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Finding the best method for screening for gestational diabetes mellitus: fetal thymic-thoracic ratio or fetal thymus transverse diameter

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SUMMARY

OBJECTIVE: The aim of this study was to compare the efficiency of fetal thymic-thoracic ratio and fetal thymus transverse diameter measurements in gestational diabetes mellitus.

METHODS: Fetal thymic-thoracic ratio and fetal thymus transverse diameter were assessed in 360 pregnant women. Patients were examined in two groups: 180 gestational diabetes mellitus (study group) and 180 healthy pregnant women (control group).

RESULTS: There were no statistically significant differences between the cases with gestational diabetes mellitus and the control group in terms of fetal thymus transverse diameter; however, the fetal thymic-thoracic ratio was found to be significantly lower in cases with gestational diabetes mellitus compared to that in the control group ($p<0.001$).

CONCLUSION: The fetal thymic-thoracic ratio is superior to the fetal thymus transverse diameter in evaluating the fetal thymus size.

KEYWORDS: Fetus. Diabetes, gestational. Thymus gland. Ultrasonography, prenatal.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as the glucose tolerance that occurs or is determined for the first time during pregnancy in an individual with no preexisting diabetes[1]. It has been estimated to affect 5–20% of all pregnancies[2]. Although the pathophysiology of GDM has not yet been fully elucidated, it has been suggested that it causes low-grade systemic inflammation that exacerbates maternal immune responses[3]. As it leads to serious maternal and fetal complications if not monitored, it is of great importance that it should be screened during pregnancy and, if detected, should be appropriately followed up and treated[2].

The thymus is a lymphoepithelial organ originating from the third brachial cleft at the 9th gestational week and descending to the anterior/superior mediastinum at the 12th gestational week[4]. The fetal thymus is detected ultrasonographically at three-vessel levels, in front of the pulmonary artery, aorta, and superior vena cava, behind the sternum, and between both lungs[5-7]. Various methods have been reported for the ultrasonographic measurement of fetal thymus size including transverse diameter, anterior-posterior diameter, circumference, volume, and thymic-thoracic ratio[8-11].

There are numerous studies evaluating the fetal thymus size. It has been reported that the fetal thymus size increases in proportion to the gestational week in healthy pregnant women while the fetal thymic-thoracic ratio remains constant[8]. However, it has been reported that this ratio decreased in some complicated pregnancy cases, including diabetic pregnancies[12-16].

To the best of our knowledge, there are studies investigating the fetal thymic-thoracic ratio in diabetic pregnant women[14-16]; however, there are no studies evaluating the fetal thymus transverse diameter in GDM. Being the first study on this subject, the aim was to compare fetal thymic-thoracic ratio and fetal thymus transverse diameter in the evaluation of fetal thymus size in GDM.

METHODS

This study was approved by the Sakarya University Ethics Committee (decision no.: 40019-376, approval date: June 30, 2021). It included pregnant women diagnosed with gestational diabetes (n=180), who were admitted to the Sakarya University Education and Research Hospital, Gynecology and Obstetrics Clinic Perinatology Department between November 1, 2018, and June 15, 2021, and delivered in the same hospital. GDM was defined as a single abnormal result from a 2-h 75-g oral glucose tolerance test or two abnormal results from a 3-h 100-g oral glucose tolerance test[17]. These pregnant women were classified into two groups: diet-controlled gestational diabetes (GDd, n=106) and insulin-dependent gestational diabetes

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(GDi, n=74). In the control group, completely healthy pregnant women (n=180) at a similar gestational week without any pregnancy complications were included in the study. The data of both groups were obtained from the medical records of the hospital. The fetal thymic-thoracic ratio data were measured in the third trimester in both groups. The values of fetal thymus transverse diameter and fetal thymic-thoracic ratio measured in the third trimester were obtained from medical records. Preeclamptic pregnant women, pregnant women diagnosed with pre-GDM, pregnant women with any known medical disease (chronic hypertension, chronic liver disease, chronic kidney disease, and rheumatological diseases), pregnant women with HIV or other accompanying chronic inflammatory diseases, amniotic fluid disorders (polyhydramnios and oligohydramnios), preterm labor, pregnant women diagnosed with premature rupture of membranes, pregnant women with suspected fetal macrosomia in ultrasonographic measurements, cases with fetal structural or chromosomal disorders, cases with a history of corticosteroid use during pregnancy, cases with evidence of placental insufficiency in Doppler parameters, and pregnant women with sonographic estimated fetal weight <10% were not included in the study.

All ultrasound examinations were performed by a single sonographer (Koray Gök) using a Voluson 730 and a Voluson E6 (GE Medical Systems, Milwaukee, WI, USA) ultrasound machine. Thus, the measurements were standardized and the bias was limited. All measurements were carried out in the absence of fetal movements. Fetal thymus transverse diameter measurements were performed as previously described by Zalel et al.[7] The thymus was identified in the three vessels as a homogeneous structure in the anterior mediastinum. The transverse diameter of the fetus was measured by placing the ultrasound calipers perpendicular to the junction between the sternum and the spine. Fetal thymic-thoracic ratio measurement was performed as previously described by Chaoui et al.[8] Thymus was detected in the three vessels and trachea (3VT) views as a hypoechogenic structure with echogenic dots filling the space between the vessels posteriorly and the anterior chest wall (sternum and ribs) anteriorly. The anteroposterior diameter of the thymus was determined in addition to the midline between the transverse aortic arch border posteriorly and the posterior chest wall anteriorly. Also, the mediastinal sagittal diameter was determined in addition to the line traced to measure the thymic diameter, as the distance between the anterior edge of the thoracic vertebral body at the level of the transverse arch posteriorly and the internal edge of the sternum anteriorly.

The statistical evaluations were carried out using the SPSS 24.0 software (SPSS Inc. and Lead Tech. Inc., Chicago, USA). The Kolmogorov-Smirnov test was used to examine the normality of the distribution of the data. Nonparametric data were reported as the median and interquartile range . Nonparametric data were compared using the Mann-Whitney U test. Multiple groups were compared using the Kruskal-Wallis test and the Bonferroni post-hoc correction. Receiver operating characteristic (ROC) analysis was used to evaluate the predictive performance of the fetal thymic-thoracic ratio for GDM. An alpha <0.05 for Bonferroni correction and a p-value <0.05 for other tests were considered to be statistically significant.

RESULTS

The characteristics of the GDM cases and the control group and the comparison of fetal thymus transverse diameter and fetal thymic-thoracic ratio in both groups are presented in Table 1. No statistically significant differences were found between the gestational diabetes cases and the control group in terms of

Table 1. Comparison of characteristics, fetal thymic-thoracic ratio, and fetal thymus transverse diameter between gestational diabetes mellitus cases and control group.

	Gestational diabetes group (n=180)	Control group (n=180)	p-value
Maternal age (years)	32 (20–44)	32 (20–43)	0.901
Gravidity	3 (1–8)	3 (2–7)	**0.000**
Parity	1 (0–5)	2 (0–4)	**0.000**
Body mass index (BMI) (kg/m^2)	26.8 (23.7–29.6)	26.4 (22.8–29.4)	0.081
Gestational age at the time of the study (weeks)	31.42 (29.7–33.84)	31.56 (29.56–33.42)	0.226
Gestational age at birth (weeks)	38.84 (36–40.14)	39 (37–39.56)	**0.043**
Birth weight (g)	3405 (2580–4400)	3387 (2640–3900)	0.068
Transverse diameter (mm)	32.8 (27.8–36.6)	33.1 (27.9–35.6)	0.070
Thymic-thoracic ratio	0.324 (0.292–0.408)	0.43 (0.392–0.462)	**0.000**

Data are expressed as median (minimum–maximum). p<0.05 indicates a significant difference (denoted in bold).

age and body mass index (BMI). There were no statistically significant differences between the cases with GDM and the control group in terms of fetal thymus transverse diameter; however, the fetal thymic-thoracic ratio was found to be significantly lower in cases with GDM compared to that in the control group (p<0.001).

The fetal thymic-thoracic ratio was evaluated using the Kruskal-Wallis test between the diet-controlled gestational diabetes and insulin-dependent gestational diabetes group and the control group, and statistically significant differences were determined between the groups (p<0.001) (Table 2). By evaluating the fetal thymic-thoracic ratios within the groups using the Mann-Whitney U test, a statistically significant difference was found among all three groups (p<0.001).

A cutoff value was determined for the fetal thymic-thoracic ratio using the ROC curve, and its success in predicting GDM was analyzed. By setting the fetal thymic-thoracic ratio cutoff value as 0.407 for the prediction of GDM, the sensitivity was found to be 92.8% and the specificity to be 86.1% (p<0.001) (Figure 1).

DISCUSSION

The following results were obtained in the present study:

1. The fetal thymic-thoracic ratio was found to be lower in the GDM than that in the control group.
2. Evaluating the patients with GDM among themselves, it was found that the fetal thymic-thoracic ratio was lower in the insulin-dependent gestational diabetes group.
3. Contrary to the fetal thymic-thoracic ratio, there were no differences between the groups in terms of fetal thymus transverse diameter measurements.

The first study on the fetal thymic-thoracic ratio in diabetic pregnant women was carried out by Dörnemann et al. The researchers included healthy pregnant women, gestational diabetic pregnant women, and pregestational diabetic pregnant women at gestational weeks similar to those adopted in the present study. The fetal thymic-thoracic ratio was found to be lower in diabetic pregnant women compared to that in healthy pregnant women; however, no statistically significant differences were found when examining the diabetic pregnant women among themselves. Accepting the fetal thymic-thoracic ratio cutoff value as 0.332, it has been reported that the sensitivity of this value in predicting GDM was 87.6%, the specificity was 76.2%, and the AUC value was 0.895. The researchers have stated that the fetal thymic-thoracic ratio could be used in the management of diabetic pregnancies[14]. In a study by Ghalandarpoor-Attar et al. with a fewer number of patients, patient groups similar to those of Dörnemann et al. were evaluated and found that the fetal thymic-thoracic ratio decreased in diabetic pregnant women compared to that in the healthy pregnant women. The researchers also found that the decrease in the fetal thymic-thoracic ratio in diabetic pregnant women was more evident in the pregestational group; however, they did not determine a cutoff value. The researchers, though, recommended its use to predict diabetes during pregnancy[15]. In the present study, it was found that the thymic-thoracic ratio decreased in pregnant women with GDM compared to that in healthy pregnant women. By setting the cutoff value

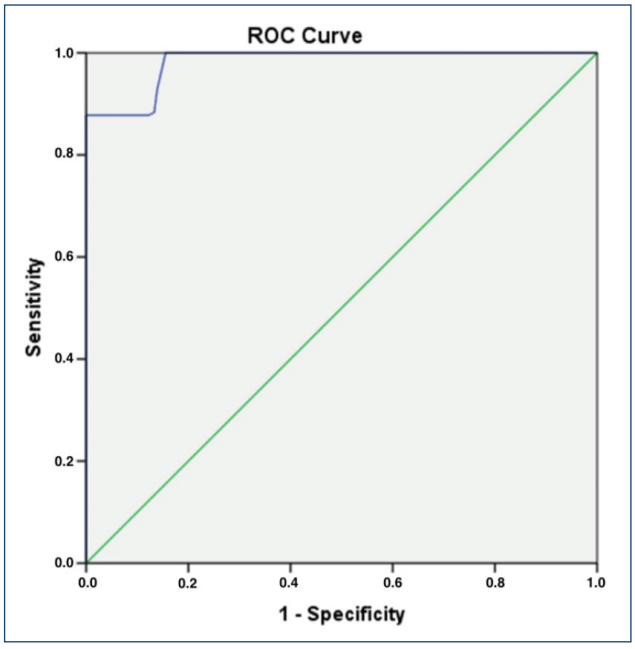

Figure 1. Receiver operating characteristic curve of fetal thymic-thoracic ratio to predict gestational diabetes. Diagonal segments are produced by ties.

Table 2. Comparison of fetal thymic-thoracic ratio between diet-controlled gestational diabetes and insulin-dependent gestational diabetes group and control group using Kruskal-Wallis test.

	Control group (n=180)	Diet-controlled gestational diabetes (n=106)	Insulin-dependent gestational diabetes (n=74)	p-value
Thymic-thoracic ratio	0.43 (0.392–0.462)	0.326 (0.296–0.408)	0.317 (0.292–0.348)	**0.000**

Data are expressed as median (minimum–maximum). p<0.05 indicates a significant difference (denoted in bold).

of the thymic-thoracic ratio in determining gestational diabetes as 0.407, the sensitivity was calculated as 92.8% and the specificity as 86.1%. The reason for the higher sensitivity and specificity of the cutoff value that was set in the present study than that of Dörnemann et al. can be the better standardization of the present study. Unlike the others, the present study included only gestational diabetic pregnant women. In addition, the number of patients in the study was higher, BMI values known to be associated with insulin resistance were similar, and all the pregnant women comprised only patients in the third trimester. Furthermore, it was determined that the thymic-thoracic ratio decreased more significantly in the insulin-dependent gestational diabetes group in parallel with the severity of GDM. Ghalandarpoor-Attar et al. reported that the decrease in the thymic-thoracic ratio was more pronounced in the pre-GDM, which is a more severe form of diabetes[15]; however, Dörnemann et al. did not report such a case[14]. In both studies, a more significant decrease in this ratio was not determined in insulin-dependent GDM, which is considered to be a more serious case[14,15]. In another recent study, researchers found that the anteroposterior diameter of the fetal thymus and the fetal thymic-thoracic ratio decreased in GDM. However, in this study, it is seen that the researchers did not divide diabetic pregnant women into groups according to the severity of the disease, as in our study[16]. In the present study, it is possible to discuss about a relationship between the severity of diabetes and the decrease in the thymic-thoracic ratio in gestational diabetic pregnant women, whereas in other studies, it is not possible to discuss about such a relationship between the severity of diabetes and the decrease in the thymic-thoracic ratio.

In the present study, although the fetal thymic-thoracic ratio has been argued to be the best ultrasonographic method for evaluating fetal thymus size in the literature, fetal thymus transverse diameter was also evaluated. However, no differences were found between diabetic pregnant women and healthy pregnant women. This may be due to the fact that fetal thymus transverse diameter measurement is a simpler method to evaluate fetal thymus size compared to fetal thymic-thoracic ratio measurement. However, there are studies showing that fetal thymus transverse diameter may be valuable in some complicated pregnancies[18,19].

For healthy fetal development, it is necessary to have various maternal anatomical and physiological adaptations. Sex hormones play an important role in the coordination of these adaptations. Sex hormones use mediators such as receptor activators of nuclear factor kappa-B (RANK) to perform these functions[20]. During pregnancy, RANK has been shown to regulate thymus functions in addition to bone metabolism through sex hormones. Regulatory T cells (Treg) in the thymus are expected to increase via RANK for a healthy pregnancy. Thymic depletion of RANK causes Treg cells to accumulate in adipose tissue while reducing their level in the placenta. Its effect on adipose tissue leads to an increase in the size of adipocyte cells, tissue inflammation, increased glucose intolerance, and the development of gestational diabetes. The decrease in these Treg cells in the placenta results in fetal losses. In addition to fetal losses, the decrease in Treg cells in the placenta in gestational diabetic pregnancies indicates the presence of abnormal placentation[20]. The hypoxic and metabolic stress environment caused by this abnormal placentation may have led to a decrease in fetal thymus size in pregnant women with GDM, as determined in the present study.

Although this study is retrospective, it has strong strengths including a large sample with similar BMI values and gestational weeks among the groups, and the measurements were made by a single specialist.

CONCLUSION

It was determined that the fetal thymic-thoracic ratio decreased in gestational diabetic pregnant women, which was more pronounced in the insulin-dependent gestational diabetes group, indicating more severe form of GDM. It was shown that the fetal thymic-thoracic ratio is superior to the fetal thymus transverse diameter in evaluating the fetal thymus size. The measurement of the fetal thymic-thoracic ratio was seen to be beneficial in determining the severity of the disease in gestational diabetic pregnant women.

ETHICAL APPROVAL

This study was approved by the clinical research ethics committee of the Sakarya University Clinical Research Ethics Board (decision no.: 40019-376, approval date: June 30, 2021).

AUTHORS' CONTRIBUTIONS

KG: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **SÖ:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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