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# Evaluation of fetal thymus size in pregnancies complicated with fetal growth restriction

# Fetal büyüme kısıtlılığı ile komplike gebeliklerde fetal timus boyutunun değerlendirilmesi

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## ÖZ

Amaç: Fetal büyüme kısıtlılığı (FBK) ile komplike gebeliği olan kadınlarda timik-torasik oran (TTO) kullanarak fetal timus boyutunu değerlendirmek ve olumsuz perinatal sonuçlarla olan ilişkisini belirlemek.

Gereçler ve Yöntem: Bu prospektif çalışmaya FBK ile komplike toplam 35 gebe kadın ile benzer demografik özellikte sağlıklı toplam 42 gebe kadın dahil edildi. FBK grubunda, patolojik Doppler akım parametreleri olan umbilikal arterde end-diyastolik akım kaybı (EDAK) ve serebroplasental oran (SPO) <1 olan ve tahmini fetal ağırlığı (TFA) <3. persantil olan olgular ayrıca kayıt altına alındı. Gruplar arasında demografik özellikler, klinik ve sonografik özellikler ve fetal TTO açısından karşılaştırmalar yapıldı. Elde edilen verilerin istatistiksel analizinde, gruplar arası ortanca (median) değerlerin ve kategorik değişkenlerin karşılaştırılmalarında Mann-Whitney U ve Fisher's Exact testleri kullanıldı. Fetal TTO ile olumsuz perinatal sonuçlar arasındaki ilişki Spearman korelasyon katsayısı ile araştırıldı. P<0.05 değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: TFA <3. persantil, oligohidramniyoz, patolojik Doppler akımı dışındaki olumsuz perinatal sonuçlar ve diğer parametreler her iki grupta da benzerdi (p>0.05). Fetal TTO'nun FBK grubunda kontrol grubuna göre anlamlı derecede daha düşük olduğu belirlendi (0.37±0.02 [0.33-0.42] ve 0.40±0.02 [0.36-0.45], p<0.001, sırasıyla). Fetal TTO ile TFA <3. persantil, patolojik Doppler akımı (EDAK ve SPO <1) arasında istatistiksel olarak anlamlı, orta düzeyde negatif bir korelasyon saptandı (r= -0.703, r= -0.588, r= -0.383, r= -0.418 ve p<0.001, p<0.001, p=0.023, p=0.012, sırasıyla).

Sonuç: Düşük fetal TTO, FBK ile fetal timik involusyon ilişkisini desteklemektedir. Bununla birlikte, olumsuz perinatal sonuçların öngörüsünde fetal TTO bir sonografik indikatör olabilir.

Anahtar Kelimeler: Fetal büyüme kısıtlılığı, timik-torasik oran, ultrason

## ABSTRACT

Aim: To evaluate fetal thymus size using the thymic-thoracic ratio (TTR) in women with a pregnancy complicated with fetal growth restriction (FGR) and to assess the relationship with adverse perinatal outcomes.

Materials and Method: A total of 35 pregnant women with FGR and 42 healthy pregnant women with similar demographic characteristics were included in this prospective study. In the FGR group, cases with pathological Doppler flow parameters of absent end-diastolic flow (AEDF) in an umbilical artery and cerebroplacental ratio (CPR) <1 and estimated fetal weight (EFW) <3rd percentile were also recorded. The groups were compared in terms of demographic features, clinical and sonographic characteristics and fetal TTR. In the statistical analysis of the data obtained, the Mann-Whitney U and Fisher's Exact tests were used to compare the median values of the groups and categorical variables. The association between fetal TTR and adverse perinatal outcomes was investigated using Spearman's correlation coefficient. The level of statistical significance was set at p<0.05.

Results: Other than the adverse perinatal outcomes of EFW <3rd percentile, oligohydramnios, pathological Doppler flow, all the other parameters were similar in both groups (p>0.05). The fetal TTR was determined to be significantly lower in the FGR group than in the control group (0.37±0.02 [0.33-0.42] and 0.40±0.02 [0.36-0.45], p<0.001, respectively). A statistically significant, negative moderate correlation was determined between fetal TTR and the EFW <3rd percentile, pathological Doppler flow (AEDF and CPR<1) (r= -0.703, r= -0.588, r= -0.383, r= -0.418 and p<0.001, p<0.001, p=0.023, p=0.012, respectively).

Conclusion: A lower fetal TTR supports the relationship between FGR and fetal thymic involution. Moreover, fetal TTR might be a sonographic indicator for predicting adverse perinatal outcomes.

Keywords: Fetal growth restriction, thymic-thoracic ratio, ultrasound

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## INTRODUCTION

Fetal growth restriction (FGR) is a condition in which the normal fetal genetic growth potential is not reached due to a defect in any of the maternal, fetal, or placental factors. It occurs in about 10% of pregnancies and poses a significant risk of adverse perinatal outcomes, perinatal morbidity, and mortality (1). Although the underlying primary pathophysiological mechanisms differ, the final stage of these mechanisms has been shown to be insufficient uterine-placental perfusion and impaired fetal nutrition. As a result, it is well understood that uteroplacental and fetal blood flow evaluation with Doppler ultrasonography (USG) is useful in the prediction and management of fetal hypoxia and acidemia, and is the primary component of clinical management. However, advanced diagnostic prognostic factors are still required to predict perinatal outcomes in FGR-complicated pregnancies (2).

The role of the placenta is crucial in maintaining gestational biological pathways and a stabilized maternal-fetal coaction. A balanced environment in the intervillous space (maternal-fetal interface) and adequate fetal perfusion are required for normal fetal growth. Various epigenetic, metabolic, immunological and infectious factors could impress the cellular fragments of the intervillous space (endovascular trophoblasts, syncytiotrophoblasts etc.) and may cause obstetric complications (3, 4). The fetal thymus gland is a vital organ that contributes to the immune system of the fetus by producing T-lymphocytes. The thymus gland starts to develop from the endoderm at about fifth weeks of gestation. This is followed by lymphatic progenitor cell migration from other immune organs (eg liver, spleen). The maturation of thymocytes and differentiation into T-lymphocytes occur in the thymus, and at approximately 16-20 weeks of gestation, fetal thymus maturation is completed. Therefore, it is important for a healthy immune system (5, 6). There have been studies in recent years suggesting that a change in the dimensions of the fetal thymus may be a sensitive and significant parameter in the prediction of complications during the pregnancy (7). The activation of the hypothalamo-pituitary-adrenal gland axis and fetal inflammatory response syndrome (FIRS) due to stress-related conditions during pregnancy have also been suggested to be associated with thymic involution (8, 9).

Consequently, a few studies have reported that there may be an involution in fetal thymus size in pregnancies complicated by preterm prelabor rupture of membranes (PPROM), chorioamnionitis, pre-eclampsia, diabetes mellitus, and fetuses with chromosomal anomalies (especially cardiac anomaly) (10). Ekin et al. suggested that small fetal thymus size could be an early sign of adverse perinatal outcomes in pregnancies which are complicated by intrauterine growth restriction (11).

As the fetal thymic-thoracic ratio (TTR) is unaffected by body mass index, fetal sex, or gestational week, it is an important parameter used in thymus size standardization. The fetal sternum-vertebra anterior surface distance is calculated in the three-vessel trachea transverse section of the fetal thorax on USG by dividing the fetal sternal-aorta anteroposterior fetal thymus length by the thorax length (12). There is a limited number of studies in literature evaluating fetal thymus size with TTR in pregnancies complicated with FGR (13). Therefore, the aim of this study was to assess fetal thymus size with TTR in women with a pregnancy complicated with FGR and to investigate the relationship with adverse perinatal outcomes.

## MATERIALS AND METHOD

This prospective, case-control study included pregnant women who were admitted to the Obstetrics and Gynecology Department of University of Health Sciences, Konya City Hospital, between 22th July 2022, and 20th October 2022. This hospital is a tertiary-level referral centre with an average of 700 births per month (14). The sample size required and the power of the study were calculated using G*Power software (Ver.3.1.9.2, Universit□t Düsseldorf, Germany). A total of 62 subjects, as 31 in each group, was calculated to be necessary to obtain effect size of (d)=0.84, α=0.05, 1-β=0.9 ratio for 90% actual power (5, 15). The study included 35 pregnant women with a singleton pregnancy who were diagnosed with FGR by ultrasonographic (USG) evaluation in the last trimester, at ≥32 gestational weeks, and 42 healthy pregnant women with no additional systemic pathology, matched in terms of demographic characteristics and gestational age (determined by dating from the first trimester early USG measurements). FGR was diagnosed from USG evaluation of fetuses with an estimated fetal weight (EFW) <10th percentile for gestational age (2). Pregnant women were excluded from the study if they were <32 weeks of gestation, had a multiple pregnancy, had been previously treated with corticosteroid (betamethasone) for fetal lung maturation, had fetal structural and chromosomal malformations, a known maternal/fetal infection, intrauterine fetal death, preterm rupture of membranes or active labor, fetal malposition, maternal morbid obesity, or if the optimal thymus size could not be measured for technical reasons such as anhydramnios. The study protocol

was in accordance with the Helsinki II declaration. Approval for the study protocol was granted by the Institutional Ethics Committee of KTO Karatay University (Decision Number:2022/001, Date:17/06/2022) and the Institutional Review Board of University of Health Sciences, Konya City Hospital (Decision Number:07-41, Date:21/07/2022). Informed consent was provided by all the study participants.

The same maternal-fetal medicine specialist (SAE) performed the USG evaluations with a Samsung HS70A USG device (5-MHz transabdominal transducer) which is used for routine examination in the Perinatology Clinic. Fetal biometric parameters, amniotic fluid measurements, routine Doppler flow velocity measurements (e.g. umbilical and middle cerebral artery) were performed. The diagnosis of oligohydramnios was determined as single deepest pocket (SDP) <2 cm. Cases with pathological Doppler flow parameters of absent end-diastolic flow (AEDF) in an umbilical artery, cerebroplacental ratio (CPR) <1 and EFW<3rd percentile were also recorded. In a three-vessel trachea transverse section of the fetal thorax on USG, the fetal TTR was calculated by dividing the fetal sternal-aorta anteroposterior fetal thymus length by the thorax length, which is the fetal sternum-vertebra anterior edge distance (Figure 1) (16). The study group of pregnant women complicated with FGR and the control group of pregnant women without any defined risk factors were compared in respect of demographic features, clinical and sonographic characteristics, and fetal TTR.

Data obtained in the study were analyzed statistically using the Statistical Package for the Social Sciences vn.25.0 software (SPSS Inc, Chicago, IL, USA). Conformity of the data to normal distribution was assessed with the Shapiro-Wilk test and the Kolmogorov-Smirnov test. As the data were seen to not be normally distributed, descriptive analysis results were presented as median and interquartile range values. The Mann-Whitney U test was applied to comparisons of median values between the groups. Numbers (n) and percentages (%) were used to express categorical variables. Comparisons of categorical variables between the groups were performed with Fisher's Exact test. was utilized to investigate The relationships between fetal TTR and adverse perinatal outcomes were investigated with Spearman's correlation coefficient . A two-tailed value of $p < 0.05$ was accepted as the level of statistical significance.

## RESULTS

The comparisons of demographic, clinical and sonographic characteristics and fetal thymic-thoracic ratios (TTR) between pregnant women complicated with FGR (n=35) and healthy control subjects (n=42) are shown in Table 1.

**Table 1.** Comparison of demographic features, clinical characteristics and fetal thymic-thoracic ratios (TTR) between pregnant women complicated with fetal growth restriction (FGR) and the healthy control group

| Variables | Pregnant women complicated with FGR (n=35) | Healthy control group (n=42) | p value |
|---|---|---|---|
| Maternal age (years) (median, IQR)[a] | 28 (6) | 27.5 (8.25) | 0.902 |
| BMI (kg/m$^2$) (median, IQR)[a] | 26.59 (2.52) | 26.80 (2.42) | 0.301 |
| Gravidity (median, IQR)[a] | 2 (2) | 2.5 (2) | 0.807 |
| Parity (median, IQR)[a] | 1 (2) | 1 (2) | 0.493 |
| Miscarriage (median, IQR)[a] | 0 (1) | 0 (1) | 0.119 |
| Gestational age at the screening (weeks) (median, IQR)[a] | 36 (1.25) | 37 (3) | 0.838 |
| Gestational diabetes mellitus (n,%)[b] | 3 (8.5%) | 0 (0%) | 0.089 |
| Gestational hypertension (n,%)[b] | 3 (8.5%) | 0 (0%) | 0.089 |
| Pre-eclampsia (n,%)[b] | 3 (8.5%) | 0 (0%) | 0.089 |
| ICP (n,%)[b] | 2 (5.7%) | 0 (0%) | 0.203 |
| <3$^{th}$ percentile (n,%)[b] | 9 (25.7%) | 0 (0%) | **<0.001** |
| Oligohydramnios (n,%)[b] | 8 (22.8%) | 0 (0%) | **0.001** |
| Pathological Doppler flow (n,%)[b] | 7 (20%) | 0 (0%) | **0.003** |
| • AEDF (n,%) | 2 (5.7%) | 0 (0%) | 0.203 |
| • CPR<1 (n,%) | 5 (14.2%) | 0 (0%) | **0.016** |
| TTR (mean±SD) (median, IQR)[a] | 0.37±0.02 (0.33-0.42) | 0.40±0.02 (0.36-0.45) | **<0.001** |

FGR: Fetal growth restriction, BMI: Body-mass index, IQR: Interquartile range, ICP: Intrahepatic cholestasis of pregnancy, AEDF: Absent umbilical arterial end-diastolic flow, CPR: Cerebroplacental ratio, SD: Standard deviation, TTR: fetal thymic-thoracic ratio

a Statistical analysis was performed with the Mann-Whitney U test

b Statistical analysis was performed with the Fisher's Exact test

With the exception of the adverse perinatal outcomes of EFW <3rd percentile, oligohydramnios and pathological Doppler flow, the remaining parameters evaluated showed no significant difference between the two groups (p>0.05). Significantly lower fetal TTR values were determined in pregnant women complicated with FGR than in the control group (0.37±0.02 [0.33-0.42] and 0.40±0.02 [0.36-0.45], p<0.001, respectively) (Figure 2).

**Figure 1.** In a three-vessel trachea transverse section of the fetal thorax on ultrasonography, the measurement of the fetal thymic-thoracic ratio (TTR) was calculated by dividing the fetal sternal-aorta anteroposterior fetal thymus length by the thorax length, which is the fetal sternum-vertebra anterior edge distance

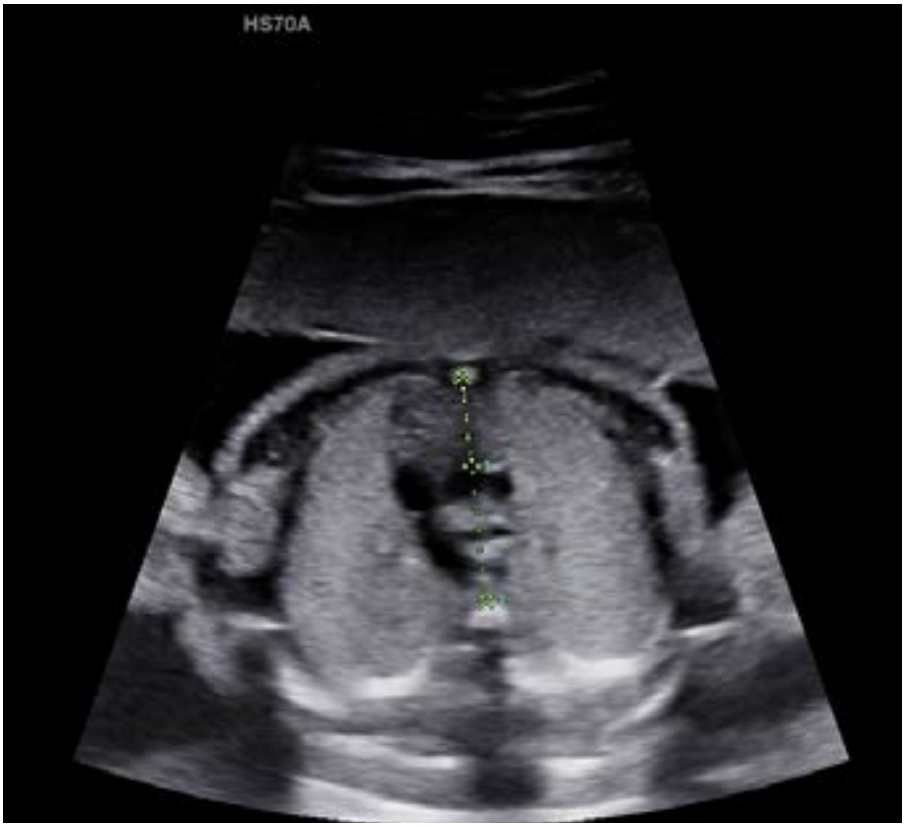
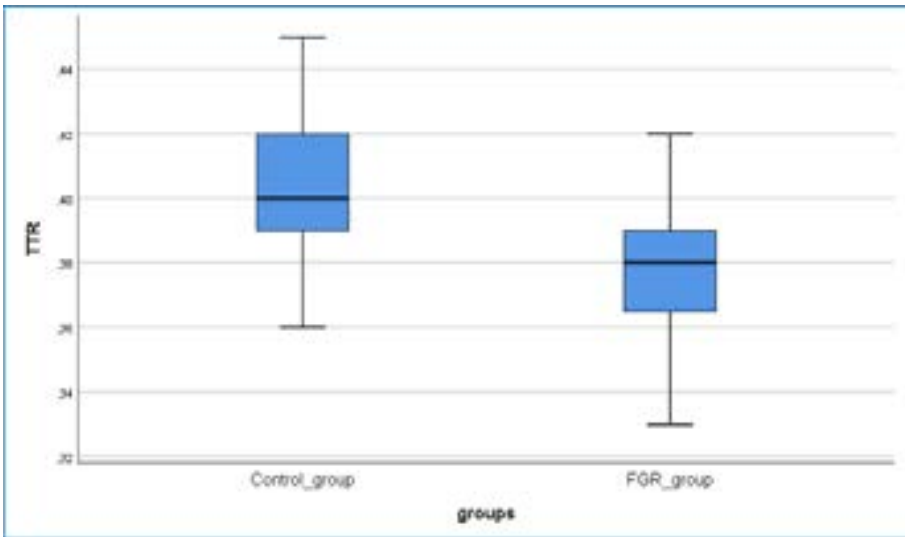



**Figure 2.** Comparison of fetal thymic-thoracic ratios (TTR) between pregnant women complicated with fetal growth restriction (FGR) and the healthy control group



The correlations between fetal thymic-thoracic ratio (TTR) and adverse perinatal outcomes (EFW <3rd percentile, oligohydramnios, pathological Doppler flow) in pregnant women complicated with FGR are shown in Table 2.

**Table 2.** Correlations between the fetal thymic-thoracic ratio (TTR) and adverse perinatal outcomes in pregnant women complicated with FGR

| | TTR | |
|---|---|---|
| | r[a] | p[a] |
| <3th percentile | -0.703 | **<0.001** |
| Oligohydramnios | -0.167 | 0.336 |
| Pathological Doppler flow | -0.588 | **<0.001** |
| • AEDF | -0.383 | **0.023** |
| • CPR<1 | -0.418 | **0.012** |

TTR: Fetal thymic-thoracic ratio, AEDF: Absent umbilical arterial end-diastolic flow, CPR: Cerebroplacental ratio

[a] Correlation analysis was performed with the Spearman test

A negative statistically significant, moderate correlation was determined between fetal TTR and the EFW <3rd percentile, pathological Doppler flow (AEDF and CPR<1) (r= -0.703, r= -0.588, r= -0.383, r= -0.418 and p<0.001, p<0.001, p=0.023, p=0.012, respectively). No other significant correlation was determined for oligohydramnios (r= -0.167 and p=0.336).

## DISCUSSION

The results of this study demonstrated that fetal TTR is lower in FGR-complicated pregnancies compared to healthy control subjects. A moderate negative correlation was determined between fetal TTR and the adverse perinatal outcomes of EFW <3rd percentile and pathological Doppler flow (AEDF and CPR<1). Numerous genetic, immune, neuroendocrine, and nutritional factors which can influence fetal thymus function and size have been previously reported. Some environmental factors, such as stress, malnutrition, toxic exposure, and infectious processes, have also been shown to cause a decrease in the size of the fetal thymus due to cortical and medullary lymphocyte depletion, particularly during the perinatal period (17). Furthermore, it has been reported that uteroplacental insufficiency and chronic malnutrition due to vascular adaptation defect cause some neuroendocrine adaptations and a decrease in leptin levels in the fetus, which may trigger fetal thymus involution (18, 19). It has also been suggested that abnormal trophoblast differentiation may result in a decrease in 11 hydroxysteroid dehydrogenase type 2 enzyme activity and thymic involution by exposing the fetus to more maternally active cortisol (20). Thymus involution is observed after puberty as a result of physiological apoptosis of cortical lymphocytes. However, the earlier occurrence of this condition due to the above-mentioned factors such as inadequate nutrition, stress, and immunotoxins is known as thymus atrophy, and it has been linked to various cancers, autoimmune diseases, and immune deficiency states (21).

Previous studies have evaluated the size of the fetal thymus in different adverse pregnancy conditions. In a study investigating the prognostic value of fetal thymus size in 150 healthy and 143 pregnant women complicated with IUGR at 24-40 weeks of gestation, Ekin et al. stated that the fetal thymus transverse diameter was smaller (<5th percentile) in pregnant women complicated with IUGR. In addition, even smaller thymus dimensions were reported in the IUGR group with abnormal Doppler flow (n=62) compared to the IUGR group with normal Doppler flow (n=81). Small thymus size has also been linked to early delivery, respiratory distress syndrome, early neonatal sepsis, and long (>7 day) NICU stays in pregnant women with IUGR. Therefore, it was concluded that pregnancies complicated by IUGR may be associated with fetal thymic involution and that small fetal thymus may be a sign predicting adverse perinatal outcomes (11). Olearo et al. calculated a lower fetal thymic volume (TV)/fetal abdominal circumference (AC) ratio in growth restricted fetuses (n=27) compared to a healthy control group (n=36) using three-dimensional (3D) USG

(0.096±0.041 ve 0.208±0.070 cm3/cm, respectively). In the IUGR group with abnormal Doppler findings, the TV/AC ratio was lower than in the IUGR group with normal Doppler findings. It was stated that a specific trigger, such as early subclinical infection, could be linked to both defective trophoblast invasion and thymus invasion, which could explain the relationship between pre-eclampsia/IUGR and thymocyte depletion (18). In the current study, fetal thymus size was measured using fetal TTR, a newer, more standardized sonographic marker which is unaffected by BMI or fetal gender. TTR has been reported to be constant around 0.44 in normal healthy fetuses regardless of gestational week, and <0.3 (mean 0.25) in fetuses complicated by congenital heart disease and microdeletion 22q11 deletion syndrome (16). In the healthy control group of the current study, the TTR was within the normal range and consistent with the literature (0.40±0.02 [0.36-0.45]). When compared to the healthy control group, the decreased fetal TTR seems to support the relationship between FGR and fetal thymic involution in pregnant women complicated with FGR. Furthermore, the negative moderate correlation of fetal TTR with EFW <3rd percentile and pathological (abnormal) Doppler flow, which are adverse perinatal outcomes, strengthens the conclusion that a small fetal thymus may be an indicator predicting adverse perinatal outcomes, which is consistent with the literature.In a study comparing the fetal thymus size using fetal TTR in pregnancies complicated with diabetes, Ghalandarpoor-Attar et al. reported that the diabetic group (including subgroups such as overt diabetes, insulin/non-insulin dependent gestational diabetes, total n=80) had lower TTR values than the healthy control group (n=80) (0.321±0.219 ve 0.438±0.023, respectively) (10). Impaired glucose metabolism has been linked to placental dysfunction as a consequence of subacute metabolic/hypoxic stress, thymus cortical lymphocyte atrophy and thinning (histopathological starry sky appearance) as a result of hypothalamo-pituitary-adrenal axis activation. Therefore, it has been concluded that TTR may be predictive for diabetes-related adverse pregnancy effects (10, 22). Similarly, Dörnemann et al. reported reduced TTR and thymus-head ratio (THR) in diabetic pregnant women (n=161, including all subgroups) compared to healthy control subjects (n=161). The cut-off point for maternal diabetes predictivity was calculated to be 0.33, with sensitivity of 87.6% and specificity of 76.2% (23). Similarly in the current study, pregnant women complicated with FGR, as an adverse pregnancy condition, had lower TTR values. However, because of the relatively small sample size, cut-off points could not be calculated in this study. Other studies of pre-eclampsia, which is another adverse pregnancy condition common with diabetes, and FGR have also revealed small thymus measurements (24, 25).

There are also studies in literature which have investigated fetal immunological effects and fetal thymus size in maternal infective processes. Yinon et al. stated that there was a decrease in fetal thymus dimensions especially in pregnancies complicated with chorioamnionitis due to preterm pre-labor rupture of membranes (PPROM), specificity for ≤5th percentile thymus perimeter was reported as 66.7%, with a positive predictive value 69% (26). Fetal inflammatory response syndrome (FIRS) is characterized by fetal immune system activation and multiorgan involvement, with an increase in pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α in amniotic fluid or umbilical cord blood samples.This has been reported at the rate of approximately 50% in PPROM. Postnatal histopathological diagnosis has indicated chronic umbilical cord inflammation (funisitis) and vasculitis. It has been indicated that in the presence of FIRS, involution may occur as a result of previously highlighted mechanisms such as an increase in endogenous corticosteroids due to systemic infection/inflammation in the thymus gland, which is critical for the fetal immune system, activation of the hypothalamus-pituitary-adrenal axis, proinflammatory microenvironment shift, lymphocyte migration, and induction of thymocyte apoptosis. As a result, studies have indicated that a small thymus may be a sonographic marker for FIRS (9, 27). Vitamin D deficiency during pregnancy has been associated with a systemic inflammatory response in the fetus, which has been related to a small fetal thymus (28). Recently, it was discovered that the median TTR in pregnant women recovering from coronavirus disease 2019 (COVID-19) (mild/moderate) was lower than in healthy control subjects (0.33 ve 0.39, respectively). In addition, a moderate correlation was reported between TTR and maternal monocyte counts, monocyte to lymphocyte ratio (MLR), and red cell distribution width (RDW) (12). A lower fetal TTR was reported in pregnancies complicated with FGR and small for gestational age (SGA) in a recent study similarly. Furthermore, it was emphasized that, SGA pregnancies were accompanied by smaller fetal thymus size and higher adverse neonatal outcomes (29).The major strong aspects of this study were its novelty and prospective design. The study limitations could be said to be that the number of FGR cases complicated with <3rd percentile and pathological Doppler positivity was relatively low, so there was no cut-off point, ≤5th percentile thy-

mus perimeter, 3D fetal TV, and that THR measurements were not performed, and neonatal results were not available.

## CONCLUSION

A lower fetal TTR supports the relationship between FGR and fetal thymic involution. Moreover, fetal TTR might be a sonographic indicator for predicting adverse perinatal outcomes.

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