control (Sinaci & Sahin, 2023). Similarly, a reduced fetal TTR may be useful in predicting severe preeclampsia (Gök & Ozden, 2023). Another study showed that the fetal TTR was decreased in maternal familial Mediterranean fever and systemic lupus erythematosus accompanied by inflammation, and this decrease was statistically significantly associated with maternal inflammatory markers (Beser et al., 2023; Uyan Hendem et al., 2024).

Our results are similar to those of previous studies in which fetal thymus size was measured

Table 1: Baseline Data of Study Population

Variable	mean ± SD		P value
	Case group (n=50)	Control group (n=60)	
Maternal age (years)	28.6 ± 5.8	28.9 ± 6.1	0.815
Maternal body mass index (kg/m2)	27.8 ± 3.5	27.1 ± 3.3	0.445
Nulliparity (n,%)	26 (52)	24 (48)	0.106
Gestational age at scan (weeks)	30.9 ± 3.0	31.9 ± 2.9	0.077
Female gender (n,%)	21 (48.8)	14 (35)	0.202

Note: Data given as mean±SD, number (n) and percentile (%). * A p-value of < 0.05 was considered statistically significant.
SD: standard deviation

Table 2: Demographic Data and The Fetal Thymic-Thoracic Ratio In Two-Subgroups of The Case Group

Variable			P value
	PPROM before 32 weeks (n=36)	PPROM after 32 weeks (n=14)	
Thymic-thoracic ratio	0.31 ± 0.06	0.29 ± 0.07	0.470
Early neonatal death (n, %)	4 (11.1)	0	0.294
Neonatal intensive care unit (n, %)	25 (69.4)	7 (50)	0.058
Emergency caesarean section (n, %)	9 (25)	1 (7.1)	0.112
Birth week*	32 ± 3.6	34.8 ± 1.86	0.012
Birth weight (g) *	1890 ± 679	2423 ± 302	0.010
APGAR score, first minute *	5.9±1.8	7.4±0.6	0.007
APGAR score, fifth minute	7.6±1.7	8.5±0.6	0.073
Maternal White blood counts (per microliter)	12.1 ± 3.3	11.7 ± 4	0.838
Maternal Neutrophil-to-lymphocyte ratio	6.6 ± 2.7	4.9 ± 2	0.323
Maternal C-reactive protein (mg/dL)	28.5 ± 75.2	18.4 ± 22.4	0.726

Table 3: The Fetal Thymic-Thoracic Ratio and Fetal Thymus Transverse Diameter In Two Groups

Variable	mean ± SD		P value
	Case group (n=50)	Control group (n=60)	
Thymus transverse diameter*	26 ± 7.06	35.1 ± 11.9	<0.001
Thymic-thoracic ratio*	0.30 ± 0.06	0.39 ± 0.08	<0.001

Note: Data given as mean ± standard deviation (SD). * A p-value of < 0.05 was considered statistically significant.

in pregnancies complicated by PPROM. Intrauterine inflammation is the cause of the vast majority of preterm births, regardless of the presence of chorioamnionitis, and this inflammation ruptures the membranes through contractions (Humberg et al., 2020). In a previous extensive study, a small proportion of fetuses with intrauterine inflammation were proven to have sepsis after birth. However, most newborns had elevated levels of inflammatory markers (Jung et al., 2020). This clinical picture is referred to as fetal inflammatory response syndrome. One of the distinct findings of this syndrome is a fetal plasma IL-6 level greater than 11pg/ml. Similar to the mentioned study, neonates had higher inflammatory markers in our study. Therefore, we evaluated fetal thymus size based on neonatal inflammatory cytokines, such as IL-6 and CRP, rather than chorioamnionitis findings.

One of the significant studies on PPROM and fetal thymus size was conducted by Yinon et al., reporting a relationship between small fetal thymus size and neonatal chorioamnionitis. In addition, the authors found that fetal thymus

Table 4: Correlation Between The Fetal Thymic-Thoracic Ratio And Maternal Blood Inflammation Markers

Variable	WBC		NLR		CRP	
	r	p	r	p	r	p
TTR	-0.318	0.010	-0.103	0.418	-0.128	0.314

*Correlation analysis was performed by Pearson test
A p-value of < 0.05 was considered statistically significant.
TTR: thymic-thoracic ratio, WBC: white blood count, NLR: neutrophil-to-lymphocyte ratio, CRP: c-reactive protein

Table 5: Correlation Between The Fetal Thymic-Thoracic Ratio and Neonatal Parameters

Variable	Neonatal blood CRP		Neonatal blood IL-6	
	r	p	r	p
TTR	-0.227	0,164	-0.122	0.486

*Correlation analysis was performed by Pearson test
A p-value of < 0.05 was considered statistically significant.
TTR: thymic-thoracic ratio CRP: c-reactive protein

measurement had a sensitivity of 100%, a specificity of 66.7%, a positive predictive value of 69%, and a negative predictive value of 100% compared to CRP in the diagnosis of chorioamnionitis (Yinon et al., 2007). Another study that explained the depletion of thymic lymphocytes through inflammation and glucocorticoid release, i.e., fetal thymic evolution, belongs to Di Naro et al. (Di Naro et al., 2006). The authors showed that thymus size remained below the fifth percentile in fetuses with histological and microbiological intrauterine infections. These findings are further supported by a decrease in fetal thymus growth following corticosteroid administration in preterm births (Jones, Nisenbaum, De Souza, & Berger, 2020).

It should also be noted that different outcomes have been documented in fetal TTR studies. In a meta-analysis including 1,744 fetuses, there was a relationship between small thymus size and an increased incidence of chorioamnionitis and preterm birth, whereas a prospective study involving 520 fetuses failed to establish a relationship between thymus size and adverse obstetric outcomes (Brandt, Bastek, Wang, Purisch, & Schwartz, 2016; Caissutti et al., 2018). New studies are needed to further investigate the relationship of fetal thymus size and TTR with obstetric complications and maternal morbidities. A limitation of the study is the small number of patients and the lack of histological tissue diagnosis.

In this study, we found a decrease in the fetal TTR and the fetal thymus transverse diameter in pregnancies complicated by PPROM. The thymus, an important lymphoid organ of the fetal immune system, seems to be associated with PPROM, a condition accompanied by inflammation.

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