Association of increased fetal epicardial fat thickness with maternal pregestational and gestational diabetes

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Abstract

Objective: To evaluate the changes of fetal epicardial fat thickness (EFT) in pregnancies with pregestational (PGDM) and gestational diabetes mellitus (GDM) and to identify the diagnostic effectiveness of fetal EFT in differentiating PGDM and GDM from normal pregnancies. **Methods:** The study was conducted with pregnant women who admitted to perinatology department between November 2020 and September 2022. Patients were analyzed as 3 groups: PGDM (n=161), GDM (n=171) and control group (n=170). EFT was measured in all three groups at 29 weeks of gestation. Demographic characteristics and ultrasonographic findings were recorded and compared. **Results:** The mean fetal EFT was significantly higher in PGDM (1.47±0.083 mm, p<0.001) and GDM (1.40±0.082 mm, p<0.001) groups compared to control group (1.19±0.049 mm) and was also significantly higher in PGDM group than GDM group (p<0.001). Fetal EFT was significantly positively correlated with maternal age, fasting, 1 st hour, 2 nd hour glucose values, HbA1c, fetal abdominal circumference and deepest vertical pocket of amniotic fluid (p<0.001). Fetal EFT value of 1.3 mm diagnosed PGDM patients with a sensitivity of 97.3% and a specificity of 98.2%. Fetal EFT value of 1.27 mm diagnosed GDM patients with a sensitivity of 94% and a specificity of 95%. **Conclusions:** Fetal EFT is greater in pregnancies with diabetes than in normal pregnancies, and also greater in PGDM than in GDM. In addition, fetal EFT is strongly correlated with maternal blood glucose levels in diabetic pregnancies.

Introduction

The most common metabolic disorder in pregnancy is hyperglycemia resulting from impaired blood glucose tolerance which is defined as either pregestational (PGDM) or gestational diabetes mellitus (GDM)[1]. Diabetes in pregnancy may cause many adverse perinatal outcomes including fetal macrosomia, stillbirth, neonatal hypoglycemia, preeclampsia and birth trauma[2,3]. The incidence of diabetes in pregnancy varies substantially across countries, ranging between 0.9% and 5.7% for PGDM and 1.8% and 25.4% for GDM[4,5]. Both type 2 PGDM and GDM could be diagnosed by various screening methods including fasting plasma glucose (FPG), HbA1c and oral glucose tolerance test (OGTT), but which one of them is the most successful for the diagnosis is still controversial.

Epicardial fat tissue is located between the visceral pericardium and myocardium and is usually distributed adjacent to the right ventricle[6,7]. Proinflammatory vasoactive peptides, tumor necrosis factor-α, interleukin-6 and anti-inflammatory substances (adiponectin, omentin, adrenomedullin) are released from epicardial fat tissue[8,9]. Furthermore, epicardial fat tissue contributes to myocardial energy production[6]. In recent years, measurement of epicardial fat thickness (EFT) in adults has been frequently used to detect insulin resistance[10]. It has been shown that there is a correlation between EFT and cholesterol, adiponectin and diastolic blood pressure[11]. Since EFT is not affected by changes in skin and muscle tissue, it is thought to be more reliable than some other measurements such as abdominal circumference[12]. However, conditions

related to EFT are not clearly demonstrated in antenatal life as in non-pregnant adults. It has been proposed that increase in maternal EFT in pregnant women might be related to preeclampsia and vascular complications[13,14].

Limited studies in the literature have shown that fetal EFT is higher in pregnant women with diabetes[15-18]. However, in these studies, the comparison of fetal EFT was conducted only in pregnancies with PGDM or GDM. Due to the methodology of previous studies, it could not be clarified whether there is a difference for fetal EFT values between pregnancies with PGDM and GDM. Therefore, the aim of this study is to identify whether fetal EFT differs in pregnant women with PGDM and GDM and also to correlate fetal EFT values with demographic parameters of diabetic pregnancies.

Objectives

To evaluate the changes of fetal epicardial fat thickness (EFT) in pregnancies with pregestational (PGDM) and gestational diabetes mellitus (GDM) and to identify the diagnostic effectiveness of fetal EFT in differentiating PGDM and GDM from normal pregnancies.

Methods

The study was planned as a prospective cohort and performed among patients who applied to the Perinatology Department of Izmir Tepecik Training and Research Hospital between November 2020 and September 2022. A detailed consent form was obtained from all pregnant women participating in the study. The study was carried out in accordance with the conditions specified in the Declaration of Helsinki.

The aim of our study was to evaluate and compare the effects of maternal PGDM and GDM on EFT by ultrasonography. Therefore, we needed a group with PGDM, a group with GDM and a control group (without PGDM or GDM) to compare measurements in fetuses of the same gestational age. After the identification of patients with PGDM at first trimester of pregnancy, we performed GDM screening in order to determine the GDM and control groups. All patients without a previous diagnosis of PGDM underwent 75-gr OGTT between 26 and 28 weeks of gestation. In order to compare EFT measurements at the same gestational week for standardization, all EFT measurements were performed at 29 weeks of gestation in all pregnant women who participated in the study. Gestational week was confirmed both according to the last menstrual period and first trimester ultrasound. 161 patients with PGDM, 171 patients with GDM and 170 patients as a control group were included in the study. Pregnant women with at least one high blood glucose level in the 75-gr OGTT and with no diagnosis of previous diabetes were considered as GDM (FPG [?] 92 mg/dl, 1st hour glucose [?] 180 mg/dl, 2ndhour glucose [?] 153 mg/dl). OGTT was not performed to pregnant women with PGDM. Multiple pregnancies, pregnant women with chromosomal and structural anomalies, insufficient EFT measurements (inability to obtain a clear measurement due to severe maternal obesity, unsuitable fetal position, etc.) and comorbidities accompanying pregnancy (preeclampsia, intrauterine growth retardation, metabolic disorders, etc.) were not included in the study. A flow chart of our study population was shown in Figure 1. HbA1c was measured at the 29th weeks of gestation by high-performance liquid chromatography method supplied by the Bio-Rad Diagnostic Group (Hercules, CA, USA). The treatment of GDM began with lifestyle interventions including nutritional counseling, dietary changes, and daily exercise. Fasting and postprandial self-monitoring of blood glucose were recommended in pregnancies with GDM to achieve optimal glucose levels. Glucose targets were FPG <95 mg/dL and either 1-h postprandial glucose <140 mg/dL or 2-h postprandial glucose <120 mg/dL. If blood glucose targets were not maintained in more than half of measurements during 1 week assessment, insulin treatment was initiated. Demographic characteristics (age, gravida, parity, HbA1C, body mass index (BMI), birthweight), results of the 75-gr OGTT and ultrasonographic parameters including EFT, biparietal diameter (BPD), abdominal circumference (AC), femur length (FL) and deepest vertical pocket of amniotic fluid (DVP) were evaluated. Macrosomia was defined as a birthweight >90th percentile corrected for gestational age and gender. Samsung® HS 70A4D real time ultrasonography system (2017, Seoul, Korea) was used for all patients by the same clinician as described previously[19].

Patients whose fetal position was not suitable (the back of the fetus was close to the probe) and patients

who did not have appropriate EFT measurements due to maternal morbid obesity were not included in the study. EFT is located along the right ventricular wall. Dimensions of EFT are highest towards the fetal heart apex and thickness decreases towards the base of the heart[20,21]. Thickest area of epicardial fat was chosen to measure the EFT. In an attempt to standardize the measurement technique as much as possible, images from cardiac long axis views of left outflow tract or short axis view of right outflow tract as close to the level of the aortic valve as possible were utilized (Figure 2). Measurement should be taken at the end of diastole and mean thickness of 3 consecutive measurements should be recorded. Adipose tissue can be easily distinguished from pericardial effusion as it is more echogenic. Furthermore, pericardial fusion-EFT distinction can be made with color Doppler[6]. In ultrasonographic measurement, calipers should be placed inwardly between epicardium and myocardium.

Data obtained in the study were analyzed using SPSS (Statistical Package for Social Sciences) for Windows 25.0 program. While evaluating data, descriptive statistical methods (number, percentage, min-max values, mean, standard deviation) were used. The normal distribution of data depends on skewness and kurtosis values being between ±3. In the comparison of normally distributed data and quantitative data, independent t-test was used for difference between two independent groups, and one-way analysis of variance (ANOVA) was used for comparing more than two independent groups. Chi-square test was used for categorical variables. The significance level was accepted as 0.05. Since OGTT was not performed in patients with PGDM, ANOVA for OGTT variables was not performed in this group. Independent t-test was used for these variables. Post Hoc-Bonferroni test was applied to determine which group make a difference after a statistically significant result in the comparison of the 3 groups. Correlation test was performed between EFT and other demographic measurements, and Pearson coefficient was checked for data with normal distribution. Receiver-operating-characteristic (ROC) curve analysis was used to calculate cut-off values in differentiating pregnancies with pregestational DM and GDM from normal pregnancies according to fetal EFT value.

Results

A total of 502 patients, including 161 pregnant women with PGDM, 171 pregnant women with GDM and 170 controls, were evaluated. The PGDM group consisted of 98 (60.8%) women with Type 1 and 63 (39.2%) women with Type 2 DM. Demographic characteristics and ultrasound findings of three groups were showed in Table 1. Patients in PGDM group were significantly older than both control and GDM groups (p=0.002) (Table 1). FPG, 1-h and 2-h blood glucose values of patients in GDM group were found to be significantly higher than control group (p<0.001). HbA1C values were significantly higher in both GDM and PDGM groups compared to control group (p<0.001). As expected, HbA1c values of patients with PGDM were significantly higher than those with GDM (p=0.021). Body mass index was significantly higher in PGDM group compared to control group (p=0.047). In ultrasound measurements, AC and DVP were found to be significantly higher in PGDM and GDM groups compared to control group and also significantly higher in PGDM group compared to GDM group (p<0.001).

The mean of EFT measurements were found to be 1.19 ± 0.049 mm, 1.40 ± 0.082 mm and 1.47 ± 0.083 mm for the control, GDM and PGDM groups, respectively (Table 1). There was a significant difference between all three groups in terms of EFT (p<0.001). After adjusting by Bonferroni correction, it was observed that the mean EFT of control group was lower than the mean values of GDM and PGDM groups. Furthermore, the mean EFT of PGDM group was higher than the mean EFT of GDM group (p<0.001). Comparison of the mean values of EFT using a box plot among three groups were demonstrated in Figure 3a.

Correlation analysis was performed to test the relationship between EFT and demographic characteristics of patients (Table 2). There was a statistically significant weak positive correlation between EFT and maternal age (r=0.184, p<0.001), FPG (r=0.188, p=0.005) and DVP (r=0.332, p<0.001), moderate positive correlation between EFT and fetal AC (r=0.422, p<0.001), HbA1C (r=0.559, p<0.001) and strong positive correlation between EFT and 1st hour (r=0.650, p<0.001) and 2nd hour glucose values (r=0.719, p<0.001). ROC analysis was performed to identify optimal cut-off points in differentiating pregnancies with GDM and pregestational DM from normal pregnancies (Figure 3b,c). The ROC curve of the multivariate logistic regression model for the diagnosis of GDM demonstrated EFT with other variables (FPG, 1hPG, 2hPG,

HbA1c, AC and DVP) have an AUC of (1.000, 95% CI 1.000-1.000), which is larger than when using the individual factors of EFT (0.985, 95% CI 0.973-0.997), FPG (0.643, 95% CI 0.565-0.720), 1hPG (0.956, 95% CI 0.927-0.984), 2hPG (0.976, 95% CI 0.953-0.999), HbA1c (0.902, 95% CI 0.861-0.944), AC (0.696, 95% CI 0.628-0.764) and DVP (0.669, 95% CI 0.595-0.742). The ROC curve of the multivariate logistic regression model for the diagnosis of PGDM demonstrated EFT with other variables (HbA1c, AC and DVP) have an AUC of (1.000, 95% CI 1.000-1.000), which is larger than when using the individual factors of EFT (0.999, 95% CI 0.998-1.000), HbA1c (0.934, 95% CI 0.902-0.967), AC (0.858, 95% CI 0.810-0.906) and DVP (0.814, 95% CI 0.756-0.873). Using a cut-off level of 1.27 mm, EFT diagnosed GDM with a sensitivity of 94% and specificity of 95% (AUC:0.95 [95 CI 0.973-0.997]). Furthermore, using a cut-off level of 1.3 mm, EFT diagnosed PGDM with a sensitivity of 97.3% and specificity of 98.2% (AUC:0.999 [95 CI 0.998-1.000]). We also performed a ROC curve analysis for assessing the performance of fetal EFT value in predicting macrosomia. The AUC was 0.945 (95% CI 0.912-0.979) for macrosomia. The optimal fetal EFT threshold for predicting macrosomia was found as 1.36 mm, with a sensitivity of 93.4% and specificity of 95.8%. We did not calculate inter-observer reproducibility for EFT because all measurements were obtained by a single clinician. However, intra-observer analysis demonstrated good repeatability and reproducibility of EFT. The interclass correlation coefficient of intra-observer reproducibility for EFT measurement was 0.755 (95 % CI 0.526-0.984). Intra-observer variability of measurements of EFT was found to be 0.5 ± 0.4 mm.

Discussion

Diabetes is the most common endocrine disorder during pregnancy. Fetal-maternal morbidity is significantly reduced if diabetes is diagnosed and precautions are taken. In this study, we evaluated fetal EFT, which is a candidate to be a new marker to determine maternal diabetes status in pregnancy. Unlike other studies in the literature, we took one step further by separately evaluating fetal EFT in pregnancies with both PGDM and GDM. Cut off values of EFT for the diagnosis of diabetes risk were also identified.

It is known that epicardial adipose tissue has important paracrine and metabolic effects. EFT is closely related to excess fat tissue in the body. However, the main reason for EFT to be a reliable marker is that EFT is not affected by changes in subcutaneous and muscle tissues[12]. Previous studies in adults revealed that increase in EFT is an important diabetic marker and may be a determinant in terms of morbidities that may occur due to diabetes[22]. Furthermore, a close relationship was found between EFT and metabolic syndrome, obesity and insulin resistance[8].

Some recent studies investigated whether use of EFT as a marker in adults could be beneficial for pregnant women and their fetuses. In the study by Jackson et al., EFT of fetuses was compared between diabetic and non-diabetic pregnant women[16]. They found that fetal EFT was statistically significantly higher in diabetic pregnant women (EFT mean=1.43mm). However, in their studies, diabetic pregnancies were not grouped and evaluated as PGDM and GDM. Similarly, we found that EFT of fetuses was higher in diabetic pregnant women compared to non-diabetic pregnancies. Unlike to other studies, we also demonstrated that fetal EFT was significantly higher in pregnancies with PGDM compared to those with GDM.

In our study, we found that maternal age and values of HbA1C, AC and DVP were significantly higher in PGDM and GDM groups. Although maternal age was not significantly different between GDM and control groups, pregnant women with PGDM were significantly older than both GDM and control groups. We've also oberved a statistically significant correlation between fetal EFT and maternal age. Most of the previous studies did not explore any significant relationship between fetal EFT and maternal age[15,17,18]. Only in the study of Akkurt et al., maternal age was found to be greater in diabetic pregnant women as in our study[6]. The reason for higher maternal age in pregnant women with PGDM may be explained by the desire of women with existing diabetes to postpone their pregnancy to a later age. Another explanation is that these women with PGDM are more likely suffer from comorbidities which increase the risk of failure to conceive.

Since diagnosis of PGDM was established at the first trimester of pregnancy in our study population, OGTT was performed to GDM and control groups. We found that fetal EFT was significantly positively correlated with every parameter of OGTT values (fasting, 1st hour and 2nd hour). Although this correlation

was weak for FPG level, it was strong for 1st hour and 2nd hour glucose levels after OGTT. Similarly, Yavuz et al. compared and correlated fetal EFT values and blood glucose measurements obtained during a 75-gr OGTT[18]. In their study, fetal EFT had a significantly weak and moderate correlation with 1st hour and 2nd hour glucose level after controlling for maternal age, gestational age, body mass index and abdominal circumference. However, when only GDM pregnancies were included, fetal EFT was positively and moderately related to 2-h glucose values[18]. Furthermore, we also explored that there was a significant and moderate positive correlation between fetal EFT values and maternal HbA1c levels. Confirming our results, Aydin et al. observed a strong positive correlation between fetal EFT and maternal HbA1C values[17]. In this study, fetal EFT was found to be significantly associated with adverse perinatal outcomes of diabetes including macrosomia and polyhydramnios. Fetal EFT was significantly positively correlated with fetal AC and DVP of amniotic fluid volume. Akkurt et al. were also demonstrated a higher fetal EFT in pregnancies with GDM compared to normal pregnancies[6]. Unlike from our study, Aydin et al. were determined a positive correlation between fetal EFT and DVP values instead of AC values[17]. However, they compared fetal EFT values only between GDM and control groups. Among all three groups in our study, HbA1c, AC and DVP values were significantly higher in PGDM group followed by GDM group. These findings provide strong evidence that high EFT value is a fetal reflection of poorly controlled maternal glucose level.

In this study, we investigated the diagnostic value of fetal EFT on diabetic pregnancies and determined cut-off EFT values for both PGDM and GDM. Until recently, there are two studies in the literature that calculate which values of fetal EFT can be used as cut-offs for diabetes in pregnancy. The first of these was done by Akkurt et al. in 2018[6]. The recommended equation of the mentioned study for calculation of EFT in pregnant women with diabetes was EFT = 0.05 x gestational age + 0.07 (R2 = 0.70). In our study, we did not calculate the equation related to the gestational week. Instead, we evaluated EFT of all pregnant women in the same week to ensure standardization. Another study in the literature was performed by Aydin et al. in 2020[15]. They conducted a study to determine the relationship between fetal EFT and weight. Aydin et al. stated that a cut-off fetal EFT value above 1.38 mm was predictive for diagnosis of fetuses with large for gestational age with a sensitivity of 94.4% and a specificity of 97.6%[15]. All patients in that study were evaluated at 22 weeks of gestation, but diabetic pregnancies were not grouped as PGDM and GDM. In the present study, cut-off EFT values for pregnant women with PGDM and GDM were 1.30 mm (sensitivity 97.3%, specificity 98.2%) and 1.27 mm (sensitivity 94%, specificity 95%), respectively. Both EFT cut-off values of our study were found to be lower than the values calculated by Aydin et al. and Akkurt et al.[6,17] We believed that the reason for this difference is related to patient selection criteria and classification of study population rather than measurement technique of fetal EFT.

Conclusion

This study revealed that fetal EFT was significantly increased in diabetic pregnancies with either PGDM or GDM but the increase in fetal EFT was significantly higher in PGDM compared to GDM. Furthermore, fetal EFT is strongly correlated with maternal blood glucose levels in diabetic pregnancies. Therefore, fetal EFT value could be used as a prognostic marker for PGDM and GDM and also for adverse perinatal outcomes related to diabetes.

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Variables	Variables	Control (n=170)	GDM (n=171)	PGDM (n=161)	ANOVA p value	Post Hoc-Bonferroni test p value	Post Hoc-Bonferroni test p value	Post Hoc-Bonferroni test p value
		Mean ± SD	Mean ± SD	Mean ± SD		Control vs GDM	Control vs PGDM	GDM vs PGDM
Age (y)	Age (y)	27.4±5.1	28.4±4.2	30.9±3.9	**0.002**	0.415	**<0.001**	**0.011**
OGTT (fasting) (mg/dl)	OGTT (fasting) (mg/dl)	75.4±5.4	83.3±10.4	-	-	**<0.001**	-	-
OGTT (1st hour) (mg/dl)	OGTT (1st hour) (mg/dl)	158.3±8.4	188.2±14.7	-	-	**<0.001**	-	-
OGTT (2nd hour) (mg/dl)	OGTT (2nd hour) (mg/dl)	131.4±13.3	163.1±13.4	-	-	**<0.001**	-	-
HbA1c (%)	HbA1c (%)	4.7±0.4	6±1.1	6.3±0.3	**<0.001**	**<0.001**	**<0.001**	**0.021**
BMI (kg/m^2)	BMI (kg/m^2)	28.8±3.1	29.4±1.9	30.7±0.9	0.345	0.974	**0.047**	0.119
Gravida	Gravida	2.1±0.7	2.8±1.4	3±0.5	0.764	0.541	0.081	0.314
Parity	Parity	1.1±0.6	1.5±1.1	1.6±1.2	0.614	0.405	0.097	0.611
Birthweight (g)	Birthweight (g)	3516±451	3496±397	3584±442	0.087	0.265	0.341	0.106
BPD (mm)	BPD (mm)	71.5±1.9	72.8±2.7	71.9±2.4	0.208	0.461	0.219	0.304
HC (mm)	HC (mm)	263.4±5.1	267.7±5.3	264.4±6.7	0.358	0.109	0.271	0.186
AC (mm)	AC (mm)	244.1±6.6	253.7±4.5	257.7±5.1	**<0.001**	**<0.001**	**<0.001**	**<0.001**
FL (mm)	FL (mm)	54.7±1.7	54.3±5.7	58.5±5.9	0.482	0.457	0.387	0.297
DVP (mm)	DVP (mm)	50.7±4.7	54.3±5.7	58.5±5.7	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Gender (%)	Male	49.4	50.7	48.1	0.772	0.548	0.427	0.588
	Female	50.6	49.3	51.9				
EFT (mm)	EFT (mm)	1.19±0.049	1.40±0.082	1.47±0.083	**<0.001**	**<0.001**	**<0.001**	**<0.001**

Table 1. Demographic features, laboratory and ultrasound findings of the three groups (BMI, body mass index; DVP, deepest vertical pocket; EFT, epicardial fat thickness; FL, femur length; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; PGDM, pregestational diabetes mellitus)

	Epicardial fat thickness	Epicardial fat thickness
	r-value	p-value
Demographic features		
Age	0.184[a]	**<0.001[a]**
BMI	0.101	0.066
Gravida	-0.002	0.967
Parity	0.020	0.712
Birthweight	0.742[d]	**<0.001[d]**
Laboratory findings		
OGTT (fasting)	0.188[a]	**0.005[a]**
OGTT (1-h)	0.650[d]	**<0.001[d]**
OGTT (2-h)	0.719[d]	**<0.001[d]**
HbA1c	0.559[c]	**<0.001[c]**
Ultrasound findings		
BPD	0.087	0.114
HC	0.104	0.059
AC	0.422[c]	**<0.001[c]**
FL	0.018	0.738
DVP	0.332[b]	**<0.001[b]**

Table 2. Correlation analysis between epicardial fat thickness and demographic features, laboratory and ultrasound findings ([a]very weak positive, significant;[b]weak positive, significant;[c]moderate positive, significant;[d]strong positive, significant. AC, abdominal circumference; BMI, body mass index; BPD, biparietal diameter; DVP, deepest vertical pocket; HC, head circumference; FL, femur length; OGTT, oral glucose tolerance test).

Figure 1. Flow chart of the study population. IUGR, intra uterine growth restriction; GDM, gestational diabetes mellitus; PGDM, pregestational diabetes mellitus; OGTT, oral glucose tolerance test.
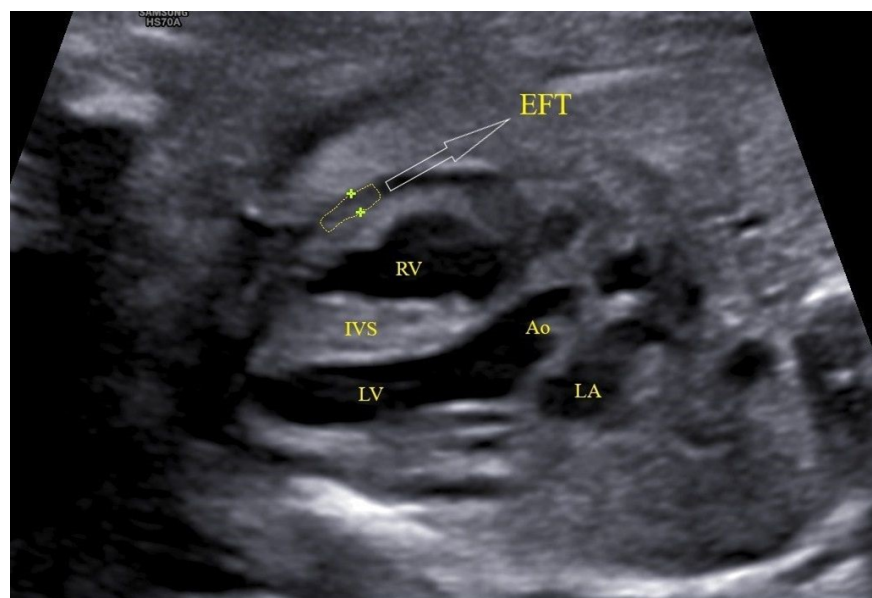

Figure 2. Ultrasonographic image of fetal epicardial fat tissue. EFT, epicardial fat thickness; RV, right ventricle; LV, left ventricle; IVS, interventricular septum; Ao, ascending aorta; LA, left atrium.
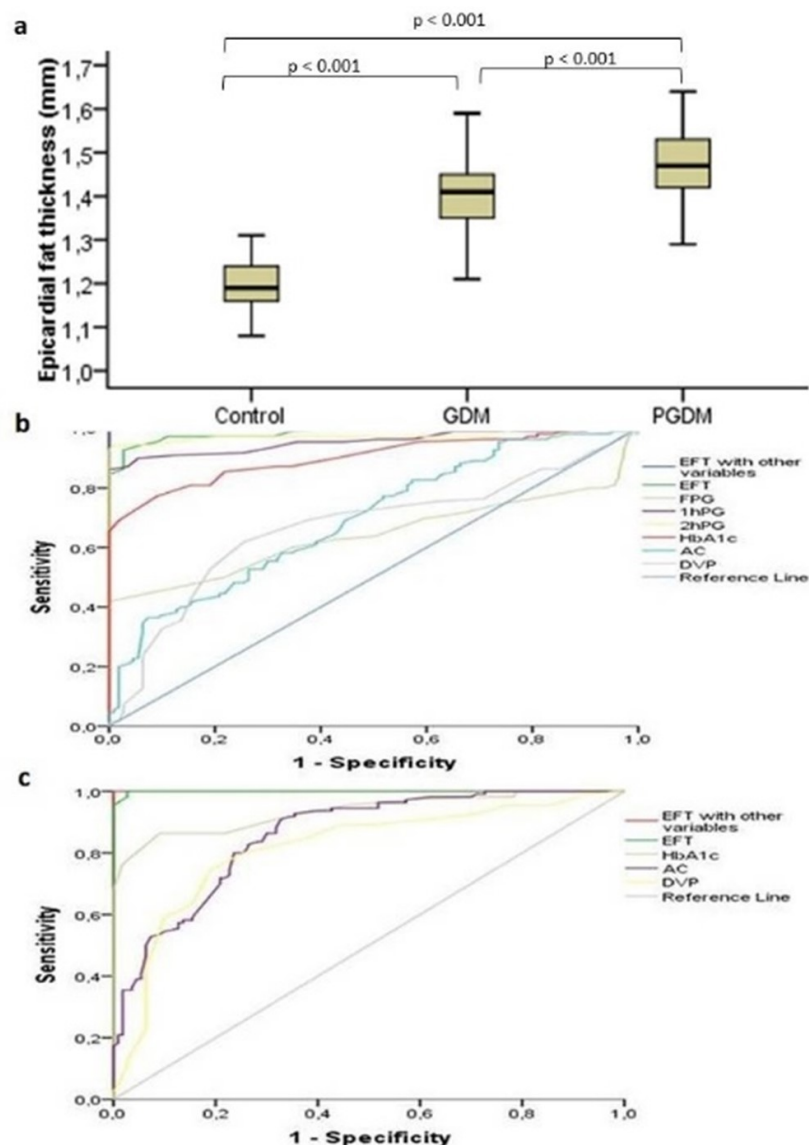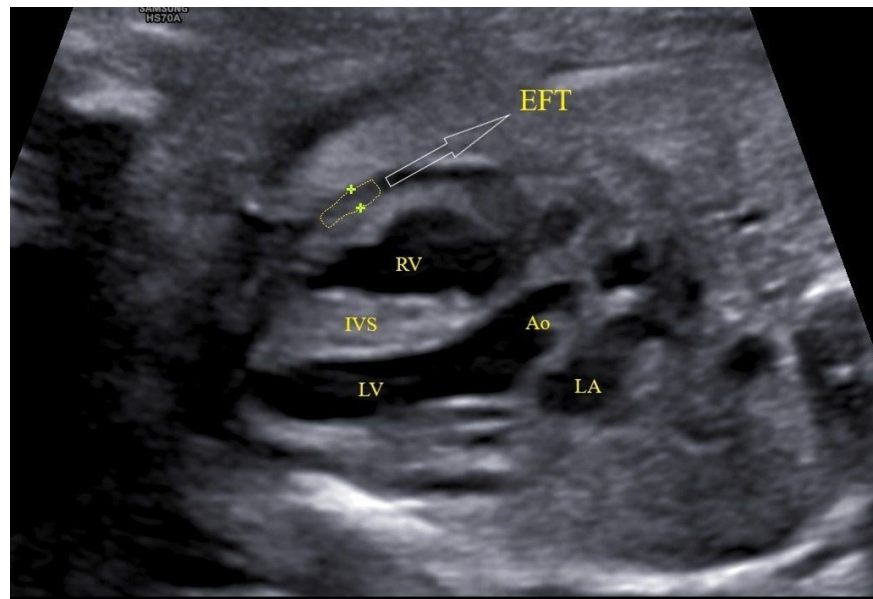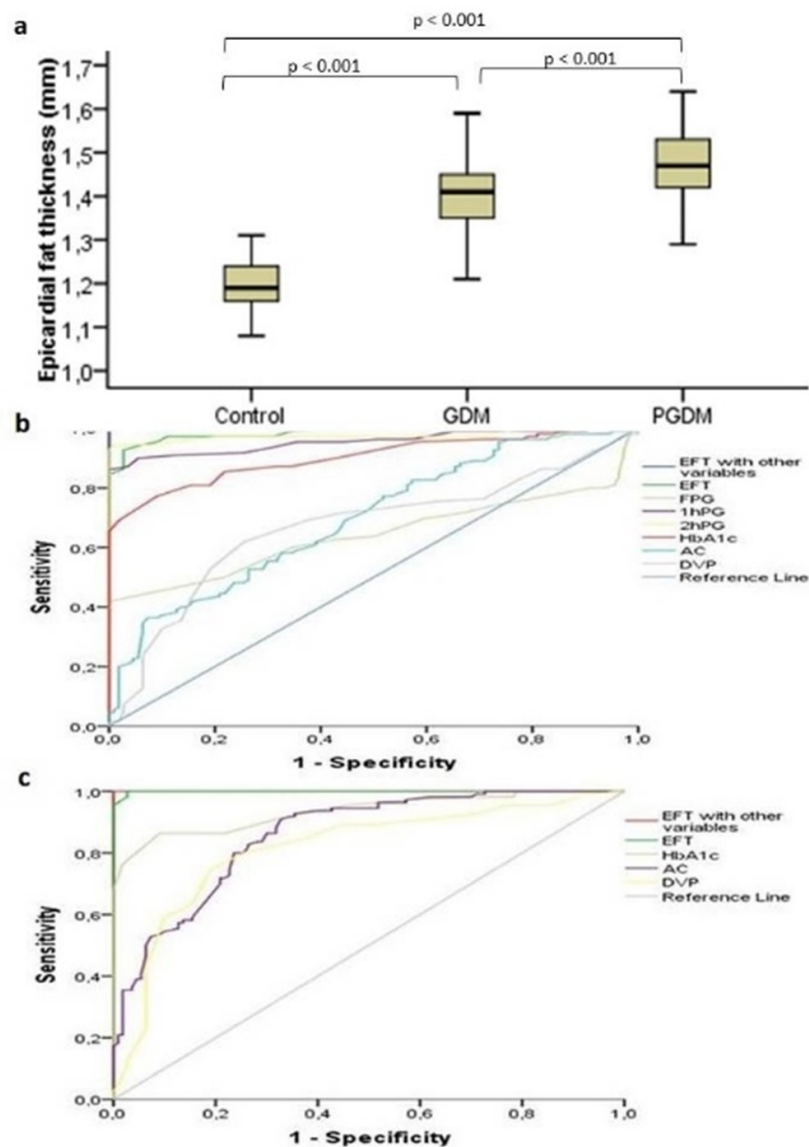
Figure 3. Distribution of EFT values of GDM, PGDM and control groups **(a)** . ROC curves constructed with the multivariate logistic regression model. The AUC of EFT with other variables (FPG, 1hPG, 2hPG, HbA1c, AC and DVP) for the diagnosis of GDM (1.000) is larger than when using the individual factors of EFT (0.985), FPG (0.643), 1hPG (0.956), 2hPG (0.976), HbA1c (0.902), AC (0.696) and DVP (0.669) **(b)** . The AUC of EFT with other variables (HbA1c, AC and DVP) for the diagnosis of PGDM (1.000) is larger than when using the individual factors of EFT (0.999), HbA1c (0.934), AC (0.858) and DVP (0.814) **(c)** . 1hPG, 1 hour plasma glucose; 2hPG, 2 hour plasma glucose; AC, abdominal circumference; DVP, deepest vertical pocket; EFT, epicardial fat thickness; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; PGDM, pregestational diabetes mellitus.

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