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Essay

Effects of Gestational Diabetes Mellitus on Fetal Cardiac Morphology

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Abstract: Objective: This study aims to investigate the possible effects of gestational diabetes mellitus (GDM) on fetal heart structure and the relationship of this effect with maternal blood sugar control. **Materials and Methods:** In this cross-sectional study, 19 women with GDM at 24–36 weeks of gestation (case group) and 21 healthy pregnant women at the same weeks of gestation (control group) were examined. Fetal heart structure was evaluated by ultrasonography, interventricular septum (IVS) thickness, right and left ventricular sphericity indices, global sphericity index (GSI) and cardio-thoracic ratio were measured. In addition, mothers' HbA1c values (an indicator of blood sugar control) were recorded. **Result:** An increase in IVS thickness was observed in the fetuses of mothers with GDM. A more rounded trend was observed in the right ventricular structure, but this did not create a significant difference. No significant relationship was found between maternal blood sugar control and fetal heart structure. **Conclusion:** This study examined the effects of gestational diabetes on fetal cardiac morphology and the relationship of this effect with maternal glycemic control. Babies of mothers with GDM had a significantly thicker interventricular septum. A more rounded trend was detected in the right ventricular structure. However, this change was not found to be statistically significant. In addition, no significant correlation was found between maternal glycemic control and fetal cardiac morphology.

Keywords: BMI (body mass index); OGTT (oral glucose tolerance test); GDM (gestational diabetes mellitus); echocardiography; fetal cardiac morphology

1. Introduction

Gestational diabetes mellitus (GDM) is a common metabolic disorder during pregnancy that significantly increases perinatal morbidity and mortality [1]. When we look at the long-term risks in addition to the effects of GDM in the perinatal period, childhood obesity, type 2 diabetes and cardiovascular complications are seen at older ages. Early detection and proper management of GDM is critical not only to ensure a healthy pregnancy outcome, but also to promote the long-term health and well-being of both mother and child. The pathogenesis of GDM is associated with insulin resistance and various hormonal changes [2]. It is well known that maternal hyperglycemia adversely affects fetal development, particularly with notable effects on the fetal heart [3,4]. Animal studies have shown that maternal hyperglycemia can lead to remodeling in fetal myocardial fibers, which may increase the risk of cardiovascular diseases later in life.

Although there are studies in the literature examining the effects of GDM on the fetal cardiovascular system, these studies typically focus on pre-gestational diabetes and cardiac functions [5].

In this study, the effects of GDM on fetal cardiac morphology and the relationship of these effects with maternal glycemic control were examined. Specifically, the study evaluated the structural cardiac changes in fetuses of pregnant women with GDM and the correlation of these changes with maternal blood glucose control. This study may provide important insights into understanding the effects of GDM on fetal cardiac morphology and developing potential intervention strategies.

2. Materials and Methods

In this study, cardiac morphological malformations in the fetuses of pregnant women diagnosed with Gestational Diabetes Mellitus (GDM) between 24-36 weeks of gestation and the relationship between these changes and maternal glycemic control level were analyzed.

The study included women who applied to the Perinatology Polyclinic of the Department of Obstetrics and Gynecology of Ege University between February 2022 and June 2022 and were diagnosed with GDM between 24-28 gestational weeks. A total of 40 patients, including 19 diabetic pregnant women and 21 control groups, were selected according to the single-step 75 g oral glucose tolerance test (OGTT). This test includes three-step glucose level measurements, and in this study, IADPSG's cut-off values were taken as basis.

All examinations were performed by the same, single observer, with the patient in the supine position, using the GE Voluson E8 ultrasound device's 2-9 MHz wide-band convex abdominal probe (C2-9-D) and obstetric transducer. Cardiac structure was evaluated using gray scale and fetal M mode. Images were taken for two or three seconds while the mother was holding her breath and the fetus was not moving, in a 4-chamber view of the fetal heart, perpendicular to the long axis or as close to the perpendicular position as possible. Measurements were made end-diastolically, and the interventricular septum (IVS) thickness (with M-mode), left ventricular (LV) and right ventricular (RV) sphericity index (ratio of the apico-basal ventricular length to the transverse length at the level of the relevant atrio-ventricular valve) was measured, and the global sphericity index (GSI) was calculated by dividing the basal-apical length of the fetal heart at the end of diastole by the transverse width at the end of diastole. In addition, the fetal heart rate was recorded and the fetal cardiothoracic ratio (fetal heart circumference divided by the fetal thoracic circumference) was calculated. HbA1c(%) was recorded as biochemical parameter.

The inclusion criteria for the GDM group were; singleton pregnancies of mothers aged 18 years and over, a positive diagnosis for GDM at Ege University Hospital, and a gestational age between 24-36 weeks. The exclusion criteria for the GDM and control groups were: fetuses with structural or chromosomal anomalies; fetal tachycardia (FHR > 160 beats/minute); maternal smoking during pregnancy; twin or multiple pregnancies; inadequate ultrasonographic images; any maternal disease including chronic hypertension, diabetes mellitus, human immunodeficiency virus or hepatitis infection before pregnancy, thyroid disease or other uncategorized diseases that would impair fetal heart morphology and function, and fetuses with congenital heart disease, arrhythmia or malformations involving other organs; fetuses with intrauterine growth retardation (EFW<10p) and mothers' refusal to give written informed consent.

2.1. Ethics Committee Decision

Our study was designed in accordance with the Declaration of Helsinki. Ethical approval of our study was obtained from Ege University ethics committee (Study Ethics Committee no: 22-2T/28). The patients included in the study were informed, and written informed consent was obtained.

2.2. Statistical Analysis

The statistical analysis of the data was conducted using the SPSS 22.0 software package. The Kolmogorov-Smirnov test was employed to assess whether the data followed a normal distribution. For data with a normal distribution, results are expressed as mean \pm standard deviation, whereas for data not following a normal distribution, results are presented as median (minimum-maximum). Comparisons between groups were made using the independent samples t-test for normally distributed data, and the Mann-Whitney U test for data not normally distributed. Pearson correlation analysis was used for correlation assessment. A significance level of $p < 0.05$ was considered statistically significant.

3. Results

A total of 40 pregnant women were included in the study, consisting of 19 GDM patients as the case group and 21 healthy pregnant women as the control group. These participants were selected from pregnant women who presented to the Perinatology Clinic of Ege University's Department of Obstetrics and Gynecology between February and June 2022, following the application of various exclusion criteria.

The age range of participants in the study was 19-41 years, with a mean age of 29 years. Among all cases, the smallest gestational week was 25 and the largest gestational week was 35. The mean BMI index of the participants was found to be 26.6. The mean HbA1c value was 5.02 across the entire study population. 40% of all participants have a family history of diabetes. In the GDM group, 63.2% of the pregnant women managed their blood sugar levels through diet, while 36.8% required insulin therapy. No patients were using oral antidiabetic medications. Blood glucose regulation thresholds were determined according to ACOG (American College of Obstetricians and Gynecologists) recommendations (Table 1).

Table 1. Distribution characteristics of demographic data and patient measurements of all participants.

		All participants
		Mean \pm SD (Min-Max)
Age		29,1 \pm 4,6 (19-41)
BMI		26,6 \pm 4,3 (18,8-37,8)
Family history of diabetes n (%)		16 (40,0)
Gestational week		30,4 \pm 2,97 (25-35)
OGTT n (%)	Normal	21 (52,5)
	GDM	19 (47,5)
HbA1c		5,02 \pm 0,38 (4,4-6)
IVS thickness		5,07 \pm 1,08 (2,9-7,5)
LV sphericity index		1,85 \pm 0,48 (1-2,9)
RV sphericity index		1,71 \pm 0,39 (0,7-3)
Global sphericity index		1,27 \pm 0,15 (0,9-1,6)
CTR		0,43 \pm 0,11 (0,2-0,6)
GDM therapy n (%)	Diet	12 (63,2)
	insulin	7 (36,8)
FHR		142,8 \pm 7,9 (124-160)

BMI: Body mass index, IVS: Interventricular septum, LV: Left ventricul, RV: Right ventricul, CTR: Cardio thoracic ratio, FHR: Fetal heart rate, GDM: Gestational diabetes mellitus, OGTT: Oral glucose tolerance test.

There was no significant difference between the GDM and control groups in terms of age and gestational week. However, BMI and HbA1c values were significantly higher in the GDM group ($p=0.033$ and $p=0.049$, respectively). It was observed that 42.1% of pregnant women with GDM had a family history of diabetes in first-degree relatives (mother, father, and siblings). The fetal heart rate was similar in both groups. Ultrasound measurements revealed that IVS thickness was significantly increased in the GDM group ($p=0.048$). While there was no significant difference in the global sphericity index (GSI) and LV sphericity indices, the RV sphericity index was lower in the GDM group, but this difference was not statistically significant. The cardiothoracic ratio was significantly lower in the GDM group ($p<0.001$) (Table 2).

Table 2. Comparisons of demographic data and patient measurements by case and control groups.

	Normal	GDM	p*
	Mean \pm SD	Mean \pm SD	
	Min-Max (Median)	Min-Max (Median)	
Age	28,4 \pm 4,5	29,9 \pm 4,7	0,320
	19-37 (29)	23-41 (29)	
BMI	25,2 \pm 3,3	28,1 \pm 4,83	0,033
	18,8-30,1 (25)	22-37,8 (26,9)	
Family history of diabetes n (%)	8 (38,1)	8 (42,1)	0,796 [†]
Gestational week	30,81 \pm 3,04	30,0 \pm 2,91	0,396
	25-35 (31)	26-35 (30)	
HbA1c	4,9 \pm 0,26	5,15 \pm 0,45	0,049
	4,6-5,5 (4,9)	4,4-6 (5)	
IVS thickness	4,75 \pm 1,01	5,42 \pm 1,07	0,048
	2,9-7,5 (4,54)	3,1-7 (5,35)	
LV sphericity index	1,81 \pm 0,52	1,89 \pm 0,45	0,587
	1-2,9 (1,75)	1,3-2,8 (1,74)	
RV sphericity index	1,73 \pm 0,42	1,68 \pm 0,37	0,742
	1,2-3 (1,7)	0,7-2,3 (1,75)	
Global sphericity index	1,27 \pm 0,13	1,27 \pm 0,17	0,998
	1-1,5 (1,29)	0,9-1,6 (1,27)	
CTR	0,50 \pm 0,04	0,36 \pm 0,13	<0,001
	0,5-0,6 (0,49)	0,2-0,5 (0,42)	
FHR	142,8 \pm 9,1	142,8 \pm 6,6	0,991
	124-160 (145)	130-155 (143)	

BMI: Body mass index, IVS: Interventricular septum, LV: Left ventricul, RV: Right ventricul, CTR: Cardio thoracic ratio, FHR: Fetal heart rate, GDM: Gestational diabetes mellitus.

According to the data in the study, there was no significant correlation between the HbA1c value of fetal cardiac morphological ultrasonographic measurements in the GDM group (Table 3).

Table 3. Investigation of the relationship between HbA1c and fetal cardiac indices.

N=19		HbA1c	IVS thickness	LV sphericity index	RV sphericity index	Global sphericity index	CTR
IVS thickness	r	0,149					
	p	0,542					
LV sphericity index	r	-0,419	0,329				
	p	0,074	0,169				
RV sphericity index	r	-0,321	0,071	0,29			
	p	0,180	0,772	0,228			
Global sphericity index	r	-0,051	-0,201	0,226	-0,021		
	p	0,836	0,408	0,353	0,933		
CTR	r	0,041	0,187	0,134	0,339	-0,35	
	p	0,867	0,443	0,585	0,156	0,142	
FHR	r	0,052	-0,166	-0,063	0,118	0,317	-0,335
	p	0,832	0,498	0,797	0,632	0,187	0,161

N: Number, IVS: Interventricular septum, LV: Left ventricular, RV: Right ventricular, CTR: Cardio thoracic ratio, FHR: Fetal heart rate.

4. Discussion

Gestational diabetes mellitus (GDM) is a common metabolic disorder encountered during pregnancy that negatively affects maternal and fetal health [6]. The emergence of GDM is linked to insulin resistance and various hormonal changes [2]. It is well established that elevated blood sugar levels (hyperglycemia) in the mother can adversely affect fetal development, particularly the fetal heart [7,8]. Animal studies have demonstrated that maternal hyperglycemia can lead to remodeling of the fetal heart muscle fibers, which may increase the risk of cardiovascular disease later in life [3,4].

There are several studies in the literature investigating the effects of GDM on the fetal cardiovascular system; however, these studies generally focus on pre-gestational diabetes and cardiac functions [5]. In this study, the effects of GDM on fetal heart structure and the relationship between these effects and maternal blood sugar control were examined. Specifically, changes in the heart structure of fetuses of mothers with GDM and the correlation of these changes with maternal blood sugar control were evaluated. Consistent with previous studies, this study found that body mass index (BMI) and HbA1c (average blood sugar level) values were significantly higher in the GDM group compared to the control group. The higher percentage of firstdegree relatives with a history of diabetes in the GDM group (42.1%) also underscores the genetic predisposition associated with GDM. The strengths of the study include the similar number of cases in the case and control groups, the comparable average ages, and the fact that the control group was selected from pregnancies with gestational weeks similar to those in the GDM group.

In a study conducted by Wang et al., it was reported that the fetal heart in the GDM group had a rounder shape compared to the control group [9]. However, in this study, the global sphericity index (GSI) was found to be similar in both groups, and no significant difference was detected between the groups. This discrepancy could be due to the fact that most of the women with GDM in this study had good glycemic control achieved through diet, without the need for medication. Nevertheless, consistent with Wang et al.'s study, this study also found that the right ventricle (RV) sphericity index was significantly lower than the left ventricle (LV) sphericity index, indicating that the RV had a more spherical shape. This finding is also in line with the results of studies by Vore et al. [10] and Patey et al. [11].

Garg et al. reported that even when blood sugar levels were controlled in mothers with GDM, there was a significant increase in the end-diastolic wall thickness of the IVS, LV, and RV in their fetuses [12]. Similarly, Balli et al. observed a marked increase in IVS thickness, particularly in the third trimester, in the fetuses of mothers with diabetes [13]. Consistent with these findings, this study also found that IVS thickness was significantly higher in the GDM group compared to the control group. However, the limitations of this study include its cross-sectional design, the lack of follow-up on IVS thickness and other morphological changes throughout the later weeks of pregnancy, the wide range of gestational weeks (24-36 weeks) among the included cases, and the absence of subgroup analyses based on gestational week or glycemic control.

In a study by Al-Biltagi et al., it was shown that increased IVS thickness in the fetuses of women with pregestational diabetes and poor blood sugar control was associated with adverse pregnancy outcomes, including stillbirth [14]. This finding is important as it suggests that fetal heart changes could be predictive of perinatal complications and offer opportunities for early intervention. In addition, postnatal ultrasound heart evaluations could be conducted in future studies to examine the neonatal implications of GDM's fetal effects.

A study by Tejaswi et al. reported a significant relationship between fetal myocardial thickening and maternal glycemic control in pregnancies complicated by GDM [15]. However, in this study, no significant relationship was found between fetal cardiac morphological ultrasound parameters and HbA1c levels in the GDM group. The conflicting results could be attributed to the small sample size, the use of HbA1c as a single biochemical marker instead of daily maternal blood sugar monitoring, and the fact that most of the cases included in the study were well-controlled through diet alone. From another perspective, considering the findings of Balli et al., who observed significant structural changes in the fetal heart and an increase in IVS thickness towards the end of pregnancy, the early average gestational age of 30 weeks in this study might have been too soon for cardiac morphological changes to fully manifest, potentially leading to inconsistent results.

In a study on rats conducted by Lehtoranta et al., it was shown that hyperglycemia, as a result of impaired maternal glucose metabolism, led to general enlargement of the fetal heart and an increase in the cardiothoracic ratio, as calculated through ultrasound evaluation [16]. Similarly, a study by Gandhi et al. on pregnancies complicated by GDM reported an increase in the cardiothoracic ratio [17]. However, in contrast to the literature, this study found that the fetal cardiothoracic ratio was significantly lower in the GDM group compared to the control group. This discrepancy may be due to the fact that only one observer was involved in the study, the absence of a second control observer, and potential errors that may have occurred during the imaging/measurement process.

5. Conclusions

This study was conducted between February and June 2022 at Ege University, involving 19 pregnant women with GDM and 21 healthy pregnant women at 24-36 weeks of gestation. Fetal heart structure was evaluated using ultrasonography, and measurements of interventricular septum (IVS) thickness, ventricular sphericity indices, global sphericity index (GSI), cardiothoracic ratio, and HbA1c levels were recorded.

In the GDM group, BMI and HbA1c values were found to be significantly higher compared to the control group. If we look at the ultrasonographic measurements; IVS thickness was significantly increased in the GDM group compared to the control group. While the RV sphericity index was lower in the GDM group, this difference was not statistically significant. The cardiothoracic ratio was significantly lower in the GDM group. No significant correlation was found between fetal cardiac measurements and HbA1c levels in the GDM group.

Limitations

The limitations of this study include the small sample size, the use of a single glycemic control parameter, and the lack of subgroup analysis. Future research should be supported by larger, multicenter, prospective randomized controlled trials to confirm and expand upon these findings.

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