European Review for Medical and Pharmacological Sciences 2023; 27: 10620-10630

Predicting adverse perinatal outcomes with fetal modified myocardial performance index and epicardial fat tissue thickness in diabetes-complicated pregnancies

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Abstract. – OBJECTIVE: The aim of this study was to evaluate fetal modified myocardial performance index (mod-MPI) and fetal epicardial fat tissue (EFT) thickness and its association with adverse perinatal outcomes in diabetic pregnant women.

PATIENTS AND METHODS: This was a prospective case-control study including 90 gestational diabetes mellitus (GDM) and 45 pregestational diabetes mellitus (PGDM) and 90 healthy pregnant women (control group). Two-dimensional gray-scale and Doppler fetal echocardiography were used to calculate the mod-MPI. EFT thickness was measured in the hypoechogenic area between the myocardium and the visceral pericardium on the right ventricle by distinguishing it from the pericardial fluid by Doppler ultrasound.

RESULTS: Both mod-MPI values and EFT thickness were significantly higher in diabetic pregnant women ($p<0.001$; for both). No significant differences were observed in mod-MPI values and EFT thickness between pregnant women with GDM and PGDM. In addition, there was no significant difference in fetal mod-MPI values and EFT thicknesses among diabetic pregnant women based on their treatment requirements. The receiver operating characteristic (ROC) curve revealed that mod-MPI value (cut-off 0.54, 95% CI: 0.629-0.837, $p<0.001$, sensitivity 64.6%, specificity 61.7%) and EFT thickness (cut-off 1.85 mm, 95% CI: 0.524-0.750, $p=0.014$, sensitivity 65.8%, specificity 63.9%) could predict adverse neonatal outcomes in diabetic pregnant women. Multivariate regression analysis revealed that both mod-MPI ($p=0.003$) and EFT thickness ($p=0.008$) were independently associated with adverse outcomes.

CONCLUSIONS: Fetal mod-MPI values and EFT thickness increase in pregnancies complicated by diabetes, and these measurements may serve as valuable predictors of adverse perinatal outcomes.

Key Words:
Diabetes, Modified myocardial performance index, Epicardial adipose tissue, Epicardial fat tissue, Pregnancy.

Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic disorder in pregnancy. Its prevalence is approximately 18% and widely varies between populations[1]. Pregestational diabetes mellitus (PGDM) is defined as preconceptionally diabetes mellitus (DM) type I or type II or glucose intolerance, and complicates 1-2% of all pregnancies[2,3]. Glucose intolerance during

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pregnancy can give rise to a spectrum of adverse maternal, fetal, and neonatal outcomes. In the case of PGDM, inadequate glucose control, particularly during conception or the first trimester, may lead to spontaneous recurrent miscarriages and significant congenital abnormalities[4,5]. Furthermore, pregnancies affected by diabetes are linked to unfavorable perinatal consequences, such as shoulder dystocia due to fetal macrosomia, preterm delivery, neonatal hypoglycemia, respiratory distress syndrome (RDS), and neonatal intensive care unit (NICU) admissions[6-8]. Moreover, there is evidence suggesting that diabetes in pregnancy may contribute to long-term adverse outcomes, including myocardial contractility abnormalities in infants or cardiovascular diseases in adulthood[9-12].

Detecting risk factors for adverse outcomes during fetal development is of paramount importance and a central focus of fetal imaging. It has been described in previous studies[13-15] that changes in fetal cardiac structure and function may occur in GDM, apart from structural anomalies. Interventricular septum thickening, myocardial hypertrophy, and increased preload index have been reported[13-15] in the fetal heart during the intrauterine period. Recent investigations[16-18] have also revealed that fetuses of diabetic mothers exhibit an elevated myocardial performance index (MPI), which serves as an indicator of cardiac dysfunction. MPI is a Doppler index that amalgamates systolic and diastolic ventricular myocardial performance, and it has been proposed as a potentially valuable predictor of global cardiac function by Tei et al[19]. Hernandez-Andrade et al[20] also described the modified myocardial performance index (mod-MPI) as an alternative technique with increased interobserver reproducibility that uses mitral and aortic valve opening and closing to clearly reveal the three time periods used for an index of myocardial performance. Mod-MPI has recently been examined[21,22] in various pregnancy-related conditions, including the assessment of fetal cardiac dysfunction in pregestational and gestational diabetes, suggesting its potential in predicting adverse perinatal outcomes[16-18].

Recently, the echocardiographic parameter, epicardial fat tissue (EFT), has emerged[23,24] as a change in fetal cardiac tissue in GDM. EFT is closely associated with metabolic syndrome and diabetes in adults. It is located between the myocardium and the visceral pericardium and is directly attached to the myocardium[25]. Recent studies[26,27] have shown that maternal EFT thickness is associated with adverse perinatal outcomes in diabetic pregnancies. In addition, it has been shown that second-trimester fetal EFT thickness is associated with GDM risk.

In this study, we aimed to evaluate the changes that may occur in fetal cardiac function and cardiac tissue in GDM and PGDM with mod-MPI measurement and EFT thickness measurement, and its association with adverse perinatal outcomes.

Patients and Methods

This prospective case-control study was conducted with pregnant women followed in the Department of Perinatology, University of Health Sciences Tepecik Training and Research Hospital between January 1, 2021, and January 31, 2022. The study protocol was approved by the University of Health Sciences Tepecik Training and Research Hospital Institutional Ethics Committee (approval number: 2020/14-46) and informed consent was obtained from all participants.

A total of 90 GDM and 45 PGDM pregnant women who were referred to our clinic and had no systemic or pregnancy-related disease were included in the study. According to the criteria established by The International Association of Diabetes and Pregnancy Study Groups (IADPSG), a 75-gram oral glucose tolerance test (OGTT) was performed between the 24th and 28th weeks of gestation. GDM was defined as having a fasting plasma glucose (FPG) value of ≥92 mg/dl (5.1 mmol/L) and/or a 1-hour glucose value of ≥180 mg/dl (10.0 mmol/L) and/or a 2-hour glucose value of ≥153 mg/dl (8.5 mmol/L)[28]. PGDM was defined as preconceptional DM type I or type II or glucose intolerance[29]. Additionally, diabetic pregnant women were categorized into subgroups based on their need for insulin therapy. The control group consisted of 90 healthy pregnant women whose gestational age matched that of the diabetic group and who had normal pregnancy follow-up without any comorbidities.

The exclusion criteria for the study were multiple pregnancies, maternal smoking, fetal congenital malformations, fetal cardiac heart rate abnormalities, evidence of placental-related disease (placental-related disease was defined by either the presence of fetal growth restriction, sonographic estimated fetal weight <10th percen-

tile and umbilical artery resistance index >90th percentile for gestational age and/or the presence of hypertensive diseases), tocolytic therapy administration, betamethasone administration.

Ultrasound Examinations

Ultrasound assessments in the third trimester were conducted using a Samsung Ultrasound System HS70A (Samsung Medison Company, Seoul, Republic of Korea) equipped with an abdominal 4-8 MHz curvilinear transducer.

The mod-MPI was calculated in the fetal left ventricle. To calculate the left ventricular mod-MPI (LMPI), a cross-sectional image of the fetal thorax was obtained at the four-chamber view level with the apical projection of the heart. The Doppler sample was opened to 3-4 mm and placed at the internal leaflet of the mitral valve (MV). Due to the proximity of this position to the aortic valve (AV), clicks of both valves corresponding to opening and closing were recorded. The insolation angle was kept as close to 0°-30°. The wall motion filter was set at 300 Hz, and the Doppler sweep velocity was at 5 cm/s. The Doppler gain was minimized to clearly visualize the echoes corresponding to the clicks of the two valves during mitral and aortic waveforms. The time cursor was placed at the beginning of each Doppler click, and three time periods were defined as follows: isovolumetric contraction time (ICT) from the beginning of MV closure to aortic valve AV opening, ejection time (ET) from AV opening to closure, and isovolumetric relaxation time (IRT) from AV closure to MV opening. The mod-MPI was calculated as (ICT+IRT)/ET (Figure 1). The MPI measurement showed a high level of intra-observer agreement [intra-class correlation coefficient (ICC) 0.94 (0.90; 0.98)]. The

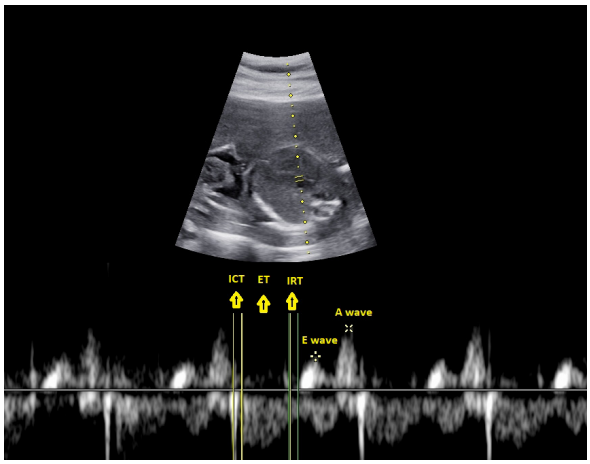

Figure 1. Doppler trace of isovolumetric contraction time (ICT), ejection time (ET), and isovolumetric relaxation time (IRT), and E wave/A wave peak velocities.

E/A ratio was calculated by showing the peak velocities of the E wave (premature ventricular filling) and the A wave (active atrial filling). The E/A ratio measurement showed a high level of intra-observer agreement [ICC 0.94 (0.91; 0.98)].

EFT thickness was measured by obtaining a left ventricular outflow (LVOT) image, as it is ideal for imaging the space between the myocardium and epicardium throughout the right ventricle. EFT was defined as the hypoechogenic area between the visceral pericardium and myocardium, and color Doppler was applied to differentiate it from the pericardial fluid. EFT thickness was measured from the area closest to the baseline, with calipers inner-to-inner (Figure 2). The measurement was repeated three times, and the average was recorded. The EFT thickness measurement showed a high level of intra-observer agreement [ICC 0.95 (0.92, 0.99)].

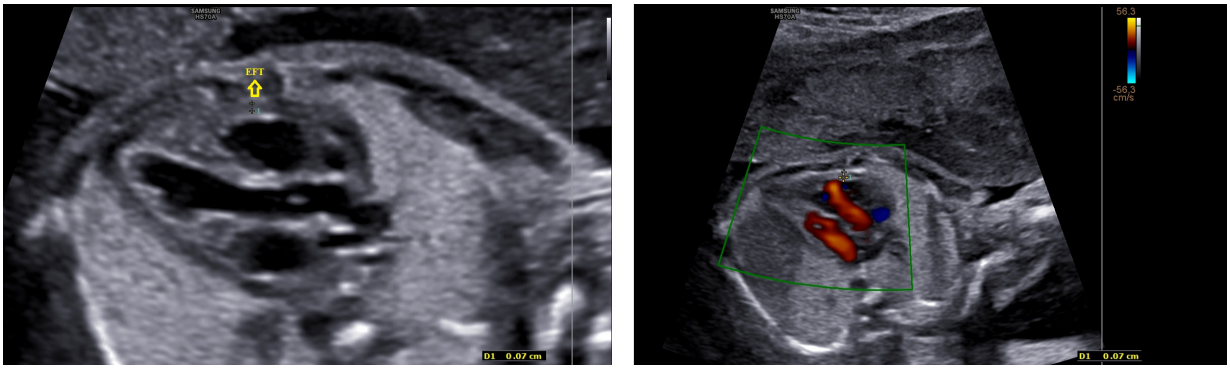

Figure 2. Standardized epicardial fat tissue (EFT) thickness measurement *via* left ventricular outflow tract (LVOT) view was applied to differentiate it from pericardial fluid by Doppler sonography.

The association between fetal ultrasonographic cardiac parameters (LMPI, E/A, and EFT thickness) and adverse perinatal outcomes such as RDS, hypoglycemia, hypocalcemia, hyperbilirubinemia, sepsis, infection of unknown origin, and neonatal intensive care unit (NICU) admission, which may be associated with GDM, were evaluated. In addition, the presence of at least one of the adverse outcomes was defined as a composite adverse outcome and its association with cardiac parameters was examined.

Statistical Analysis

Statistical Package for the Social Sciences version 26.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. The normality distribution of the data was analyzed using the Shapiro-Wilk test. Normally distributed data underwent the Analysis of Variance (ANOVA) test for multiple comparisons, while non-normally distributed data were subjected to the Kruskal-Wallis test. In case of significant difference as a result of the analysis, the homogeneity of the variances was checked to determine between which groups the difference was. If the variances were homogeneous, the Scheffe test, one of the post hoc multiple comparison tests, was used. In cases where the Scheffe test did not determine between which groups the difference was, Bonferroni test, one of the post hoc multiple comparison tests, was used. If the variances were heterogeneous, the Tamhane T2 test, one of the post hoc multiple comparison tests, was used. Independent *t*-test was used in the analysis of paired groups. The Chi-square test was used for categorical variables between groups. Receiver Operating Characteristic (ROC) curves were calculated for mod-MPI and EFT thickness to predict adverse neonatal outcomes in the study groups. Univariate and multivariate regression analysis was used to assess the effect of covariates on adverse perinatal outcomes. Intra-observer variability was assessed using the intra-class correlation coefficient (ICC). $p<0.05$ was considered significant.

Results

Intra-observer variability was assessed using the intra-class correlation coefficient (ICC). A total of 235 pregnant women were included in the study, comprising 135 diabetics and 90 controls. Among the diabetic group, 45 had PGDM and 90 had GDM. Table I presents the maternal characteristics, pregnancy characteristics, and perinatal outcomes for both the diabetic and control groups. Insulin therapy was required for 55 (61.1%) pregnant women with GDM and all pregnant women with PGDM. Gestational weeks at fetal cardiac examinations were similar in all groups ($p=0.714$). The mean gestational weeks at delivery were 37±2 weeks in GDM, 36±1 weeks in PGDM, and 39±2 weeks in controls, and the difference between all groups was significant ($p<0.001$). Adverse perinatal outcomes (including RDS, hypoglycemia, hypocalcemia, hyperbilirubinemia, and NICU admission) and composite adverse outcomes were significantly more common in diabetic pregnancies (both GDM and PGDM).

Fetal cardiac examinations of all groups are presented in Table II. The mod-MPI values of the PGDM and GDM groups were significantly higher than the control group ($p<0.001$). There was no significant difference between the mod-MPI values of the GDM and PGDM groups (0.54±0.06 *vs.* 0.55±0.03). E/A ratios were similar in all groups ($p=0.591$). EFT thickness was similar in the GDM (1.83±1.20) and PGDM (2.04±0.43) groups, but both were significantly higher than the control (1.19±0.28) group ($p<0.001$).

Fetal cardiac examinations according to the treatment requirements of diabetic pregnancies are presented in Table III. There was no significant difference between all fetal cardiac examinations according to treatment requirements in diabetic pregnancies. However, mod-MPI values and EFT thickness were significantly higher in diabetic pregnancies requiring or not requiring treatment than controls.

Echocardiographic and Doppler measurements in study groups with and without adverse perinatal outcomes are presented in Table IV. Mod-MPI values were significantly higher in diabetic pregnancies with adverse perinatal outcomes (0.57±0.05 *vs.* 0.53±0.04; $p<0.001$). In addition, EFT thickness was significantly higher in diabetic pregnancies with adverse perinatal outcomes (2.04±0.59 *vs.* 1.85±1.13; $p=0.013$). However, there was no significant difference between the E/A ratios of the groups ($p=0.542$). The ROC curve analysis for mod-MPI and EFT thickness was evaluated to predict adverse neonatal outcomes. Mod-MPI and EFT thickness revealed significance in predicting adverse neonatal outcomes. According to the ROC analysis, the area under the curve (AUC) for mod-MPI was 0.733 (cut-off 0.54, 95% CI: 0.629-0.837, $p<0.001$, sen-

Table I. Maternal characteristics, pregnancy characteristics, and perinatal outcomes of the diabetic and control groups.

	Gestational diabetics (n:90)	Pregestational diabetics (n:45)	Control group (n:90)	p
Maternal age (year) (mean ± SD)	31 ± 6	31 ± 5	25 ± 6	< 0.001[b,c]
Parity (n,%)				0.022[b,c]
Nulliparous	24 (26.7%)	9 (20%)	37 (41.1%)	
Multiparous	66 (73.3%)	36 (80%)	53 (58.9%)	
BMI at during test (kg/m^2) (mea n ± SD)	31.6 ± 6.4	31.9 ± 6.7	27.9 ± 5.8	< 0.001[b,c]
Treatment requirements (n,%)				< 0.001*
A1	35 (28.9%)	0	0	
A2	55 (61.1%)	45 (100%)	0	
Gestational age at measurement (week) (mean ± SD)	32 ± 4	32 ± 4	32 ± 5	0.714
Gestational age at delivery (week) (mean±SD)	37 ± 2	36 ± 1	39 ± 2	< 0.001[a,b,c]
Primary cesarean section delivery (n,%)	40 (44.4%)	15 (33.3%)	28 (31.1%)	0.154
Birth weight (g) (mean ± SD)	3,235 ± 576	3,043 ± 479	3,192 ± 450	0.115
1st minute APGAR scores < 7 (n,%)	14 (15.6%)	16 (35.5%)	1 (1.1%)	< 0.001[a,b,c]
5th minute APGAR scores < 7 (n,%)	6 (6.6%)	8 (17.7%)	1 (1.1%)	< 0.001[a,b,c]
Neonatal Complications (n,%)				
RDS	16 (17.7%)	12 (26.6%)	2 (2.2%)	< 0.001[b,c]
Hypoglycemia	15 (16.6%)	11 (24.4%)	0	< 0.001[b,c]
Hypocalcemia	9 (10%)	7 (15.5%)	0	0.001[b,c]
Hyperbilirubinemia	8 (8.8%)	7 (15.5%)	1 (1.1%)	0.006[b,c]
Sepsis	2 (2.2%)	2 (4.6%)	2 (2.2%)	0.702
Infection of unknown origin	1 (1.1%)	2 (1.1%)	1 (1.1%)	0.318
NICU admission (n,%)	19 (21.1%)	14 (31.1%)	4 (4.4%)	< 0.001[b,c]
Composite adverse outcomes (n,%)	22 (24.4%)	16 (35.5%)	4 (4.4%)	< 0.001[b,c]
Perinatal mortality (n,%)	0	0	0	N/A

BMI: Body mass index, RDS: Respiratory distress syndrome, NICU: Neonatal intensive care unit. [a]Difference between group 1 and group 2. [b]Difference between group 1 and group 3. [c]Difference between group 2 and group 3 is significant. *Group 1 and group 2 were compared.

Table II. Comparison of fetal cardiac examinations of the groups.

	Gestational diabetics (n:90)	Pregestational diabetics (n:45)	Control group (n:90)	p
Mod-MPI (mean ± SD)	0.54 ± 0.06	0.55 ± 0.03	0.44 ± 0.03	< 0.001[b,c]
E/A (mean ± SD)	0.67 ± 0.12	0.69 ± 0.12	0.66 ± 0.14	0.591
Epicardial fat tissue thickness (mm) (mean ± SD)	1.83 ± 1.20	2.04 ± 0.43	1.19 ± 0.28	< 0.001[b,c]

MPI: Myocardial performance index, E/A: E wave/A wave peak velocity ratio. [b]Difference between group 1 and group 3. [c]Difference between group 2 and group 3 is significant.

Table III. Comparison of fetal cardiac examinations in diabetic pregnancies on treatment requirements and controls.

	Treatment A1 (n:35)	Treatment A2 (n:100)	Control group (n:90)	p
Mod-MPI (mean ± SD)	0.54 ± 0.06	0.54 ± 0.05	0.44 ± 0.03	< 0.001[b,c]
E/A (mean ± SD)	0.69 ± 0.11	0.67 ± 0.12	0.66 ± 0.14	0.527
Epicardial fat tissue thickness (mm) (mean ± SD)	2.15 ± 1.81	1.82 ± 0.48	1.19 ± 0.28	< 0.001[b,c]

MPI: Myocardial performance index, E/A: E wave/A wave peak velocity ratio. [a]Difference between group 1 and group 2. [b]Difference between group 1 and group 3. [c]Difference between group 2 and group 3 is significant.

Table IV. Echocardiographic and Doppler measurements in study groups with and without adverse perinatal outcomes.

	Mod-MPI (mean ± SD)	p	E/A (mean ± SD)	p	Epicardial fat tissue thickness (mm) (mean ± SD)	p
Composite adverse outcomes		< 0.001		0.542		0.013
Yes (n:38)	0.57 ± 0.05		0.67 ± 0.13		2.04 ± 0.59	
No (n:97)	0.53 ± 0.04		0.67 ± 0.12		1.85 ± 1.13	
Neonatal Complications (n,%)						
RDS		0.015		0.696		0.628
Yes (n:28)	0.55 ± 0.05		0.66 ± 0.11		1.94 ± 0.50	
No (n:107)	0.53 ± 0.05		0.67 ± 0.12		1.86 ± 1.29	
Hypoglycemia		0.573		0.128		0.891
Yes (n:26)	0.54 ± 0.05		0.70 ± 0.14		1.88 ± 0.55	
No (n:109)	0.54 ± 0.05		0.66 ± 0.11		1.90 ± 1.10	
Hypocalcemia		0.540		0.590		0.576
Yes (n:16)	0.54 ± 0.05		0.68 ± 0.14		1.77 ± 0.62	
No (n:119)	0.55 ± 0.07		0.67 ± 0.11		1.92 ± 1.05	
Hyperbilirubinemia		0.522		0.252		0.878
Yes (n:15)	0.54 ± 0.07		0.71 ± 0.10		1.95 ± 0.76	
No (n:120)	0.54 ± 0.05		0.67 ± 0.12		1.89 ± 1.03	
Sepsis		0.734		0.001		0.852
Yes (n:4)	0.55 ± 0.04		0.73 ± 0.04		1.96 ± 0.73	
No (n:131)	0.54 ± 0.05		0.66 ± 0.12		1.89 ± 1.03	
Infection of unknown origin		0.315		0.270		0.555
Yes (n:3)	0.56 ± 0.04		0.72 ± 0.04		2.20 ± 0.76	
No (n:132)	0.54 ± 0.05		0.67 ± 0.12		1.88 ± 1.02	
NICU admission		0.112		0.805		0.855
Yes (n:33)	0.55 ± 0.05		0.67 ± 0.11		1.88 ± 0.49	
No (n:102)	0.53 ± 0.05		0.67 ± 0.12		1.91 ± 1.39	

MPI: Myocardial performance index, E/A: E wave/A wave peak velocity ratio, RDS: Respiratory distress syndrome, NICU: Neonatal intensive care unit. Composite adverse outcomes include the presence of at least one of the adverse outcome: respiratory distress syndrome, hypoglycemia, hypocalcemia, hyperbilirubinemia, sepsis, infection of unknown origin and, neonatal intensive care unit admission.

sitivity 64.6%, specificity 61.7%), for EFT thickness, it was 0.637 (cut-off 1.85 mm, 95% CI: 0.524-0.750, p=0.014, sensitivity 65.8%, specificity 63.9%) (Figure 3).

Univariate and multivariate regression analysis of parameters affecting adverse perinatal outcomes in study groups are shown in Table V. Univariate analysis revealed that nulliparity

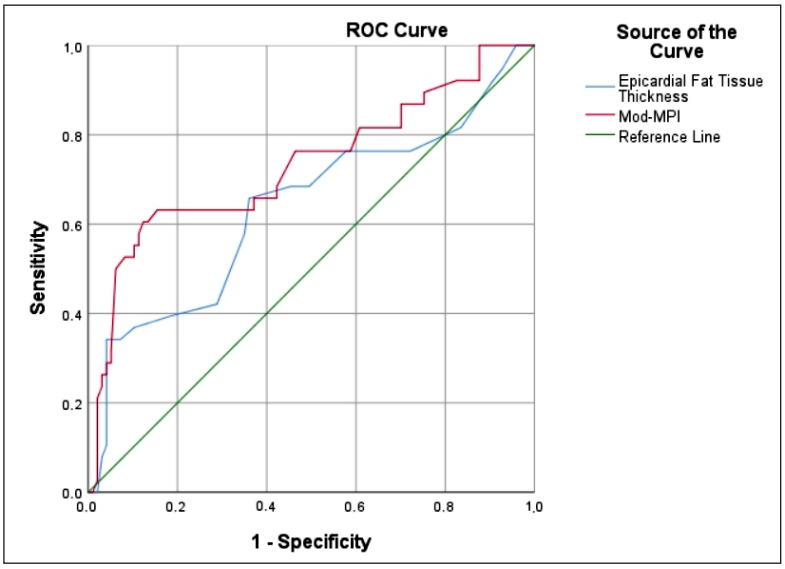

Figure 3. Receiver operating characteristic (ROC) curve for fetal mod-MPI and EFT thickness in predicting adverse neonatal outcomes in the study groups: (AUC: 0.733, 95% CI: 0.629-0.837, p<0.001 for mod-MPI), (AUC: 0.637, 95% CI: 0.524-0.750, p=0.014 for EFT).

Table V. Univariate and multivariate analysis of the parameters affecting adverse perinatal outcomes in study groups.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Maternal age (year)	1.038 (0.974-1.107)	0.248	1.054 (0.963-1.154)	0.257
Nulliparity	4.098 (1.779-9.441)	0.001	2.963 (0.944-9.300)	0.063
BMI at during test (kg/m^2)	1.063 (1.002-1.127)	0.044	1.046 (0.971-1.126)	0.239
A2 treatment requirements	1.446 (0.590-3.549)	0.420	1.679 (0.500-5.635)	0.401
Gestational age at delivery (week)	0.918 (0.709-1.189)	0.518	1.196 (0.782-1.831)	0.409
Birth weight (g)	1.000 (1.000-1.001)	0.327	1.000 (0.999-1.001)	0.714
1st minute APGAR scores < 7	0.706 (0.520-0.959)	0.026	1.563 (0.578-3.192)	0.133
5th minute APGAR scores < 7	0.785 (0.501-1.232)	0.293	1.301 (0.497-3.402)	0.592
Mod-MPI	2.649 (1.721-6.183)	< 0.001	2.051 (1.425-5.607)	0.003
E/A	0.963 (0.042-22.217)	0.981	1.049 (0.012-90.934)	0.983
Epicardial fat tissue thickness (mm)	2.217 (1.547-4.529)	0.001	1.416 (1.354-3.639)	0.008

BMI: Body mass index, MPI: Myocardial performance index, E/A: E wave/A wave peak velocity ratio.

(p=0.001), body mass index (BMI) (p=0.044), 1st minute APGAR scores <7 (p=0.026), mod-MPI (p<0.001) and, EFT thickness (p=0.001) were associated with adverse perinatal outcomes. Multivariate analysis was analyzed to determine which parameters were independently related to adverse outcomes and revealed that mod-MPI (p=0.003), and EFT thickness (p=0.008) were independently associated with adverse perinatal outcomes.

Discussion

In this study, we evaluated fetal cardiac mod-MPI and EFT thickness in pregnancies complicated with GDM and PGDM. Our data showed that fetal MPI values indicating globular (systolic and diastolic) cardiac function were significantly higher in diabetic pregnant. Fetal EFT thickness was also significantly higher in diabetic pregnant women. Fetal mod-MPI values and EFT thicknesses did not differ significantly between the GDM and PGDM groups, and also between the groups requiring and not requiring treatment in diabetic pregnant women. Importantly, our study demonstrated that fetal mod-MPI values and EFT thicknesses were significantly increased in diabetic pregnant women with adverse perinatal outcomes, suggesting that mod-MPI and EFT thickness may serve as predictive indicators for adverse perinatal outcomes. Additionally, our analysis revealed that fetal mod-MPI and EFT were independently associated with adverse perinatal outcomes.

Numerous studies[30,31] have illuminated the impact of diabetes on cardiac function in adults. Moreover, prior research[13-15] has indicated that pregnancies complicated by diabetes can influence fetal heart structure. These effects manifest as interventricular septal thickening, myocardial hypertrophy, and an increased preload index observed in gestational diabetic fetuses. Furthermore, studies[9-11] have postulated that intrauterine exposure to a diabetic environment can lead to long-term adverse outcomes, including myocardial contraction abnormalities in infancy and cardiovascular diseases in adulthood.

Recent studies[16-18] have suggested that fetal mod-MPI values, indicative of fetal cardiac dysfunction, increase in pregnancies complicated by diabetes. In addition, gestational or pregestational diabetic pregnancies do not make a significant difference in fetal mod-MPI values. Our data align with these prior findings, as we observed no significant difference in fetal mod-MPI values between GDM and PGDM pregnancies. However, studies showed conflicting results between glucose regulation and treatment requirements and fetal mod-MPI. Figueroa et al[18] found that the fetal mod-MPI values of the pregnant women who required insulin therapy for glucose regulation were significantly higher than the pregnant women who had glucose regulation only with diet. Conversely, in the study of Bhorat et al[16] with well-controlled diabetic pregnancies, they showed that the requirement for treatment for glucose regulation did not lead to a significant difference in mod-MPI values. Similarly, Sanhal et al[17] showed that glucose regulation and insulin therapy requirements did not affect fetal mod-MPI values in diabetic pregnancies. Our findings also supported that the requirement for treatment had no effect on fetal cardiac function. HbA1c

levels reflect good control with mean blood glucose values over the past 2-3 months and do not take into account periods of blood glucose imbalance, which is the main factor causing fetal pancreatic hyperplasia. Hyperinsulinemia and hyperplasia occur with an exaggerated insulin response to any glucose load in the fetal pancreas. In addition, pregnant women who are classified as well-controlled and do not require treatment may have sub-optimal control in the pre-diagnosis period or gestational diabetes diagnosis may be delayed after fetal pancreatic hyperplasia occurs due to persistent hyperglycemia. In recent studies[32,33], ultrasonographic evaluation of the fetal pancreas in GDM cases showed a significant increase in its size even in the early second trimester. These findings suggest that early pregnancy-onset diabetes and hyperinsulinism may be associated with a long-term fetal abnormal metabolic environment.

EFT is located between myocardium and visceral pericardium and has functions such as protecting the heart against hypothermia, absorbing high circulating free fatty acids and providing energy when necessary[25,34]. It has been shown in many studies[35,36] that increased EFT thickness is associated with metabolic syndrome, coronary heart diseases, impaired glucose regulation and DM in adults. In addition, Liu et al[27] showed that maternal EFT thickness between 16-20 weeks of gestation was significantly higher in pregnant women who developed GDM and suggested that EFT thickness may predict the risk of GDM. Recent studies[26,37] have suggested that fetal EFT thickness increases in pregnancies complicated with diabetes. Yavuz et al[26] examined fetal EFT thickness in pregnant women with GDM in the second trimester and found that fetal EFT thickness was significantly higher in GDM cases. Akkurt et al[37] also found that fetal EFT thickness was significantly higher in PGDM and GDM compared to controls. They also suggested that EFT thickness increased with the week of gestation and was higher in PGDM cases than in GDM cases. Our data supported previous studies and fetal EFT thickness in the third trimester was significantly higher in diabetic pregnancies. However, in contrast to Akkurt et al[37], there was no significant difference in fetal EFT thicknesses in PGDM and GDM cases in our study. They stated that an increase in EFT is expected from early pregnancy in PGDM and that the increase in EFT is evident in the third trimester[37]. Conversely, previous studies[32,33] have shown that fetal metabolic changes in GDM can occur in the early second trimester. Additionally, evidence[27] that maternal EFT increases in pregnant women even before the onset of GDM supports our findings.

In this study, we evaluated the association of fetal mod-MPI and EFT thickness with adverse perinatal outcomes and found that both were associated with adverse perinatal outcomes. We also found a significant cut-off value with the receiver operating characteristic curve for both mod-MPI and EFT thickness in predicting adverse perinatal outcomes. Previous studies[16,17] have also shown that fetal mod-MPI values can predict adverse perinatal outcomes. Bhorat et al[16] reported a 0.83 mod-MPI z-score of area under the ROC curve with 90% sensitivity and 74% specificity for predicting adverse perinatal outcomes. Sanhal et al[17] found the optimal cut-off level for mod-MPI>0.39, with a sensitivity of 90.9% and a specificity of 47.7% for predictivity of adverse perinatal outcomes. In our study, the optimal cut-off mod-MPI value was 0.54, with a sensitivity of 64.6% and a specificity of 61.7% in the predictivity of adverse perinatal outcomes. The different mod-MPI cut-off levels in the studies may be due to differences in complication rates between studies, differences in the characteristics of the study population, and different management strategies of the clinics. To our knowledge, fetal EFT thickness to predict adverse perinatal outcomes has not been studied before. Liu et al[27] found the maternal EFT thickness cut-off value of 5.49 mm in predicting adverse perinatal outcomes in pregnant women with GDM. In this study, we found the optimal cut-off value for fetal EFT thickness was 1.85 mm, with a sensitivity of 65.8% and a specificity of 63.9% in the predictivity of adverse perinatal outcomes. Our findings showed that fetal EFT thickness may be useful in monitoring diabetic pregnancies and predicting adverse perinatal outcomes. Nevertheless, further research is warranted to assess its relationship with adverse perinatal outcomes comprehensively.

Limitations

This study is subject to certain limitations. While diabetic pregnant women were assessed based on their treatment requirements, the study did not encompass maternal serum insulin and glycosylated hemoglobin measurements. Additionally, a more comprehensive understanding of the infant's cardiac status during long-term postnatal follow-up could have been obtained

through neonatal echocardiography evaluation. This study also has strengths. In addition to its prospective design, the study included a large number of cases. Moreover, this is the first study in which fetal mod-MPI and EFT thickness were evaluated together in diabetic pregnancies. Finally, to our knowledge, this is the first study that evaluates the association between fetal EFT thickness and adverse perinatal outcomes.

Conclusions

Our findings indicate that fetal cardiac mod-MPI values and EFT thicknesses increase in pregnancies complicated by diabetes, and these alterations have predictive value for adverse perinatal outcomes. Notably, the changes in fetal cardiac EFT and mod-MPI are not influenced by treatment requirements or the type of diabetes. Nonetheless, further research tracking fetal cardiac status in the neonatal period could offer valuable support to these observations.

Conflict of Interest
The authors declare that they have no conflict of interests.

Funding
The authors received no funding for this work.

Authors' Contribution
Ibrahim Omeroglu: conducted the population study, analyzed and interpreted the data, and drafted the manuscript. Hakan Golbasi: conducted the population study and drafted the manuscript. Burak Bayraktar: participated in interpretation, and draft revision. Ceren Golbasi and Suna Yildirim Karaca: making critical revisions. Tulay Demircan: assisted with data collection and analysis. Atalay Ekin: validation and final approval of the version of the article to be published.

Availability of Data and Materials
The data supporting this study is available through the corresponding author upon reasonable request.

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Ethics Approval
The study protocol was approved by the University of Health Sciences Tepecik Training and Research Hospital Institutional Ethics Committee (approval number: 2020/14-46).

Informed Consent
Informed consent was obtained from all participants.

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