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Increased fetal epicardial fat thickness; a reflecting finding for GDM and perinatal outcomes

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[1]Ankara Etlik Zubeyde Hanim Kadin Hastaliklari Egitim ve Arastirma Hastanesi

March 29, 2022

Abstract

Objective: To study the value of fetal epicardial fat thickness (EFT) in gestational diabetes mellitus in the third trimester of pregnancy and its relationship with clinical parameters and perinatal outcomes. **Methods:** A total of 80 participants, including 40 with diagnosed GDM and 40 healthy pregnant women, were included in the study. Demographic data were obtained from medical records. Sonographic examinations were performed, such as amniotic fluid value, fetal biometric measurements, and Doppler parameters of the umbilical artery. Fetal EFT values were measured at the free wall of the right ventricle using a reference line with echocardiographic methods. Correlation tests were performed to evaluate the relationship between fetal EFT and clinical and perinatal parameters. $P < 0.05$ were interpreted as statistically significant. **Results:** The fetal EFT value was statistically higher in the GDM group than in the control group (p:0.000). Spearman correlation tests revealed statistically significant but weak positive correlations between fetal EFT value, 1-hour 100-gr OGTT, birth weight, and BMI (r: 0.198, p:0.047; r:0.395, p:0.012; r:0.360, p:0.042, respectively). The optimal fetal EFT threshold for predicting GDM disease was found as 1.55 mm, with a specificity of 74.4% and sensitivity of 75.0%. Statistically significant differences between the two groups in umbilical artery Doppler resistance index (RI), pulsatility index (PI), and systolic/diastolic ratio (S/D) were not found (p:0.337; p:0.503; p:0.155;). BMI and amniotic fluid volume were higher in the GDM group compared to the control group (p:0.009; p:0.000). **Conclusion:** This study demonstrated that increased fetal EFT may occur as a reflection of changes in glucose metabolism in intrauterine life. Future studies with larger series, including the study of neonatal metabolic parameters, will contribute to the understanding of the importance of fetal EFT in determining the metabolic status of the fetus.

Introduction

Gestational diabetes mellitus (GDM) refers to carbohydrate intolerance of varying degrees that occurs for the first time, during pregnancy [1]. The etiopathogenesis of the disease is still not fully understood. Inflammatory factors leading to insulin resistance and beta cell dysfunction triggered by placental hormones play an important role in the etiopathogenesis of the disease, along with obesity, genetic and environmental factors [2-5]. GDM remains a significant pregnancy complication causing adverse perinatal outcomes such as fetal macrosomia, birth trauma, birth polyhydramnios, respiratory distress syndrome, preterm birth, hypoglycemia, and operative delivery. [1,6,7]. It is well known that fetuses exposed to the effects of hyperinsulinemia and hyperglycemia during the intrauterine period may have poor outcomes, including the need for intensive care and low Apgar scores in the neonatal period. There is also an increased risk of long-term complications such as type 2 diabetes mellitus (DM), cardiovascular disease, obesity, and metabolic syndrome in these individuals [7-9].

Epicardial adipose tissue (EAT) is located between the visceral pericardium and the myocardium but is more prominent in the atrioventricular and interventricular grooves and the right ventricular sidewall [10,11]. It is derived from splanchnic mesoderm and shares a common embryological origin with omental and mesenteric

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fat [11,12]. In addition to adipose tissue, EAT also contains neuronal and nodular structures. It shows endocrine, immunological and inflammatory activities with its energy storage function. [13-15]. Moreover, an increase in epicardial fat thickness (EFT) has been shown to be associated with DM, cardiovascular disease and obesity [16-19]. Therefore, it is considered an important cardiometabolic marker in adults [20,21].

There are few studies that investigated the measurement of EFT in fetuses of mothers with GDM [22-25]. The need for markers that can help predict the occurrence of GDM and the increased risk of GDM-related perinatal complications remains one of the main topics of current studies. Because previous studies have shown that the increase in fetal adipose tissue in fetuses with GDM occurs most frequently in the 3rd trimester, we aimed to compare fetal EFT in the 3rd trimester in cases diagnosed with GDM with fetuses from healthy mothers [6,22]. To the best of our knowledge, this is the first paper to address the assessment of fetal EFT in patients with GDM and its relationship to neonatal outcomes and to determine the most appropriate cut-off value of EFT for predicting GDM in the 3rd trimester.

Methods

Study design and patient selection.

The protocol of this prospective case-control study was approved by the hospital ethics committee, and written informed consent was obtained from each participant before participation in the study. All phases of the study were conducted based on the universal ethical principles of the Declaration of Helsinki. The study was conducted between July and December 2019 at the Department of Perinatology, Zekai Tahir Burak Women's Health and Research Hospital, Ankara, Turkey.

A total of 80 participants were recruited for the study, 40 of whom were diagnosed with GDM and 40 healthy pregnant women with the same gestational age served as the control group. With an effect size of d=0.5, a margin of error of 5%, and a power of 80% (n1:30, n2:30), at least 60 samples were deemed adequate by the power analysis performed with the G*Power 3.0.10 program. All participants were between 28 and 39 weeks of gestation. All demographic and clinical characteristics were obtained from medical records. Gestational age was confirmed using first trimester sonographic dating. GDM was diagnosed according to the criteria of the American College of Obstetricians and Gynecologists (ACOG) guidelines in a two-stage testing procedure at 24 to 28 weeks of gestation [1]. After a positive 50g-one-hour oral glucose challenge test (one-hour glucose level [?] 140 mg/dl), the diagnosis was made if two or more glucose levels were above the normal range on the 100 g-three-hour oral glucose tolerance test (fasting glucose level: 95 mg/dl; one-hour glucose level: 180 mg/dl; two-hour glucose level: 155 mg/dl; three-hour glucose level: 140 mg/dl).

Exclusion criteria were abnormal prenatal screening results in the first and/or second trimester, multiple pregnancies, a history of coexisting chronic systemic disease, gestational diabetes and other abnormalities of glucose metabolism, pregnancy complications such as gestational hypertension, placental abruption, fetal growth restriction, premature rupture of membranes, and chorioamnionitis. Fetuses with congenital or chromosomal abnormalities were not included in the study. In addition, participants who had a single high glucose level on 100g OGTT were not included in the control group because some of them may have had insulin resistance or impaired glucose metabolism. A total of 20 individuals in both groups were excluded because of obstetric complications that developed during follow-up.

Ultrasound and Doppler Measurements All sonographic examinations were performed transabdominal using the Voluson 730 Expert sonography unit (GE Healthcare, Milwaukee, WI) with a 3.5-MHz convex transducer by a single investigator with 10 years of experience in obstetric sonography who was blinded to all clinical parameters. Sonographic assessment of fetal anatomy, maximal measurement of deepest vertical amniotic fluid (MVP) pocket, fetal biometry, estimated fetal weight (EFW), and umbilical artery Doppler measurements (umbilical artery RI, resistance index; PI, pulsatility index; S/D, systolic/diastolic ratio) were performed according to the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology and the Institute of Ultrasound in Medicine.

Measurement of epicardial fat thickness

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Epicardial fat thickness was measured on the free wall of the right ventricle using a technique that showed good correlation with the values found on MRI [12, 26]. According to this method, the apical five-chamber view of the fetal heart was first obtained in a transverse plane through the fetal thorax and left ventricular outflow tract (LVOT) as the optimal view to visualize the hypoechoic space between the epicardial surface and the parietal pericardium at the right ventricle. To improve reproducibility and standardize measurements, a reference line was drawn as an anatomic landmark extending from the descending aorta through the annulus of the aortic valve and then upward to a point on the free wall of the right ventricle. The hypoechoic area at this point was used to measure EFT. Color Doppler was used to distinguish epicardial fat and pericardial effusion. A frozen real-time ultrasonographic image was acquired during end systole, and the hypoechoic area was magnified as much as possible. Then, the EFT was measured across the reference line by placing the caliper from the inside to the outside (Figure1). Measurements were taken three times and the average values were used for the final analysis.

Statistical analysis

All statistical analyzes were performed using IBM SPSS Statistics 21.0 (IBM Corp. Armonk, NY). Numerical variables were expressed as standard deviations and means. The Kolmogorov-Smirnov test was used to interpret the relationship of the data to the normal distribution. The parametric t-test for independent samples and the nonparametric Mann-Whitney U test were used to compare statistical significance between two independent groups in relation to the distribution ranges. Spearman and Pearson correlation tests were performed to evaluate the relationship between the two quantitative variables according to their distribution ratios. Receiver operating characteristic analysis (ROC) was performed to determine the predictive value of EFT for GDM. P values of less than 0.05 were interpreted as statistically significant.

Results

A total of 80 pregnant women participated in this case-control study, 40 with GDM as the study group and 40 with healthy pregnant women as the control group. The demographic and clinical characteristics of the study groups are shown in **Table 1** . There were no statistically significant differences between the groups in maternal age, gravidity, and gestational age during the study (p:0.324; p:0.142; p:0.980; respectively). BMI and amniotic fluid volume were higher in the GDM group than in the control group (p:0.009; p:0.000). Increased one-hour glucose values on the 50 g oral glucose challenge test (OGCT) were found in the GDM group compared to the control group (p:0.000). The glucose values of the 100 g oral glucose tolerance test are shown in Table 1.

The values of epicardial fat thickness and umbilical artery Doppler parameters of the study groups are shown in **Table 2.** The fetal EFT value was statistically higher in the GDM group than in the control group (p:0.000). Statistically significant differences between the two groups in terms of umbilical artery Doppler resistance index (RI), pulsatility index (PI), and systolic/diastolic ratio (S/D) were not found (p:0.337; p:0.503; p:0.155;).

The comparison of the two groups in terms of perinatal outcomes is shown in **Table 3** . Higher birth weight, ICU admission, higher C/S rate, and nonreassuring fetal heart rate pattern were observed in the GDM group compared with the control group (p:0.049; p:0.000; p:0.038;p:0.011, respectively). Apgar scores at 1 minute and 5 minutes were statistically significantly lower in the GDM group than in the control group (p:0.000; p:0.001).

The relationship between the EFT scores and the study parameters is shown in **Table 4.** Spearman correlation tests showed statistically significant but weak positive correlations between fetal EFT value, 1-hour 100 gr OGTT, birth weight and BMI (r: 0.198, p:0.047; r:0.395, p:0.012; r:0.360, p:0.042, respectively). The optimal fetal EFT cut-off value for predicting GDM disease was found as 1.55 mm with a specificity of 74.4% and sensitivity of 75.0%.**(Figure 2).**

Discussion:

In this prospective case-control study, we demonstrated that the fetal EFT value was higher in the group

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with GDM compared to the control group. Higher BMI and amniotic fluid values were found in the GDM group than in the control group. The optimal fetal EFT cut-off value for predicting GDM disease was determined as 1.55 mm with a specificity of 74.4% and sensitivity of 75.0%. Spearman's correlation tests revealed statistically significant but weak positive correlations among fetal EFT value, 1-hour 100 gr OGTT, BMI, and birth weight. To the best of our knowledge, this is the first study to demonstrate the association between fetal EFT and perinatal outcomes of GDM disease and to identify an optimal cut-off value for fetal EFT for GDM in the 3rd trimester.

Epicardial fat, the visceral fat deposit of the heart, has endocrine, paracrine, and metabolic activities [13-16]. It secretes various inflammatory and proinflammatory factors and adipokines such as interleukin 6, omentin, tumor necrosis factor alpha, and adiponectin, which may be associated with metabolic syndrome, obesity, and heart disease [13-16]. It also serves as an important source of energy for the heart muscle by releasing free fatty acids, having a high storage capacity, and stimulating lipogenesis by insulin [13]. Recent studies have demonstrated that higher EFT levels may be associated with cardiometabolic events, particularly diabetes mellitus and coronary heart disease [17,20-22,27]. Therefore, it is proposed as a metabolic marker in adults.

It is well known that hyperinsulinemia and hyperglycemia resulting from disorders of glucose metabolism can lead to conditions such as polyhydramnios, macrosomia, fetal cardiac septal hypertrophy, changes in fetal cardiac morphology, and in subcutaneous adipose tissue distribution [1,6,7,28]. The altered fetal environment caused by diabetes results in greater and earlier fat deposition in epicardial fat than in other fat stores. Given the prolonged exposure to changes in the intrauterine fetal environment, it is expected that these conditions may occur more frequently in the third trimester. Studies have shown that long-term sequelae such as diabetes mellitus, metabolic syndrome, obesity, and heart disease may occur in children born to mothers with GDM [7-9]. It has been suggested that this situation may be caused by numerous metabolic processes triggered by high glucose and insulin levels, i.e., it may be the late reflection of diabetic fetopathy. Given this information, we examined fetal EFT in GDM in the third trimester and investigated the relationship between fetal EFT value and clinical parameters of the disease and perinatal outcomes.

The review of the literature regarding fetal EFT in diabetic pregnancies demonstrated that the significance of fetal EFT in diabetic pregnancies was first revealed in the study by Jackson et al. [22]. In this retrospective study, which included a small number of participants including 28 pregnant women diagnosed with type 1 and type 2 DM, and 28 healthy pregnant women, it was found that the mean fetal EFT value was higher in the fetuses of diabetic mothers compared with the control group. In this study, which included pregnant women in the 2nd trimester, it was shown that there was a statistically significant positive relationship between fetal EFT value and TFA, but no significant relationship was found between BMI and fetal EFT. In another retrospective study by Akkurt et al. involving 106 pregnant women diagnosed with pregestational DM and GDM, diabetic pregnancies had a higher fetal EFT value than the control group [23]. The first prospective case-control study of fetal EFT in GDM was conducted by Yavuz et al. In this study, 40 pregnant women diagnosed with GDM and 40 healthy pregnant women in the second trimester were enrolled [24]. It was found that fetal EFT values were higher in the women with GDM than in the control group. This study also found a positive and moderate correlation between 2-hour glucose level and fetal EFT. In the other study by Aydın et al. fetal EFT measurements were performed at 18-22 weeks of gestation [25]. They showed that the fetal EFT values of GDM patients were significantly higher than those of the control group. Moreover, correlation analysis showed that a strong positive correlation was observed between fetal EFT and Hba1c values and EFW.

Our study was designed as a prospective case-control study and included cases in the 3rd trimester with prolonged exposure to hyperinsulinemia and hyperglycemia. Consistent with previous studies, we found that the fetal EFT value was increased in GDM compared with the control group. Moreover, in contrast to other studies, we proposed a cut-off value of 1.55 mm with a specificity of 74.4% and a sensitivity of 75.0% that can predict GDM disease in 3rd trimester. Another strength of our study is that we also investigated the relationship between the EFT value, clinical parameters, and perinatal outcomes. In the study by Yavuz et.al, a positive and moderate correlation was shown between the 2-hour glucose level and fetal EFT,

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but we found a positive correlation between the 1-hour glucose level and fetal EFT. Although Aydın et.al. found positive correlations between Hba1c and fetal EFT at 18-22 weeks of gestation, we did not find any relationship between these parameters in the 3rd trimester. In agreement with the results of the study by Jackson et al and Aydın et.al, correlation tests in our study revealed a statistically significant but weak positive correlation between the EFT value and birth weight. Although higher NICU admission, higher C/S rate, and nonreassuring fetal heart rate recording patterns and lower Apgar scores at 1 minute and 5 minutes were found in the GDM group compared with the control group. There was no association between fetal EFT levels and these parameters.

The EFT measurement technique was first described by Iacobellis et al. [26]. The original description of the technique recommended that the measurement be performed during end systole to avoid possible changes, such as underestimation of EFT due to compression of epicardial adipose tissue during diastole. Because measurement at different sites and with different scan schedules results in different EFT values, standardization of the measured area increases the accuracy and value of the study. In contrast to other studies, the fact that our study is a prospective study allowed us to measure EFT during end systole. Another advantage of our study is that we performed the measurements based on a single reference point in a single plan, i.e., we standardized the measurement technique in each case.

This current study has some drawbacks. First, the groups in our study were not matched for BMI. However, in recent studies, similar to our study, no statistically significant association was found between BMI and EFT. Subgrouping by BMI values in GDM will contribute to our understanding of whether obesity, which plays a role in the development of diabetes, or diabetes itself is associated with high EFT. Second, our study did not examine the association with neonatal metabolic profile and fetal EFT. A prospective study with more participants and an examination of neonatal metabolic parameters will more clearly demonstrate the importance of fetal EFT and its impact on neonatal outcomes.

In conclusion, despite these drawbacks. This prospective case-control study has shown that one of the fetal effects of changes in glucose metabolism in pregnant women diagnosed with GDM may be an increase in fetal EFT value. In addition, we found a cut-off value that can predict GDM disease. This study, in which we examined the relationship between perinatal outcomes and fetal EFT in GDM, will shed light on other studies in the future adding larger randomized controlled, neonatal metabolic markers. With the contribution of future studies, the practicality of measuring EFT, which is accepted as a cardiometabolic marker in adults, in determining the impact of changes in the intrauterine environment in GDM on fetal metabolic status will become apparent.

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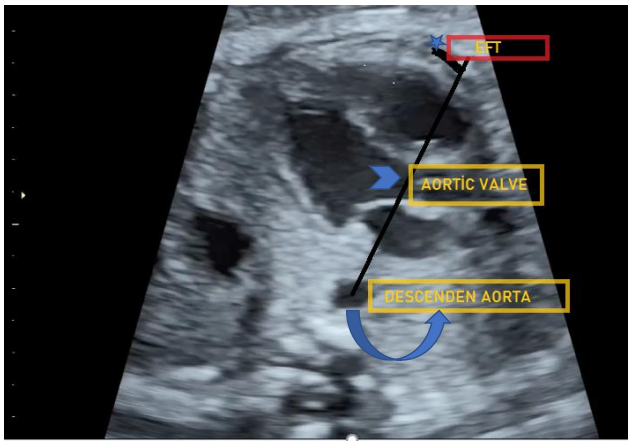

Figure1: Measurement of Epicardial Fat Thickness (EFT)

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