Prenatal Sonographic Three-dimensional Virtual Organ Computer-assisted Analysis Thymic Volume Calculation May Predict Intrauterine Growth Restriction

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Abstract

Background: Intrauterine growth restriction (IUGR) refers to fetuses that are small for their gestational age. There is no effective test to predict this disease. The aim of our study is whether fetal three-dimensional (3D) ultrasonography (USG)-assisted thymus volume (TV) measurement predicts IUGR cases. **Methods:** Fetal 3D USG thymus measurement between 15 and 24 weeks of gestation was performed in a total of 100 women of reproductive age. Fetal TV was measured using the virtual organ computer-assisted analysis system program. All cases were followed up in terms of pregnancy complications until delivery. **Results:** IUGR was developed in six cases in total. In cases with IUGR, mean fetal TV was found to be statistically significantly lower than in healthy cases without it. When the fetal TV was taken as 0.1645, the sensitivity was calculated as 89.5% and the specificity as 50% for predicting IUGR. The use of low fetal volume parameters is a significant and good indicator for predicting IUGR according to the binary logistic regression analysis result. **Conclusion:** According to the results of this study, 3D fetal TV measurement may be used in routine second-trimester sonographic anomaly screening to predict the development of fetal IUGR. In this way, fetal mortality and morbidity caused by IUGR may be reduced.

Keywords: Fetal thymus volume, intrauterine growth restriction, screening, second trimester, virtual organ computer-assisted analysis

Introduction

Intrauterine growth restriction (IUGR) is defined as the failure of the fetus to reach the expected size in the womb. According to the definition of The American College of Obstetricians and Gynecologists, if the expected fetal weight is below the 10th percentile, the diagnosis is confirmed.[1]

There are many clinical conditions that cause IUGR. According to the pathogenetically accepted hypothesis, an abnormal placental implantation process may be responsible for this clinical condition. That is, in case of insufficient trophoblast invasion to the spiral arteries in the early stages of pregnancy, uteroplacental blood flow is disrupted, causing a small baby in the womb.[2]

The fetal thymus is an organ that plays a fundamental role in the development of the immune system of the fetus.[3] It is responsible for localized, bilobular, symmetrical development in the anterior mediastinum. Development starts in early pregnancy and is generally completed at 16–20 gestational weeks.[4]

Ultrasonography (USG) imaging of the fetal thymus was first described by Felker *et al*. in 1989.[5] It is located in the anterior part of the ductal and aortic arch, at the level where the three main vessels are visualized in the superior mediastinum in the sonographic axial section. It can be seen as a mass between the fetal lungs as an oval, hypoechogenic mass which can sometimes be seen to contain echogenic points.[6] Color Doppler imaging of internal mammary arteries can facilitate the identification of the thymus.[7]

There are few studies suggesting that fetal thymus measurement has a place in the prediction of infants with IUGR. Fetal

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thymus transverse diameter was measured in a study that included 143 IUGR and 150 healthy controls at 24–40 weeks of gestation. According to the results of this study, perinatal complications were found to be higher in cases with small fetal thymus volume (TV).[2] In another study, a relationship was shown between IUGR and thymus size associated with insufficient intrauterine nutrition.[8] However, the effect of sonographic three-dimensional (3D) volume calculation of the fetal thymus on the prediction of IUGR has not been well documented previously.

In this study, it was aimed to investigate whether there is a relationship between fetal TV and the development of IUGR in cases at 15–24 weeks of gestation.

Materials and Methods

This prospective cohort study included 100 women with a single pregnancy who presented at the current clinic in 1-year and had no risk factors for high-risk pregnancy in the second-trimester screening for anomalies. IRB approval was obtained from Karadeniz Technical University faculty of medicine ethic board (Date 27/02/2017, Number 2016/181).

The study group was aged 18–35 years, who presented at the polyclinic for routine antenatal follow-up at 15–24 weeks and had no complaints (n = 100). At the first prenatal visit, it was found that the cases did not contain any high-risk pregnancy factors, and thyroid, kidney, liver, and hematological test results were normal.

Endocrine disease, systemic disease, collagen tissue disease, hypertension, diabetes, hematological disease, history of neoplasia, cardiovascular disease, history of any drug use within 3 months of pregnancy, smoking, multiple pregnancy, abnormal biochemical or hormonal, hematological test results, conditions such as the presence of any anomaly or chromosomal anomaly in the fetus, and reluctance to participate in the study were accepted as exclusion criteria.

All women signed a consent form to participate in the study. Age, gravida, parity, body mass index, sonographic fetal biometry data, biparietal diameter (BPD), abdominal circumference (AC), femur length (FL), and estimated fetal weight (EFW) were recorded in all cases. Gestational age was confirmed by first-trimester sonography data.

3D fetal TV was measured using a Voluson E10 USG device, by a single researcher experienced in the use of obstetric ultrasound (US) with a transabdominal volumetric probe. The fetal chest transverse section was determined sonographically, and three main vessels were visualized. Then, the 3D US module was activated and the TV was calculated with the same probe as described in detail in our previous study [Figure 1].[9]

3D US images were created from the section when the thymus was not under any pressure due to extremity, rib, sternum, or inappropriate fetal/maternal position. The TV

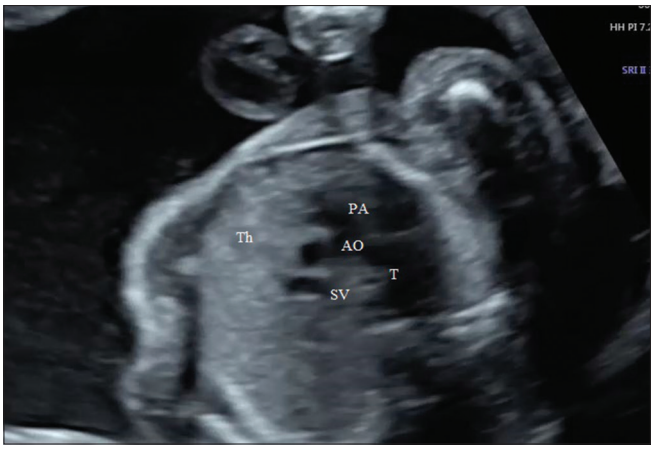

Figure 1: 2D USG imaging of the 18-week-old fetus shows fetal thymus and three-vessel trachea image. AO: Aorta, PA: Pulmonary artery, SV: Superior vena cava, Th: Thymus, T: Trachea, 2D: Two-dimensional, USG: ultrasonography

was reconstructed using the virtual organ computer-assisted analysis system (VOCAL, through the 2016 model Voluson GE E10 sonograph unit). Thymus boundaries were determined manually in each sonographic section. The 3D fetal TV data were assessed using spatiotemporal image correlation with a standard 10 s acquisition time and an acquisition sweep angle of 15°. Its volume was calculated using a VOCAL method with 15° of rotation (12 sequential planes). To complete 180°, 12 manual measurements were made by following rotational steps. Thymus boundaries were drawn manually in each plane. As a result, the computer created a reconstruction image and calculated the TV. Following the final reconstruction image, a two-lobed thymus structure was obtained and the volume value in cubic centimeter unit was calculated. Each volume measurement was made three times by a single experienced physician, and the volume value was confirmed [Figures 2 and 3].

All cases were followed up until the pregnancy was concluded with delivery and a record was made of the development of IUGR, gestational age at birth, type of birth, and infant birth weight. IUGR was accepted as EFW below the 10th percentile according to BPD, FL, and AC.

Statistical analysis

All data were analyzed using the SPSS version 13 (SPSS Inc., SPSS for Windows, Version 13.0. Chicago, USA) package program. Chi-square and MannWhitney U tests were used for statistical analysis. Receiver operating curve analysis was performed to determine which fetal TV value was most suitable for predicting fetal IUGR. All data are given as mean ± standard deviation or percent. Data on whether TV data could predict IUGR were calculated by binary logistic regression analysis. $P < 0.05$ was considered statistically significant.

Results

The data of 82 cases (6 IUGR and 76 healthy pregnancies) in total were evaluated because 5 out of 100 cases within the

scope of the study did not attend the routine follow-up program and 13 of them developed other pregnancy complications. The demographic and sonographic factors of cases who developed IUGR and those who did not develop any complications are shown in Table 1.

In cases with IUGR, mean fetal TV was found to be statistically significantly lower than in healthy cases without it [Figure 4]. When the fetal TV was taken as 0.1645 cm^3, the sensitivity was calculated as 89.5% and the specificity as 50% for predicting IUGR (area under the curve = 0.789, $P = 0.019$, 95% confidence interval 0.649–0.930). The use of low fetal volume parameters is a significant and good indicator for predicting IUGR according to the binary logistic regression analysis result ($P = 0.041$).

Table 1: The demographic and sonographic factors of cases who developed intrauterine growth restriction and control (normal singleton fetuses)

Demographic/sonographic factors	IUGR ($n=6$)	Control ($n=76$)	*P*
Age (years)	30.33±4.13	29.92±4.56	0.914
Gravida (*n*)	3.00±2.00	2.31±1.41	0.426
Parity (*n*)	1.17±0.75	1.01±0.96	0.568
BMI (kg/m^2)	28.02±3.78	28.29±4.63	0.880
Gestational week at measurement	19.23±2.69	20.00±1.99	0.482
EFW at measurement (g)	340±184	371±127	0.433
Gestational week at birth	37.17±2.40	38.56±1.64	0.130
Fetal TV (cm^3)	0.209±0.094	0.405±0.223	0.019
Cesarean section delivery (%)	66.7	60.5	0.565[a]
Fetal gender (female/male)	3/3	44/32	0.513[a]
Infant birth weight (g)	1968±228	3385±415	<0.001

[a]Fisher's exact Chi-square test were used in the statistical analyses and the Mann–Whitney *U*-test. Data are presented as mean±SD values or as number of cases and percentage. SD: Standard deviation, BMI: Body mass index, EFW: Estimated fetal weight, TV: Thymus volume, IUGR: Intrauterine growth restriction

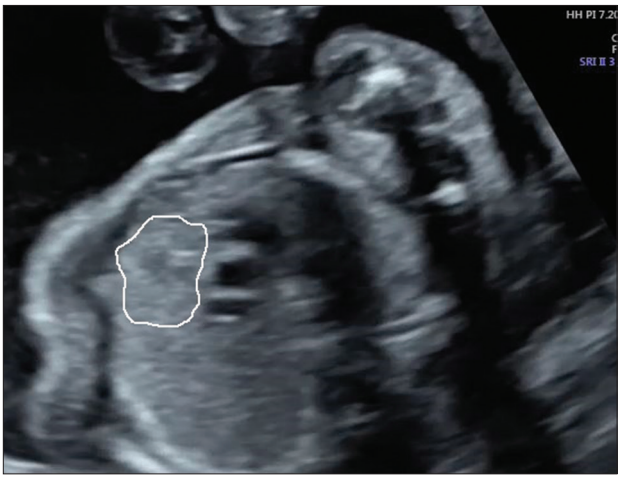

Figure 2: 2D ultrasonographic imaging in the axial plane of the 18-week-old fetus shows the fetal thymus borders. 2D: Two-dimensional, USG: ultrasonography

A moderate positive correlation was found in terms of the gestational week at measurement and fetal TV in all cases (Pearson correlation, $r = 0.471$, $P < 0.001$). However, a moderate statistically significant correlation was found in normal healthy single fetuses (Pearson correlation, $r = 0.466$, $P < 0.001$), whereas a statistically insignificant correlation was found in the IUGR group (Pearson correlation, $r = 0.712$, $P = 0.113$).

Discussion

This is one of the first studies evaluating fetal TV using 3D US (VOCAL) in respect of its use as a predictive marker of the development of IUGR later in the pregnancy. The fetal thymus has a bilobular, irregular structure, so due to this property, the 3D US VOCAL system was used in this study as it produced a more accurate reconstruction.[10,11]

It has been reported that change in thymus size (hypoplasia or hyperplasia) is associated with many diseases (infectious diseases, aneuploidies, endocrine disorders, and some genetic syndromes). The small thymus size is also associated with HIV infection, 22q11.2 deletion syndrome, and some rare genetic syndromes (Ellis–Van Creveld syndrome, chondrodysplasia punctata, etc.).[12-16]

The mechanism of thymus involution in IUGR is related to placental insufficiency originating from insufficient vascular adaptation in the uteroplacental interface. In IUGR cases with severe placental insufficiency, an effective initiating factor that limits the growth and development of the thymus is mentioned. Perhaps subclinical maternal-fetal infection during early pregnancy may affect the thymus development process and also disrupts trophoblast invasion. All these pathological processes may reveal the relationship between thymocyte loss and the development of preeclampsia and IUGR. Fetal thymus function and volume are linked to neural, nutritional, endocrine, and immune factors. As a result of early gestational and perinatal exposure to infectious diseases, malnutrition, or toxins, a small fetal thymus results in thymocyte consumption.[17]

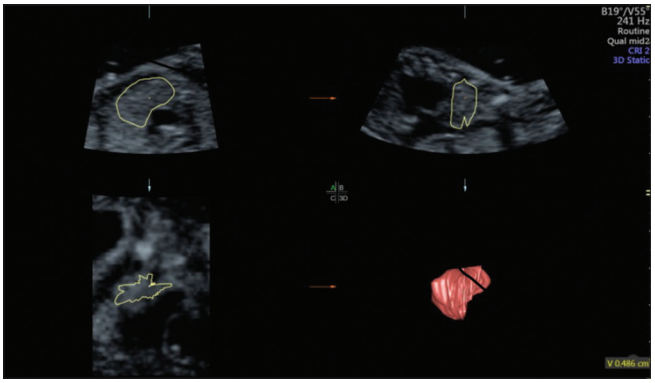

Figure 3: Fetal thymus reconstruction image with clearly visible two lobes resulting from the thymus volume calculated by VOCAL in the axial plane of an 18-week-old fetus is shown. VOCAL: Virtual organ computer-assisted analysis

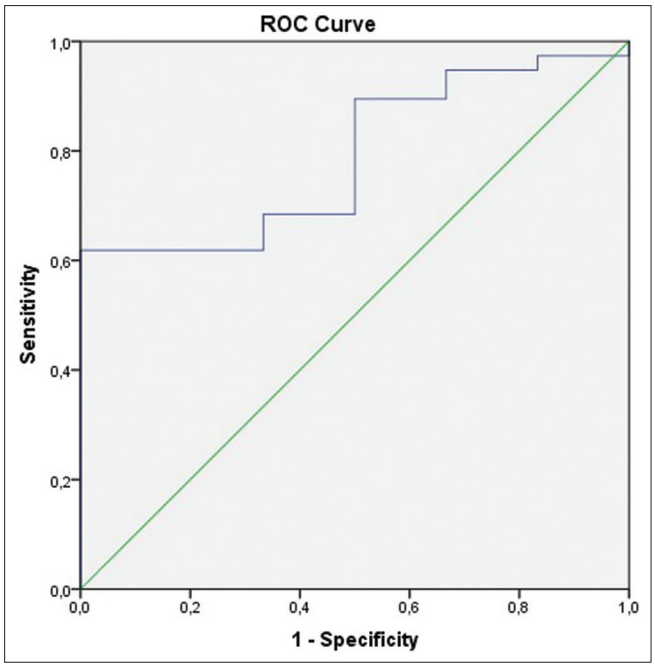

Figure 4: ROC analysis data showing the relationship between calculated fetal thymus volume and IUGR in pregnant women between 15 and 24 weeks are presented. ROC: Receiver operating curve, IUGR: Intrauterine growth restriction

In studies that investigated the relationship between IUGR and small fetal thymus, the TV in fetuses with IUGR was found to be smaller than that of the control group.[2,8,17] In one prospective, comparative, cross-sectional study, the fetal thymus measurements were determined sonographically in 39 pregnant patients with preeclampsia and 70 healthy pregnant patients, and the thymus measurements in preeclamptic and small for gestational age (SGA) fetuses were found to be smaller than those of the control group. In the same study, in five fetuses in the control group, the small thymus was determined in the first US examination, and preeclampsia developed after 1–11 weeks. Small fetal thymus was shown to be a characteristic of preeclampsia in that study.[18] Eviston *et al*. suggested that it could be an early finding of clinical disease in preeclampsia.[19] According to the results of two recent studies, preterm premature rupture of membrane (PPROM) cases with chorioamnionitis may be strongly associated with TV loss.[20,21]

In contrast to those studies, Brandt *et al*. prospectively screened 520 patients at intervals of 6 days in the 18th–23rd gestational weeks with multiple plane fetal thymus measurements and found no relationship between small fetal thymus and preterm labor, SGA, and pregnancy-related hypertension. It was concluded that fetal thymus screening in the second trimester cannot be used in the prediction of pregnancy complications.[22] On the other hand, in our two recent studies, it has been shown that 3D VOCAL fetal TV measurement is important in predicting the week of birth in twin pregnancies and the measurement of first trimester fetal TV in single pregnancies is important in predicting preeclampsia.[9,23]

According to literature data, two-dimensional (2D) USG evaluation was performed in most of the studies investigating the possible effects of the fetal thymus. As the shape of the thymus is irregular and bilobular, volumetric evaluation is thought to provide a more accurate result. Li *et al*. compared 2D and 3D US measurements of the fetal thymus and showed that the correlation of gestational age with TV was better with 3D than 2D evaluation.[24]

Thymic volume has been previously examined with 3D in uncomplicated pregnancies.[25,26] and in pregnancies complicated by IUGR.[17,27] However, the current study is the first to have shown that fetal thymus screening with the 3D US at 15–24 weeks in uncomplicated pregnancies could be used in the prediction of future IUGR development.

Conclusion

The fact that IUGR pregnancies are associated with a negative perinatal outcome is known, regardless of having a small fetus. Accordingly, the fact that these pregnancies can be predicted with various parameters can prevent perinatal mortality and morbidity. Therefore, it can be concluded that fetal thymus measurement in cases with IUGR could improve antenatal fetal surveillance and neonatal management. However, the small number of cases is the most important limitation of our study; there is a need for further more extensive studies to support this hypothesis.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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