ORIGINAL RESEARCH

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Two- and Three-Dimensional Ultrasonographic Evaluation of the Fetal Thymus in Women with Preterm Premature Rupture of Membranes: A Prospective Study

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ABSTRACT Objective: To evaluate the relationship between fetal thymus diameter and perinatal outcomes in preterm premature rupture of membranes (PPROM) cases and to compare three-dimensional (3D) fetal thymus volume in the same cases. **Material and Methods:** This was a prospective study from March 2019 through March 2020. Women diagnosed with PPROM between 24 and 33+6 weeks of gestation were included. Pregnancies were divided into 2 groups as small and normal according to the thymus size nomogram. The virtual organ computer-aided analysis software calculated the volumes automatically. **Results:** In 41 patients, measurements could be successfully acquired with two-dimensional and 3D sonography. Twenty eight (68.3%) patients were in the small thymus group and 13 patients (31.7%) were in the normal thymus group. The probability of clinical chorioamnionitis increased 7.7-fold-times in cases with small thymus (odds ratio 7.7, 95% confidence interval 1.1-67.4, p=0.038). The latency period was significantly higher in the normal thymus group. The correlation between transverse diameter and thymus volume was analyzed according to gestational age at ultrasound measurement and a significant correlation was observed between them. **Conclusion:** A small transverse diameter of the thymus in PPROM cases may be associated with clinical chorioamnionitis, and a normal thymus diameter may predict a longer latency period. In addition, although transverse thymus diameter was correlated with thymus volume, no significant volume difference was observed between the groups when percentile classification was made.

Keywords: Chorioamnionitis; fetus; preterm premature rupture of membranes; thymus; volume

Maternal and fetal immune responses due to intraamniotic infection (IAI) are the main cause of inflammation of the chorion and amnion (chorioamnionitis) and umbilical cord (funicitis).[1] In women with premature rupture of membranes, the incidence of IAI increases as a result of the ascending migration of the cervicovaginal flora, and the frequency of IAI in preterm premature rupture of membranes (PPROM) is approximately 30%.[2] Chorioamnionitis is defined as clinical chorioamnionitis and subclinical/histological chorioamnionitis according to the presence of clinical and laboratory signs.[3] It is possible to make a definitive diagnosis by invasive methods (such as amniocentesis) before birth or by histopathological examination of the placenta, fetal membranes, or umbilical cord vessels after birth.[1] Unfortunately, all these methods require invasive interventions or postnatal evaluation, and they are not practical and safe in the prenatal period. For this reason, diagnosis is made on suspicion of clinical find-

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ings (maternal fever, leukocytosis, maternal and/or fetal tachycardia, and uterine tenderness). Because late detected or unrecognized chorioamnionitis causes maternal, fetal, and neonatal morbidity, it is important to predict the presence of IAI in patients with PPROM who are undergoing expectant management, even in the absence of clinical findings.[4,5]

The thymus is the main organ in the development of the fetal immune response during the intrauterine period. It begins to develop at the 9th week of gestation, begin to descend into the anterior mediastinum at the 12th week which consists of the cortex and medulla and is differentiates approximately by the 17-week gestation completely.[6,7] Previous studies have shown that chorioamnionitis is associated with a significant reduction in thymus size at birth, associated with an increased inflammatory response.[8] In recent studies, prenatal ultrasound (US) evaluation of the fetal thymus has been used to detect chorioamnionitis in PPROM or spontaneous preterm birth. These studies showed that small fetal thymus (<5th percentile for gestational week) is associated with early diagnosis of chorioamnionitis in PPROM cases.[2,9,10] In these studies, the size of the fetal thymus was measured by two-dimensional (2D) US with a perimeter or transverse diameters. Recent studies have focused on three-dimensional (3D) US for accurate measurement due to the irregular shape of the fetal thymus.[11,12]

In this study, we aimed to evaluate the relationship between fetal thymus diameter and perinatal outcomes in PPROM cases. In addition, we made comparisons by measuring the 3-dimensional fetal thymus volume in the same cases.

MATERIAL AND METHODS

STUDY DESIGN

This prospective cross-sectional study was conducted between March 2019 and March 2020 at the Maternal-Fetal Medicine Unit of University of Health Science, Tepecik Training and Research Hospital, Türkiye. This study was conducted following the Helsinki Declaration ethical standards. The ethics committee approval for this study was obtained from the University of Health Sciences Tepecik Training and Research Hospital Non-Invasive Ethics Committee (date: February 28, 2019; no: 2019/3-25). All participants were informed and informed voluntary consent was obtained.

PATIENTS' SELECTION AND PREGNANCY MANAGEMENT

We evaluated singleton pregnancies between 24 and 33+6 gestational weeks (confirmed by first-trimester US with crown-to-rump length) and expectantly managed singleton pregnancies according to the last menstrual period with PPROM.

The exclusion criteria were fetal structural or chromosomal abnormalities, the presence of labor at the time of diagnosis, or giving birth within 48 hours of diagnosis, multiple pregnancies, fetuses that do not tend to grow normally (estimated fetal weight below the 10th percentile or over the 90 percentiles according to Hadlock et al.)[12] and pregnant women with additional diseases (i.e., hypertensive disease of pregnancy, diabetes).

PPROM was diagnosed in pregnancies with amniotic fluid leaking from the cervical os and pooling in the vaginal vault on sterile speculum examination. In patients with suspected PPROM but without amniotic fluid drainage, the diagnosis was confirmed using the placental alpha microglobulin-1 protein test from the vaginal fluid. After the diagnosis, patients between 24 and 33+6 weeks of gestation without labor and IAI findings were hospitalized for expectant management. Patients who refused inpatient follow-up, were scheduled twice weekly as an outpatient. All pregnant women received a single course of betamethasone (6 mg intramuscularly every 24 hours for 2 doses), and antibiotics (1 g of azithromycin orally and additionally 2 g of ampicillin intravenously 4 times a day for 2 days followed by 500 mg of amoxicillin orally 3 times a day for 5 days). The pregnancies were followed up to the 34th gestational week. Indications for delivery included clinical signs of IAI (maternal temperature was elevated to 38.0 °C on 2 occasions 30 minutes apart plus one or more of the following criteria: fundal tenderness, maternal tachycardia (heart rate >100 beats per minute), baseline fetal heart rate >160 beats per minute for ≥10 minutes, maternal leukocytosis (white blood cell >15.000/mm^3) or foul-smelling purulent discharge from the cervical os on sterile speculum examination),

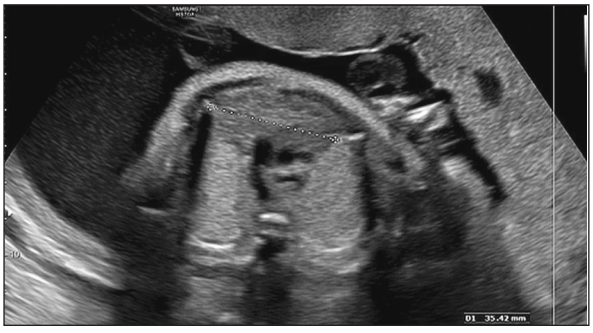

FIGURE 1: Axial plane of the fetal thorax at three-vessel trachea level.

fetal distress, labor or severe vaginal bleeding suggests ablation placenta. The optimal birth time was planned as 34 weeks and above.

US MEASUREMENT TECHNIQUES OF THE THYMUS

US measurements were obtained in both 2D and 3D with an US machine Samsung Ultrasound System HS70A (Samsung Medison Company, Republic of Korea). Fetal biometric measurements, fetal thymus diameters, and fetal thymus volumes were performed 48 hours after PPROM. WBC, C-reactive protein (CRP), and US measurements were made 48 hours after the PPROM.

The fetal thymus was visualized as described by previous studies.[11,13] In the axial plane, in the three-vessel trachea (3VT) section, between both internal mammary arteries, behind the sternum, and in front of the 3VT, the fetal thymus was localized (Figure 1). When the fetal thymus was completely visualized in the axial plane, maximal transverse diameters (mm) acquired. Maximum transverse diameter was defined as a measurement of fetal thymus perpendicular to the axis sternum and spine. Then the 3D probe was activated. Six consecutive images were acquired, and their boundaries were determined manually. The virtual organ computer-aided analysis (VOCAL) software calculated the volumes automatically (Figure 2).

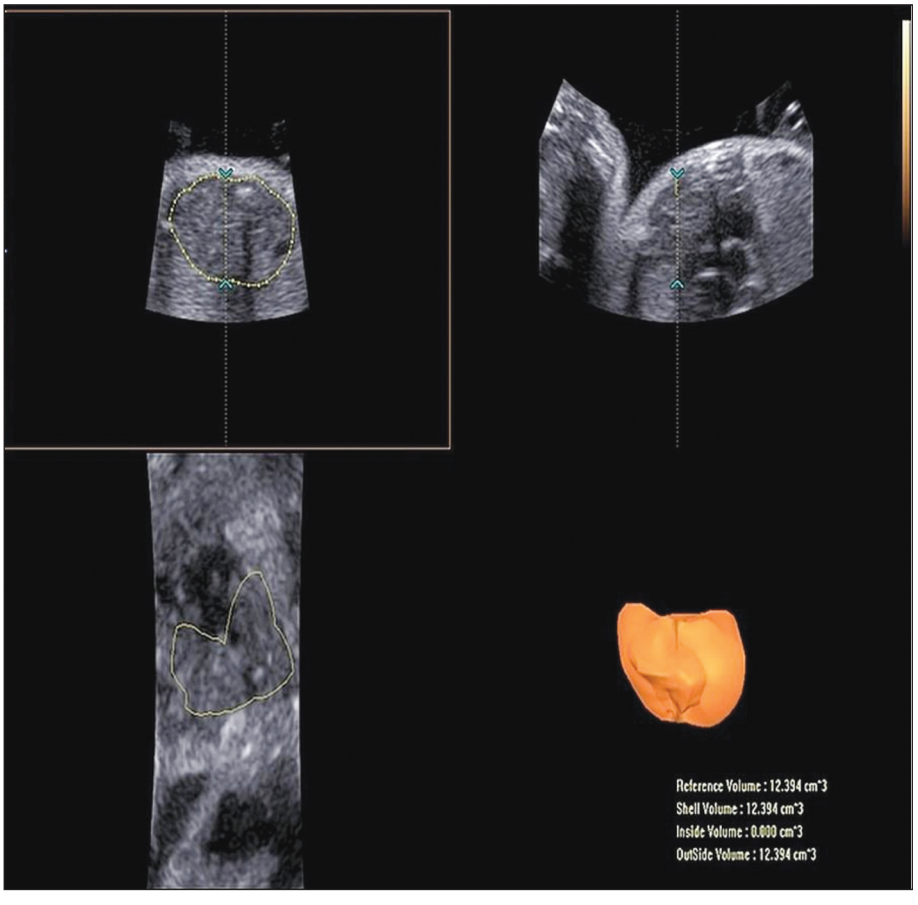

FIGURE 2: Virtual organ computer-aided analysis calculation of the fetal thymus.

All examinations were performed by one sonographer (MK) and all measurements were repeated three times and the mean value of these measurements was included in the study. According to the nomogram, 2D thymus diameter measurements made as described by Musilova et al. in 2001, and the small thymus was accepted as the transverse thymus diameter below the 5th percentile.[13]

STATISTICAL ANALYSIS

SPSS version 26.0 (IBM Corporation, Armonk, New York, USA) was used for data analysis. The significance level was taken as $p<0.05$ in all analyzes. The Shapiro-Wilk test was used to determine the distribution of the data. Student's t-test was used for normally distributed data in comparisons and data were presented as mean±standard deviation. Mann-Whitney U test was used to compare the data that could not show the normal distribution and the data were shown as median±(minimum, maximum). The chi-square test was used to compare categorical variables and odds ratio (OR) [95% confidence interval (CI)] calculations were made. Power analysis was performed with G-Power (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) according to the other studies. Accordingly, the minimum number of samples was calculated as 11 for each group.

RESULTS

In total, 45 patients with PPROM were selected in accordance with our study criteria. However, fetal thymus borders could not be determined in 4 patients due to the fetal position, maternal obesity, and oligohydramnios. In the remaining 41 patients (91.1%), measurements could be successfully acquired with sonography and enrolled in the study. Twenty eight (68.3%) patients were in the small thymus group and 13 (31.7%) patients were in the normal thymus group.

The demographic and clinical characteristics of the groups were analyzed in Table 1. Both groups were similar in terms of maternal age, parity, and body mass index. While 2 (7.1%) patients in the small thymus group were smoking, this number was 3 (23.1%) in the normal thymus group, which was statistically similar (p=0.147). Gestational age (GA) at admission (28.5±3.2 vs. 26.2±2.9, p=0.731) and GA at delivery (31±2.3 vs. 32.6±2.2, p=0.140) were statistically similar between the groups. Also, GA in the US measurement of both groups was statistically similar (29±2.9 vs. 28.6±2.6, p=0.201). The latency period between admission and delivery was significantly higher in the normal thymus group (20±13.5

TABLE 1: Demographic and clinical characteristics of the groups.

	Small thymus (n=28)	Normal thymus (n=13)	p value
Maternal age (year) ($\bar{X}$±SD)	28.1±6.9	30.1±6.7	0.395
Parity (n, %)			0.894
Nulliparous	7 (25)	3 (23.1)	
Multiparous	21 (75)	10 (76.9)	
BMI at during test ($\bar{X}$±SD) (kg/m^2)	27.3±4.2	27±4.6	0.845
Smoker (n, %)	2 (7.1)	3 (23.1)	0.147
Gestational age at admission (weeks) ($\bar{X}$±SD)	28.5±3.2	28.2±2.9	0.731
Gestational age at US measurement (weeks) ($\bar{X}$±SD)	29±2.9	28.6±2.6	0.201
Gestational age at delivery (weeks) ($\bar{X}$±SD)	31±2.3	32.6±2.2	0.140
Latency period between admission and delivery (days) ($\bar{X}$±SD)	20±13.5	30.3±21.9	0.047
Thymus diameter (mm) ($\bar{X}$±SD)	21.3±3.6	26.3±5.5	0.001
Thymus VOCAL volume (mm^3) ($\bar{X}$±SD)	1.77±1.03	1.90±1.32	0.739
WBC (US measurement time) (*10^3/mm^3) ($\bar{X}$±SD)	12.9±2.8	13.2±5.3	0.831
WBC (US measurement time) >15 (*10^3/mm^3) (n, %)	8 (28.6)	6 (46.2)	0.269
CRP (US measurement time) (mg/L) ($\bar{X}$±SD)	9.6±10.9	14.1±11.9	0.240
CRP (US measurement time) >5 (mg/L) (n, %)	16 (57.1)	10 (76.9)	0.221
Clinical chorioamnionitis (n, %)	11 (39.3)	1 (7.7)	0.038

SD: Standard deviation; BMI: Body mass index; US: Ultrasound; VOCAL: Virtual organ computer-aided analysis; WBC: White blood cell; CRP: C-reactive protein.

TABLE 2: Maternal and perinatal outcomes of the groups.

	Small thymus (n=28)	Normal thymus (n=13)	p value
Delivery type (n, %)			0.527
Vaginal delivery	8 (28.6)	5 (38.5)	
Cesarean section	20 (71.4)	8 (61.5)	
Indications of labor (n, %)			0.101
Chorioamnionitis	11 (39.3)	1 (7.7)	
Spontaneous labor	6 (21.4)	6 (46.2)	
Previous cesarean in labor	1 (3.6)	1 (7.7)	
Non-reassuring fetal status	4 (14.3)	2 (15.4)	
Vaginal bleeding/placental abruption	0	2 (15.4)	
Cord prolapses	1 (3.6)	0	
Optimal birth time	5 (17.8)	1 (7.7)	
Gender (n, %)			0.382
Male	11 (39.3)	7 (53.8)	
Female	17 (60.7	6 (46.2)	
Birth weight (g) ($\bar{X}$±SD)	1719.1±593.2	1843.5±460.9	0.348
1st minute APGAR scores <7 (n, %)	10 (35.7)	8 (61.5)	0.121
5th minute APGAR scores <7 (n, %)	4 (14.3)	3 (23.1)	0.486
NICU admission (n, %)	25 (89.3)	13 (100)	0.220
NICU hospitalization duration (days) ($\bar{X}$±SD)	33.2±27	36.6±21.7	0.696
Perinatal mortality (n, %)	1 (2.7)	1 (7.7)	0.568

SD: Standard deviation; NICU: Neonatal intensive care unit.

vs. 30.3±21.9, p=0.047). Thymus VOCAL volume values were similar between the groups (1.77±1.03 vs. 1.90±1.32, p=0.739). WBC and CRP values of both groups, and WBC>15 ($^{*}10^{3}/mm^{3}$) and CRP>5 (mg/L) values were similar between the groups. While clinical chorioamnionitis was seen in 11 (39.3%) patients in the small thymus group, it was seen in 1 (7.7%) patient in the normal thymus group, and the probability of clinical chorioamnionitis increased 7.7-fold-times in cases with small thymus (OR 7.7, 95% CI 1.1-67.4, p=0.038) (Table 1).

Maternal and perinatal outcomes of the groups were analyzed in Table 2. Accordingly, the delivery types and labor indications of the groups were similar. While the small thymus group consisted of 11 (39.3%) male and 17 (60.7%) female fetuses, there were 7 (53.8%) male and 6 (46.2%) female fetuses in the normal thymus group, the difference was not significant (p=0.382). The birth weights of both groups were similar. There was no significant difference between 1st minute, 5th minute APGAR scores and neonatal intensive care unit admission. There was one perinatal mortality in both groups and the difference between them was similar (p=0.568).

In Figure 3, the correlation between transverse diameter and thymus volume was examined according to GA at US measurement. Accordingly, there was a significant correlation between them (r=0.335, p=0.016) (Figure 3).

DISCUSSION

In this study, we showed that the probability of clinical chorioamnionitis increased 7.7-fold times in cases with small thymus diameters. There was no significant relation between other infection parameters (WBC counts and CRP levels) and thymus diameter. However, in terms of latency time, the normal thymus group was significantly higher. We also observed a significant correlation between transverse thymus diameter and thymus volume.

PPROM is a clinical condition that can be managed expectantly until 34 gestational weeks unless the maternal or fetal indications of urgent delivery

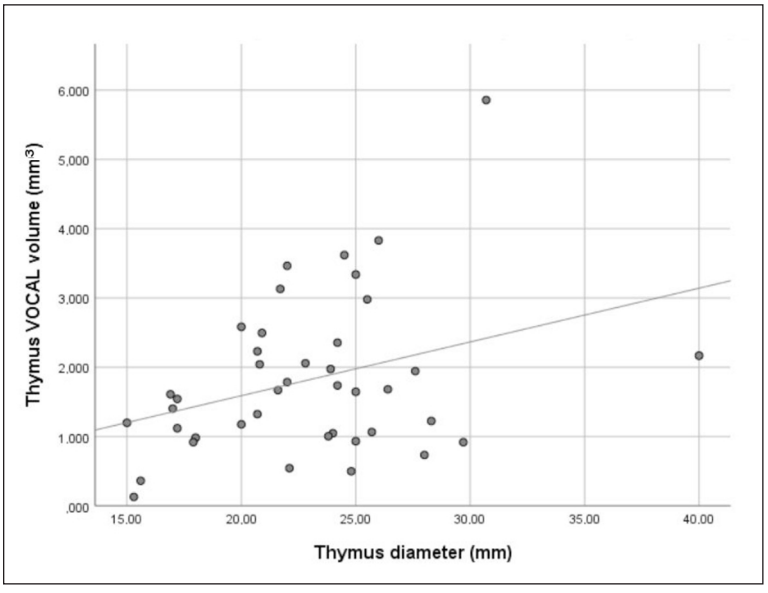

FIGURE 3: Correlation between thymus transverse diameter and 3D thymus volume. VOCAL: Virtual organ computer-aided analysis.

occur.[1] One of the delivery indications is IAI, which is related to poor maternal and perinatal outcomes when the diagnosis is delayed or unrecognized. Until the maternal or fetal symptoms of chorioamnionitis begin, the existence of IAI may remain undiagnosed and lead to an unfavorable prognosis. Therefore, it is very important to define the diagnosis of IAI rapidly and accurately. Because the definitive diagnostic tests require invasive procedures, such as amniotic fluid culture or gram staining of amniotic fluid obtained by amniocentesis, and they are useless in clinical practice, the recent studies have emphasized new simple and noninvasive markers such as maternal laboratory parameters [WBC, CRP, interleukin-6 (IL-6), procalcitonin] and sonographic markers (fetal biophysical profile, thymic diameters) for predicting chorioamnionitis.[1,11] However, there is currently no definitive reliable noninvasive marker that can predict chorioamnionitis before symptoms begin. Due to the relationship between unidentified or late detected chorioamnionitis and adverse perinatal outcomes, we aimed to know whether we could identify a new sonographic and noninvasive marker that could be used in the early prediction of chorioamnionitis with this study.

Firstly, De Felice et al. revealed the relationship between the radiological small thymus size of preterm infants at birth and the chorioamnionitis of their mothers in 1999.[14] Yinon et al. studied 21 pregnant women with PPROM in 2007 and found a statistically significant difference in terms of clinical/histological chorioamnionitis or neonatal sepsis between intrauterine small thymus and normal thymus groups.[2] In this study, all patients who developed clinical and/or histological chorioamnionitis (9/21) were in the small thymus group. Musilova et al. in 2013, and Aksakal et al. in 2014, observed a smaller transverse thymus diameter in the patient group with histological chorioamnionitis.[15,16] All these results are consistent with our study. This relationship was explained with fetal inflammatory response syndrome, which is defined as an inflammatory process of fetuses exposed to microbial agents and associated with increased major acute phase response mediator IL-6 levels in umbilical cord plasma.[10] It occurs with multiorgan involvement of the fetus when systemic mediators enter the circulation and are related to adverse perinatal and neonatal outcomes.[17] One of the fetal target organs is fetal thymus, and lymphocyte depletion in the fetal thymic cortex and medulla due to the fetal inflammatory response to cytokines (IL-6) which is released in case of acute stress situations such as chorioamnionitis, causes thymic involution.

In our study, we also looked at 3D thymus volume in patients with transverse thymus diameter and found a correlation between transverse thymus diameter and thymus volume. However, when we classified them as small and normal thymus according to transverse thymus diameter, there was no significant difference between 3D thymus volumes. Studies that have previously measured 3D thymus volume are very limited. The first of these studies was carried out by Li et al. in 2011.[11] They obtained a nomogram of fetal thymus volume according to GA in normal singleton pregnancies and demonstrated that 3D-US measurements are more correlated with GA than 2D-US due to the complex and irregular shape of the fetal thymus.[11] In their study, a significant correlation was observed between transverse diameter and 3D thymus volume, similar to our findings. Re et al. published an article on the thymus volume nomogram in 2015.[12] In their article, the correlation between thymus transverse diameter and thymus volume was not examined. In these 2 studies, the fetal thymus visualization rate was 95.3% and 77%, respectively.[11,12] Our visualization rate (91.1%) is higher than 77% but lower than 95.3%. An important point that stands out between these two studies and our study is the numerical difference in our 3D volume measurement values.[11,12] For example, while the measurement values are around 1-10 mm^3, in the study by Li et al., our volume measurement values vary between 0-6 mm^3 as can be seen in Figure 1. This may be due to the calculation difference of the VOCAL software used. Therefore, we could not compare the two studies in percentile values.[11]

In our study, we also compared WBC and CRP values with thymus diameters, but we did not observe a significant difference. In the literature, Yinon et al. examined clinical chorioamnionitis and did not find a significant relationship between thymus diameter and CRP, while Musilova et al. investigated histological chorioamnionitis and found a significant relationship.[2,15] We could not evaluate histological chorioamnionitis in our study, so histological chorioamnionitis cases that we were not aware of may have affected these results. This can be explained by the late onset of clinical signs in pregnancies with IAI because a limited inflammation/infection can not result in the systematic inflammatory response and clinical signs. In addition, the WBC and CRP measurement times and antibiotic use of all these studies were different, which may have affected the results. In this regard, studies investigating clinical chorioamnionitis with large samples are required.

The latency period was significantly longer in the normal thymus group than in the small thymus group in our patient population. Yinon et al. looked at the same parameter but found no significant difference between groups.[2] Our gestational week at admission was smaller than that of Yinon et al.'s population. This is probably why our waiting time was longer. In our study, while the mean latency was 20±13.5 days in the small thymus group, it was 30.3±21.9 days in the normal thymus group. Yinon et al. found the median latency to be 8 (0-47) and 3 (2-30) days. Results can be attributed to different study populations, different follow-ups, and treatments.

This study had some limitations. The most important limitation was that we could not differentiate histological chorioamnionitis. Clinical chorioamnionitis may manifest itself late, which may cause some cases to be missed. Our sample size was relatively small as a power-limiting factor. In addition, we examined thymus volumes with 3D VOCAL measurement, which is a very new field of study, and detected numerical classification differences, possibly due to different software. Our strength, to the best of our knowledge, this is the first study to evaluate thymus volume in PPROM patients. We think that the results of the study will contribute to the literature.

CONCLUSION

Small transverse diameter of the thymus in PPROM cases may be associated with clinical chorioamnionitis, and a normal thymus diameter may predict a long latency period. In addition, although transverse thymus diameter was correlated with thymus volume, no significant volume difference was observed between the groups when percentile classification was made. However, the 3D volume software used in the

literature is very diverse and this makes it difficult to compare the studies.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Melda Kuyucu, Burak Bayraktar;* ***Design:*** *Burak Bayraktar, Hakan Gölbaşı;* ***Control/Supervision:*** *Duygu Adıyaman;* ***Data Collection and/or Processing:*** *Melda Kuyucu, Bahar Konuralp Atakul;* ***Analysis and/or Interpretation:*** *Bahar Konuralp Atakul;* ***Literature Review:*** *Duygu Adıyaman;* ***Writing the Article:*** *Melda Kuyucu;* ***Critical Review:*** *Halil Gürsoy Pala;* ***References and Fundings:*** *Hakan Gölbaşı;* ***Materials:****Melda Kuyucu, Bahar Konuralp Atakul.*

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