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Assessment of Fetal Thymus Size in Small for Gestational Age and Growth Restricted Fetuses

Gestasyonel yaşa göre küçük (SGA) ve gelişme geriliği olan (FGR) fetüslerde timus boyutlarının değerlendirilmesi

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ÖZ

Amaç: Bu çalışmanın amacı, sağlıklı, gestasyonel yaşa göre küçük (SGA) ve fetal gelişme geriliği (FGR) olan gebeliklerde ultrasonografi (USG) ile fetal timus boyutunu değerlendirmek ve sağlıklı fetüsler ile gelişme geriliği olan fetüsler arasında fark olup olmadığını araştırmaktı.

Gereçler ve Yöntem: Vaka-kontrol çalışması olarak tasarlanan çalışmamızda, fetal timusun timik-torasik oranı (TTR), transvers çapı ve çevresi, 20 ila 37. gebelik haftaları arasındaki SGA ve FGR gebeliklerinde prospektif olarak ölçüldü ve sağlıklı kontrollerle karşılaştırıldı. Gestasyonel yaşa göre fetal karın çevresi (AC) veya tahmini fetal ağırlık (EFW) <10. persentil altında olanlar SGA ve <3. persentil altında olanlar FGR olarak tanımlandı. FGR gebelikleri, normal veya anormal Doppler değerlendirmesine göre ayrıca 2 gruba ayrıldı.

Bulgular: Çalışmamıza 128 FGR, 34 SGA ve 162 sağlıklı gebelik dahil edildi. Fetal timusun tüm ölçümleri FGR grubunda anlamlı olarak daha düşüktü ($p<0.05$). Gelişme gerilikli fetüsler arasında, anormal Doppler akışı olanlarda timus boyutu en küçüktü ($p<0.05$). Normal doppler ve SGA grubundakilerin TTR değerleri de kontrol grubuna göre anlamlı derecede düşüktü ($p<0.05$).

Sonuç: FGR, büyüme kısıtlamasının şiddeti ile orantılı olarak küçük bir fetal timus ile ilişkilidir. FGR fetüsleri arasında, anormal fetal Doppler değerleri olanlar daha küçük bir timüs ile ilişkiliydi.

Anahtar Kelimeler: Fetal gelişme geriliği, Fetal timus boyutu, Timik-torasik oran (TTR), obstetrik ultrasonografi

ABSTRACT

Aim: The purpose of this study was to analyze the fetal thymus size by sonography in healthy, small for gestational age (SGA), and fetal growth restriction (FGR) pregnancies and investigate if there is a difference between healthy fetuses and those with growth restriction.

Materials and Method: In this case-control study, the thymic-thoracic ratio (TTR), transverse diameter, and perimeter of the fetal thymus were prospectively measured in SGA and FGR pregnancies between the gestational ages of 20 and 37 weeks and compared with healthy controls. Fetal abdominal circumference (AC) or estimated fetal weight (EFW) <10th percentile for gestational age was defined as SGA, and <3rd percentile was defined as FGR. FGR pregnancies were further divided based on normal or abnormal Doppler assessment.

Results: 128 FGR, 34 SGA, and 162 healthy pregnancies were enrolled in the study. All measurements of the fetal thymus were significantly lower in the FGR group ($p<0.05$). Among growth-restricted fetuses, thymus size was smallest in those with abnormal Doppler flow ($p<0.05$). The TTR values of those in the normal doppler and SGA groups were significantly lower than those in the control group ($p<0.05$).

Conclusion: FGR is associated with a small fetal thymus, which appears to be correlated with the severity of the growth restriction. Among FGR fetuses, a smaller thymus was related to abnormal fetal Doppler values.

Keywords: Fetal growth restriction; Fetal thymus size; Thymic-thoracic ratio (TTR); Obstetric ultrasound

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INTRODUCTION

Evaluation of fetal growth is the primary focus of prenatal care. Inadequate fetal growth occurs in up to 10% of pregnancies and is related to an increased risk of perinatal mortality and morbidity (1). Fetuses with an estimated fetal weight (EFW) below the 10th percentile for gestational age are at increased risk for many neonatal problems, particularly those linked with prematurity; they also account for 30% of stillbirths (2,3). Although the question of the distinction between SGA and FGR remains debatable, it is crucial since the management will alter. Those with a birth weight below the 3rd percentile were found to have a higher risk of perinatal mortality than those with a birth weight below the 10th percentile (4-6); hence, the current and most often used threshold percentile definitions are EFW or AC below <3rd percentile for FGR and <10th percentile for SGA (7,8). FGR is the failure of the fetus to achieve its biologically predetermined growth potential. The underlying condition is reduced uteroplacental blood flow due to insufficient trophoblastic invasion of the spiral arteries. While most of the SGA fetuses are constitutional (small but normal fetuses, structurally small), the remaining factors are related to placental deficiency, such as maternal infections (toxoplasmosis, rubella, and cytomegalovirus), chronic maternal diseases (hypertension, kidney disease, and collagen vascular diseases), and nutritional factors such as malnutrition and insufficient weight gain (8-10). Personalized growth charts, Doppler velocimetric evaluation of placental and fetal circulations, biophysical profile (BPP) scoring, and cardiotocographic (CTG) assessment of the fetal heart rate are used to determine fetuses at risk for cerebral hypoxia and acidemia and make delivery decisions (1,7,8). In particular, Doppler sonography is considered as the principal method for FGR monitoring and management. However, key determinants are required to distinguish benign SGA from FGR, which carries an increased risk of perinatal mortality and morbidity.

The thymus is a lymphoepithelial organ that plays a critical role in the activation of T cells and cellular immunity. Small fetal thymus size has recently been suggested as a potentially sensitive element associated with various pregnancy-related issues. The hypothalamic-pituitary-adrenal axis activation triggered by stress is considered to produce thymic involution during pregnancy (11). Fetal thymic involution was found to be significantly correlated with the fetal inflammatory response syndrome in patients with preterm labor (11). Jeppesen et al. showed that preterm neonates (24–32 weeks of gestational age) have smaller thymus size compared to healthy term infants, and there was a strong correlation between small thymus size and perinatal infections (12). Also, the size of the fetal thymus was reported to be reduced in pregnancies complicated by chorioamnionitis following preterm premature membrane rupture (PPROM) (13,14). In a study in which the presence of a small thymus was identified by transverse thymus diameter measurement, a small thymus size was found to have a significant predictive value for the development of chorioamnionitis (15). In addition to a high rate of prediction value for chorioamnionitis, the appearance of a smaller fetal thymus was shown to be associated with severe chorioamnionitis, higher infection laboratory markers, and severe prematurity (16). It was revealed that preeclamptic women have a relatively smaller fetal thymus than those of healthy control women (17). Postnatal examinations revealed that newborns with histologically proven chorioamnionitis, as well as those with growth restriction and low birth weight had lymphocyte depletion in the thymic cortex and thymic involution (18,19). A study that analyzed fetal thymus size by measuring thymus circumference (perimeter) reported that FGR was linked to a significant reduction in fetal thymus size (20). The aforementioned studies were conducted in a single plane and used a single measurement method to examine the fetal thymus. However, the optimal prenatal evaluation of the fetal thymus presents difficulties due to the asymmetric shape of the organ. Therefore, additional research may be helpful in which the patients are subdivided based on the degree of growth restriction and the thymus size is measured using alternative methods.

The aim of this study was to perform a detailed fetal thymus size assessment using sonography in healthy, SGA, and growth-restricted fetuses and find out whether there is a difference between healthy and growth-restricted fetuses.

MATERIALS AND METHODS

Participants Characteristics and the procedure

A prospective case-control study, including 162 healthy singleton pregnancies, 34 pregnancies with SGA, and 128 pregnancies with FGR was carried out. The pregnancies with FGR were further divided into two groups: (1) FGR with normal Doppler flow (n = 111) and (2) FGR with abnormal Doppler flow (n = 17).

The study involved singleton pregnancies between 20 and 37 gestational weeks that were admitted to the [blinded], between July and November 2022. The gestational age of the patients

was established by the last menstrual period and verified by the first trimester crown-rump length (CRL). Those with multiple pregnancies, ruptured membranes, known maternal or fetal infections, or fetal structural or chromosomal malformations were excluded. Patients who were in labor and who had cardiac, renal, thromboembolic, or epileptic diseases were also excluded.

Maternal age, gravidity, parity, pre-pregnancy body mass index (BMI, determined by dividing weight in kilograms by the square of height in meters), gestational age at screening, fetal gender, route of delivery, birth week, birth weight, APGAR-scores, whether the occurrence of fetal distress and admission to neonatal intensive care unit (NICU) were also noted.

The diagnosis of SGA was made in the presence of an estimated fetal weight (EFW) or abdominal circumference (AC) below the 10th percentile for gestational age. FGR was diagnosed in the presence of an EFW or AC below the 3rd percentile for gestational age (7,21). The formula established by Hadlock et al. was used to calculate EFW (22). In pregnancies complicated with FGR; umbilical artery (UA) Doppler flow velocity, middle cerebral artery (MCA) flow velocity, and waveforms of the ductus venosus (DV) were evaluated. Abnormal Doppler flow values were defined as following: (1) UA pulsatility index above the 95th percentile, decreased end-diastolic velocity or reverse flow (2) pulsatility index for the MCA below the 5th percentile for gestational age (brain protective effect), (3) pulsality indices for the DV above the 95th percentile for gestational age and an absent or reversed A-wave of the DV (1,23).

For each patient, after a detailed examination with obstetric ultrasonography, fetal biometric parameters and amniotic fluid volume were measured, umbilical artery, middle cerebral artery, and ductus venosus doppler flow velocities were evaluated, respectively, and then fetal thymus dimensions were measured during the fetal resting period. The thymus was measured in three different ways in each patient: the transverse diameter of the thymus, the perimeter of the thymus, and the TTR (thymic-thoracic-ratio). First, the thymus was visualized as a homogeneous structure in the anterior mediastinum in a three-vessel tracheal view. Then, the transverse diameter of the fetal thymus was measured by placing ultrasound calipers perpendicular to an imaginary line connecting the fetal sternum and spine (Figure 1). Afterwards, the thymus circumference was measured (Figure 2). Finally, anteroposterior thymus diameter (from the posterior edge of the fetal sternum to the anterior wall of the aortic arch) and intrathoracic mediastinal diameter (from the posterior edge of the sternum to the anterior edge of the thoracic vertebrae) were measured. The TTR (thymic-thoracic ratio) was calculated by dividing the anterior-posterior diameter of the thymus by the anterior-posterior diameter of the mediastinum (Figure 3). In order to obtain accurate results, each measurement was made three times, and the mean of the three measurements was recorded. All ultrasound (USG) evaluations were performed transabdominally, using the GE Voluson E8 Ultrasound device and C1-5-RS convex probe (1.75–4.95 MHz).

Statistical Analyses

The statistical analysis was conducted using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, New York, USA). The mean and standard deviation for the continuous variables were demonstrated. The measurement values of two independent groups were compared using the “Mann-Whitney U” test (Z-table value), the Independent Sample-t test, and the “Kruskal-Wallis H” test, while the measurement values of three or more independent groups were compared using the “Kruskal-Wallis H” test. Statistical significance was defined as p-value 0.05. When comparing variables that indicated significant differences for three or more groups, expressions like [1-2,3] were selected. For example, [1-2,3] indicates that the difference between 1 and 2 and 1 and 3 is significant. For pairwise comparisons of variables showing a significant difference among three or more groups, the Bonferroni correction was used.

Compliance with ethical standards

The ethical board approval (E2-22-2321) from [blinded] Ethical Committee was obtained before initiating the study. The study protocol was performed according to the Declaration of Helsinki principles, and the written informed consent containing the details of the study was obtained from all participants.

RESULTS

The demographic data showed no statistically significant differences between the two groups (Table 1). As expected, the abnormal Doppler flow rate in the FGR group was higher than that of the SGA and control groups ($p<0.05$). The gestational week of delivery was significantly lower in the FGR and SGA groups than in the control group ($p<0.05$). The birth weight of the FGR group was lower than both the SGA and control groups, while the birth weight of the SGA group was significantly lower than that of the control group ($p<0.05$). Apgar 1st and 5th minute scores in the FGR group were significantly lower than those in the SGA and control groups ($p<0.05$). Fetal distress and NICU admission rates were higher in the FGR group compared to

both the SGA and control groups, while the fetal distress rate in the SGA group was significantly higher than the control group (p<0.05). Additionally, no chromosomal or structural abnormalities were discovered following birth.

Table 1. Patient characteristics

Variables	FGR group (n=128) (1)	SGA group (n=34) (2)	Control group (n=162) (3)	p value*
Maternal age (years)	27,60±5,97	28,81±5,84	27,33±5,72	0,188
Gravidity	2,20±1,63	2,36±1,51	2,22±1,60	0,339
Parity	0,87±1,28	0,85±1,06	0,82±1,09	0,791
BMI (kg/m2)	27,0 [20,0-38,0]	27,0 [22,0-31,0]	27,0 [20,0-40,0]	0,517
Gestational age at screening (weeks)	34,31±3,06	33,66±3,42	33,50±4,63	0,078
Male fetal gender	44 (%34,4)	7 (%20,6)	39 (24,1)	**0,000**
Cesarean section [% (n)]	85 (%66,4)	11 (%32,4)	38 (%23,5)	**0,000**
Abnormal doppler flow	18 (%14,1)	1 (%2,9)	-	**0,000**
Gestational age at delivery (weeks)	36,02±2,52	36,53±2,34	37,86±2,02	**0,000 [1,2-3]****
Birth weight (g)	2125,11±523,39	2459,09±485,23	3248,37±582,06	**0,000 [1-2,3] [2-3]****
APGAR 1st min	7,0 [0,0-8,0]	8,0 [1,0-8,0]	8,0 [5,0-8,0]	**0,000 [1-2,3]****
APGAR 5th min	8,0 [0,0-9,0]	9,0 [1,0-10,0]	9,0 [7,0-10,0]	**0,000 [1-2,3]****
Fetal distress	44 (%34,4)	3 (%8,8)	4 (%2,5)	**0,000**
NICU admission	43 (%33,6)	5 (%14,7)	9 (%5,6)	**0,000**

Data presented as mean ± standard deviation, median (minimum, maximum) or relative frequencies (%)

FGR: Fetal growth restriction, SGA: Small for gestational age, BMI: Body mass index; NICU: Neonatal intensive care unit

**Kruskal-Wallis H test, Pearson-χ2 cross-tab*

*** Pairwise comparisons with Bonferroni correction*

The transverse diameter of the fetal thymus was significantly lower in the FGR group than those in the control group (p<0.05). Additionally, compared with the control group, those in the SGA group and with normal doppler values had significantly lower fetal thymus perimeter values (p<0.05). The thymus perimeter values of the patients with abnormal doppler were significantly lower than those with normal doppler, as well as those in the SGA and control groups (p<0.05). While TTR values of patients with abnormal doppler values were significantly lower than those of all other groups, TTR values of patients with normal doppler and SGA were significantly lower than those of the control group (p<0.05). In addition, TTR values of those with normal doppler were found to be significantly lower than those of the SGA group (p<0.05), as seen in Table 2.

Table 2. Comparison of the fetal thymus size between study and control groups

Variables	FGR (n=128)		SGA (n=34)[3]	Control group (n=162)[4]	p value*
	Normal Doppler Flow (n=111)[1]	Abnormal Doppler Flow (n=17)[2]			
Transvers diameter of fetal thymus (cm)	24,49±5,91	23,28±5,41	26,50±5,41	35,99±15,47	**0,000 [1,2-4]****
Perimeter of fetal thymus (cm)	70,29±13,81	58,13±10,19	76,42±15,49	104,93±32,28	**0,000 [1,3-4]** [2-1,3,4]****
TTR	0,28±0,02	0,26±0,02	0,31±0,02	0,40±0,03	**0,000 [2-1,3,4]** [1,3-4]** [1-3]****

Data presented as mean ± standard deviation

FGR: Fetal growth restriction, SGA: Small for gestational age, TTR; thymic-thoracic ratio

** Kruskal-Wallis H test*

*** Pairwise comparisons with Bonferroni correction*

DISCUSSION

We concluded that the size of the thymus is considerably smaller both in growth-restricted and SGA fetuses than in healthy controls. Also, there was a significant difference between growth-restricted and SGA fetuses, and those with FGR had a smaller thymus compared to SGA. The findings of this study are valuable since the size of the thymus, which has an asymmetrical morphology, was evaluated using different methodologies. Three measurements were used to figure out the size of the thymus: the transverse diameter of the thymus, the perimeter of the thymus, and TTR. All thymus measurements were smaller in growth-restricted fetuses than in healthy controls. Additionally, growth-restricted fetuses with abnormal Doppler values had the smallest thymus sizes.

Small fetal thymus has been associated with various maternal or fetal complications, including preeclampsia (17), preterm birth (12), chorioamnionitis (14), fetal inflammatory response syndrome, and early neonatal sepsis (24). In line with our findings, Cromi et al. and Olearo et al. have detected a significant reduction in fetal thymus size in growth-restricted and SGA fetuses (20,25). The function and growth of the fetal thymus are influenced by a variety of genetic, metabolic, neurological, endocrine, and immunological parameters (26). In addition, stress, infectious diseases, and exposure to chemicals during the prenatal period are all blamed for a decreased thymus size (27).

The process of small thymic development in FGR has not been clearly demonstrated yet. However, placental insufficiency is widely accepted as the main pathology (28). Fetal malnutrition caused by impaired placentation and vasculogenesis triggers a series of neuroendocrine adjustments, and a reduction in leptin levels leads to thymic involution. Another role of leptin is to inhibit stress-induced glucocorticoid levels via the hypothalamic-pituitary-adrenal axis.

Consequently, thymic apoptosis, a physiological condition, is regulated by leptin and glucocorticoids, which are on opposite ends of the scale. In negative nutritional circumstances, such as FGR, decreased levels of leptin followed by elevated cortisol concentrations enhance thymocyte apoptosis. Eventually, thymic involution may occur as a component of the neuroendocrine adaptation of the developing fetus to starvation (29).

While the decrease in thymus size in FGR fetuses is not surprising, the decrease in thymus size observed in SGA fetuses compared to AGA (appropriate for gestational age) fetuses appears noteworthy. It appears reasonable that FGR pregnancies are associated with fetal thymic involution due to neuroendocrine modifications produced as a result of placental insufficiency

(29). However, the fact that thymic involution occurred in SGA, which is not believed to be associated with intrauterine stress, may indicate that SGA is not as harmless as previously thought (30). We found that, compared to gestational-age-matched healthy fetuses, not only FGR but also SGA are linked to reduced fetal thymic size. In accordance with our results, thymic volume was shown to be decreased in SGA fetuses compared to AGA fetuses in a study based on thymic volume analysis (25).

The visual manifestation of lymphocyte deficiency from both the cortex and the medulla is a smaller thymus, which is associated with compromised immunity in newborns (27). It has been claimed that a small fetal thymus is related to adverse neonatal outcomes, including RDS, bronchopulmonary dysplasia, and neonatal sepsis (13). On the other hand, it is generally acknowledged that FGR fetuses have an elevated risk of morbidity and mortality (1-6). The relationship between small fetal thymus size and FGR is a relatively new topic that has recently received attention. In their research utilizing transverse thymus measurement, Ekin et al. found that a small fetal thymus was substantially related to adverse perinatal outcomes regardless of gestational age or the presence of abnormal Doppler flow. They reported that in FGR fetuses, reduced fetal thymus size was independently linked with a shorter admission-to-delivery interval, an increased risk of early neonatal sepsis, RDS, and a NICU stay of more than 7 days (31). In the presented study, we observed that the gestational week of delivery, birth weight, and Apgar 1st and 5th minute scores were significantly lower in FGR pregnancies as compared to controls. Also, fetal distress and NICU admission rates were highest in the FGR group, regardless of the existence of abnormal Doppler flow. As a result, we can argue that thymus size monitoring in fetuses with growth restriction can be employed for fetal surveillance as well as delivery decisions. We should also highlight that, when compared to healthy pregnancies, SGA pregnancies are associated with smaller fetal thymus dimensions and higher unfavorable neonatal outcomes. Therefore, SGA fetuses deserve careful prenatal follow-up in terms of possible adverse neonatal outcomes.

The strengths of our study were the comparatively large sample size and the prospective design. To eliminate inter-observer error, all measurements in the study were collected by the same researcher. Since our study included three separate measurements of the thymus, the results of the presented study reinforce the previous reports based on a single thymus measurement and suggesting that FGR is associated with a small fetal thymus and that a small fetal thymus may be related to adverse neonatal outcomes. However, one of the limitations of the study was the lack of information regarding the maternal nutritional status of the evaluated pregnancies, which would have led us to assess the numerous causes of FGR. Also, comprehensive studies including detailed neonatal evaluation such as pH in cord blood may be useful in the future.

CONCLUSION

This study indicated that small fetal thymus size is typical of FGR and there is a correlation between the severity of FGR and fetal thymic growth restriction. Thymus dimensions were decreased in all growth-restricted fetuses, with or without abnormal Doppler, including SGA. However, the coexistence of FGR and abnormal Doppler flow was independently associated with a smaller thymus size than FGR alone. Additionally, FGR is associated with adverse perinatal outcomes, and SGA should not be underestimated either. Fetal thymus measurement, along with Doppler assessment, may be useful in the management of FGR pregnancies.

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