Original Research Article

Cardiac Function and Structure in Fetuses of Gestational and Pre-gestational Diabetic Mothers

Abstract

Background: The prevalence of maternal hyperglycemic disorders during pregnancy is increasing due to the obesity epidemic and increasing age of the pregnant mothers. This study aimed to assess the cardiac function and structure in fetuses of gestational and pre-gestational diabetic mothers compared to those of healthy mothers using fetal echocardiography.

Methods: This cross-sectional study included a total number of 60 pregnant women, they were classified into three equal groups; group I included 20 pregnant women with pre-gestational diabetes mellitus (GDM), group II included 20 pregnant women with GDM, and group III included 20 healthy pregnant women as the control group. These women were subjected to complete history taking, laboratory investigations, and fetal echocardiography evaluation for cardiac function using M mode, 2 dimensional, and pulsed wave Doppler.

Results: Interventricular septum (IVS) as well as left ventricular (LV**)** wall thickness were significantly increased in diabetic mothers compared to the healthy control group. Diabetes decreased LV diastolic function but did not affect LV systolic function. IVS thickness has a significant positive correlation with all indices of DM such as HbA1c, fasting blood glucose, and 2 hours postprandial glucose level. While mitral E/A ratio had a significant negative correlation with duration of DM.

Conclusions: IVS thickness is the most affected structures in fetal heart of diabetic mothers. Moreover, LV diastolic function was affected in such fetuses unlike the systolic function. Fetal echocardiography in diabetic mothers is highly important, not only to diagnose structural abnormalities but also for evaluation of cardiac function of the fetuses

Keywords: Fetal Echocardiography; Cardiac Function; Fetuses; Gestational and Pre-gestational Diabetic Mothers.

Introduction:

The prevalence of maternal hyperglycemic disorders during pregnancy is increasing in the population due to obesity epidemic and increasing age of the pregnant mother [1]. Maternal hyperglycemic disorders include type 1 and 2 diabetes mellitus (T1/T2DM) and gestational diabetes mellitus (GDM). T1/ T2DM is a state of glucose intolerance occurring independently of pregnancy, while GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy and is typically tested after the 16th week of gestation and usually resolves after delivery [2].

Maternal hyperglycemic disorders are associated with fetal cardiac structural and functional alterations such as congenital cardiac malformations and cardiac hypertrophy. Maternal DM affects the structure and function of the fetal heart and alters the fetal placental circulation from embryonic development in the first trimester until the perinatal period through the second and third trimesters. It depends on timing and blood glucose level. Hyperglycemia in the first trimester can interfere with organogenesis and leads to conotruncal defects and if occurs after that time, it increases the risk of cardiac dysfunction [3].

Hyperglycemia may influence all stages of cardiac development, including cardiac morphogenesis, placental development, and fetal circulation. Fetal hyperinsulinemia and increased expression or affinity of insulin receptors, followed by changes in the metabolism of diabetic mothers, lead to alterations in cardiomyocytes gene expression and subsequent structural and functional malformation in the fetal heart [4].

High glucose levels during critical periods of morphogenesis appear to be the major teratogen in diabetic pregnancy. An additional possible mechanism is a diabetes-induced hypoxia, apparently due to hyperglycemia [4]. Moreover, researchers have reported an inverse relationship between hemoglobin A1C (HbA1c) and fetal cardiac function [5].

The functional fetal cardiac evaluation has been a goal of many fetal medicine researchers for a long time. Whereas ultrasound (US) morphological cardiac examination is now part of routine fetal surveillance, methods of fetal cardiac function measurement have been considered difficult, poorly reproducible, and technically challenging [6-7].

This study aimed to assess the cardiac function and structure in fetuses of gestational and pre-gestational diabetic mothers, compared to those of healthy mothers, using fetal echocardiography.

Patients and Methods:

This cross-sectional study was conducted at Tanta University Hospital and Ain Shams University Hospital, during the period from January 2018 to November 2020. The research protocol was approved by the institute Ethics Committee and written informed consents for fetal echocardiography were obtained from the patients.

The study included 40 pregnant diabetic mothers (study groups) and 20 healthy pregnant mothers (control group). The subjects were classified into the three equal groups:

Group I which included 20 pregnant women with pre GDM.

Group II which included 20 pregnant women with GDM

Group III which included 20 healthy pregnant women as the control group.

Pregnant women with gestational and pre-gestational diabetes mellitus at 28 weeks of gestation were included.

Mothers with chronic diseases [e.g., cardiac, hepatic, endocrinal, hematologic or renal diseases], mothers with systemic disorders [e.g., collagen diseases as SLE, hypertension or pre-eclampsia], mothers taking drugs that can affect the function or rhythm of fetal heart [e.g., corticosteroids, thyroxin, cytotoxic drugs and antiarrhythmic drugs] and women with intrauterine fetal infections or fetal arrhythmias were excluded.

The diagnosis of pre GDM in non-pregnant individuals or in earlier pregnancy was done by a fasting blood glucose (FPG) followed by 75-g glucose load and a 2 h postprandial (2HPP) [8].

Gestational diabetes was diagnosed if two or more abnormal values of blood glucose levels in the 3-hour GTT (fasting >95 mg/dl, 1 hour >180 mg/dl, 2 hours >155 mg/dl) are present according to the American Diabetes Association criteria [9].

All subjects of the study were subjected to the following:

1- Thorough history taking: Personal history, obstetric and past history, history of onset of diabetes mellitus (pre-gestational and gestational), history of other chronic diseases, systemic disorders, history of taking drugs and intrauterine fetal conditions.

2- Maternal evaluation: Complete general, obstetric, and standard obstetric ultrasonographic examination.

3- Laboratory investigations: glycated hemoglobin (HbA1c), FPG, 2HPP, complete urine analysis, and renal function tests.

4- Fetal echocardiographic evaluation: It was performed using GE Vivid 8 machine (Horten, Norway) at Tanta university hospitals and PHILIPS Epic CX 50 at Ain Shams university hospitals, using both curved probe (C4) and sector probe (S3 and S5).

Fetal heart scanning was performed according to the standard protocol at 28 weeks of pregnancy [10]. The following parameters were measured:

1) IVS thickness, LV posterior wall thickness, left ventricular end-diastolic dimension (LVEDD), and left ventricular end-systolic dimension (LVESD) using M mode echocardiography [11].

2) LV diastolic function through estimation of mitral E/A ratio [12-13].

3) LV Systolic function through measuring left ventricular fraction shortening (LV FS%) using M mode. LV FS (%) = LVEDD—LVESD/LVEDD [14].

Statistical analysis

Statistical analysis was done by SPSS v27 (IBM©, Chicago, IL, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analyzed by ANOVA (F) test with post hoc test (Tukey). Quantitative non-parametric data were presented as median and interquartile range (IQR) and were analyzed by Kruskal-Wallis test with Mann Whitney-test to compare each group. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test. Linear correlation coefficient between echocardiographic data and various clinical and laboratory data was performed. A two tailed P value < 0.05 was considered statistically significant.

Results

There were no significant differences between the three groups as regards the age, weight, parity, and gravidity of the pregnant women. (

Table 1)

HbA1c was significantly higher in diabetic groups as compared to the control group. However, no significant difference was present between gestational and pre-gestational DM. FBS and 2HPP were significantly higher in both pre-gestational and gestational DM as compared to the control group, but no significant difference was present between gestational and pre-gestational DM groups. Fetal heart rate (FHR) was significantly higher in both pre-gestational and gestational DM as compared to the control group. As regards IVS thickness, it was significantly thicker in fetuses of diabetic mothers as compared to the control group. Furthermore, it was significantly thicker in pre GDM as compared to GDM ($P < 0.05$). Similarly, LV wall thickness was significantly higher in both pre-gestational and gestational DM as compared to the control group. However, LVEDD and LVESD were significantly lower in diabetic groups compared to the control group. As regards mitral E/A ratio, it was significantly lower in diabetic groups as compared to the control group. Furthermore, it was significantly lower in pre GDM as compared to GDM ($p < 0.05$). LV FS was comparable in the three groups. (Table 2)

IVS thickness had a significant positive correlation with HbA1c, FBS, and 2HPP ($p < 0.05$). While mitral E/A ratio had a significant negative correlation with duration of DM ($p < 0.05$). (Table 3)

Discussion

Maternal hyperglycemic disorders became a common disorder during pregnancy with a high prenatal morbidity and mortality. Hyperglycemia particularly influences cardiovascular system development and fetal heart affection is related to the time of hyperglycemia [15]. This study aimed to assess the cardiac function and structure in fetuses of gestational and pre-

gestational diabetic mothers, compared to those of healthy mothers, using fetal echocardiography.

In the current study, we found that HbA1c, FBS, and 2HPP were significantly higher in women with both GDM and pre GDM as compared to the control group, however no significant difference was found between both diabetic groups. This was in agreement with previous studies [11,15].

In our study, we noticed that FHR was significantly higher in pre GDM than GDM groups compared to the healthy control pregnant group. Cypryk et al. [16] found that elevated maternal glycemia in diabetic mothers is associated with accelerations of FHR. Moreover, Bocking et al. [17] reported an increase in the mean FHR after intravenous glucose injection. Costa et al. [18] also reported that maternal hyperglycemia is associated with elevated FHR. Also, Weissman et al. [19] reported that the significant and consistent increase in baseline FHR following maternal glucose ingestion indicates that the fetus responds to changes in its environment. However, Turan et al. [20] demonstrated insignificant difference between diabetic and control groups as regards FHR. This could be due to normal plasma glucose level at the time of examination.

In our study, we found that IVS thickness significantly increased in gestational hyperglycemic disorders as compared to the control group. This agrees with Fouda et al. [21] who reported that IVS was significantly thicker in fetuses of diabetic mothers as compared to the healthy control pregnant mothers. Furthermore, it was significantly thicker in the pre-GDM group as compared with the GDM group. Dervisoglu et al. [15] reported that IVS thickness was significantly higher in pre-gestational than gestational DM. In contrast to our results, Moradian et al. [22] reported that there was no significant difference between the diabetic and control groups in terms of IVS thickness and this might be due to early identification, appropriate treatment, and tightly controlled diabetes in their study population.

Our study showed a significant positive correlation between IVS and HbA1c. In agreement with our results, other investigators reported a positive correlation between HbA1c levels and septal thickness measurements [11,23-24]. In contrast, Chen et al. [25] reported no correlation between IVS thickness and HbA1c level and suggested that satisfactory maternal glycemic control could lessen the changes in thickening of ventricular walls, but had no obvious influences on the IVS. Moreover, Hornberger [5] reported that tightly controlled diabetes assessed by HbA1c didn't relieve greater septal thickness.

Interestingly, we found that LV wall thickness significantly increased in gestational hyperglycemic disorders as compared to the control group, but all were still within the normal range. This was in agreement with the results of previous studies [25-28].

In our study, we noticed that LVEDD was significantly lower in diabetic groups as compared to the control group. In agreement with our results, Patey et al. [29] reported lower LVEDD in diabetic mothers as compared to healthy control group.

In the current study, we found that there was a significant decrease in LV diastolic function (presented by mitral E/A ratio) in diabetic mothers versus control group. Indeed, it was significantly lower in fetuses of women with pregestational DM as compared with those of gestational DM. This agrees with the results of other investigators [11,29] suggesting increased ventricular stiffness due to altered metabolic environment and fluctuations in maternal blood sugar levels. In contrast to our results, Chen et al. [25] and Dervisoglu et al. [15] reported that no difference was found between diabetic and non-diabetic groups as regard to mitral E/A ratio. Other studies reported that during fetal life, the right ventricle is more sensitive to afterload changes than the left ventricle. Thus, in diabetic pregnancies, the tricuspid E/A ratio is lower than the mitral E/A ratio [30,31].

Moreover, we reported that mitral E/A ratio negatively correlated with the duration of DM. In agreement with our results, Fouda et al. [21] supposed that the longer the duration of

maternal hyperglycemia and fetal hyperinsulinemia, the more impairment of LV diastolic function.

In the current study, we found that fetal left ventricular systolic function measured by LV FS% was comparable in the three groups. Other investigators reported similar results denoting normal systolic function in fetuses of diabetic mothers [15,21,22,32].

Limitation of the study: small sample size of the study, no follow up was performed to assess the changes in cardiac function and structure throughout the pregnancy.

Conclusions:

IVS thickness is the most affected structures in fetal heart of diabetic mothers. Moreover, LV diastolic function was affected in such fetuses unlike the systolic function. Fetal echocardiography in diabetic mothers is highly important, not only to diagnose structural abnormalities but also for evaluation of cardiac function of the fetuses

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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Table 1. Age, weight, parity and gravidity of the three studied groups.

	Pre-GDM (n=20)	**GDM (n=20)**	**Control (n=20)**	**F**	**P-value**
Age (Years)	31.8 ± 4.2	30.5 ± 5.9	29.7± 6.1	0.462	0.631
Weight	72 ± 5	73.7 ± 5.4	72.5 ± 5.7	0.077	0.926

(kg)					
				Kruskal-Wallis Test	
				X^2	P-value
Parity	1 (0-1)	1 (0-2)	1 (1-2)	3.007	0.222
Gravidity	2 (1-3)	2 (1-3)	2 (2-3)	2.607	0.272

GDM: gestational diabetes mellitus, X^2: chi square test.

Table 2. Laboratory and echocardiographic data in the studied groups.

Parameters	Pre-GDM	GDM	Control	P
HbA1c	6.5±1.2	5.9±0.7	3.9±1.1	<0.001
FBG	101.5±21.5	97.8±15.7	78.1±4.7	<0.001

2HPP	170.6±25.8	156.3±19.4	118.6±15.9	<0.001
Urea	29.4±3.9	28.2±5.1	27.1±4.5	0.531
Creatinine	0.8±0.2	0.7±0.1	0.7±0.2	0.242
FHR	149.7±24.9	142.3±18.6	130.1±15.4	0.04
IVS thickness	3.9±0.7	3.3±0.6	2.8±0.3	<0.001
LV wall thickness	2.9±0.3	2.9±0.3	2.1±0.1	<0.001
LVEDD	10.4±0.6	10.3±0.5	11.8±0.2	<0.001
LVESD	6.3±0.6	6.4±0.5	7.5±0.3	<0.001
LV FS%	36.3±.3.5	35.7±4.1	35.9±3.2	0.341
Mitral E/A Ratio	0.66±0.11	0.70±0.05	0.77±0.02	<0.001

GDM: gestational diabetes mellitus, HbA1c: glycated haemoglobin, FBG: fasting blood glucose, 2HPP: 2 hours post prandial, FHR: fetal heart rate, IVS: interventricular septum, LV: left ventricular, LVEDD: left ventricular end-diastolic dimension, LVESD: left ventricular end-systolic dimension, LV FS: left ventricular fractional shortening.

Table 3. Correlation between fetal echocardiographic parameters and demographic data and lab investigations in the studied groups.

Parameters	IVS thickness		Mitral E/A		LV FS	
	r	P-value	r	P-value	r	P-value

Age of mothers	0.161	0.219	0.174	0.185	0.096	0.465
Weight of mothers	0.232	0.075	-0.056	0.669	-0.060	0.648
Parity	0.116	0.378	0.110	0.401	0.068	0.608
Gravidity	0.205	0.117	0.071	0.590	0.018	0.892
Duration of DM	0.240	0.065	-0.686	<0.001*	-0.700	0.289
HbA1c	0.531	<0.001*	-0.207	0.113	-0.146	0.267
FBS	0.438	<0.001*	0.129	0.325	0.133	0.312
2HPP	0.279	0.031*	0.195	0.135	0.192	0.141

GDM: gestational diabetes mellitus, HbA1c: glycated haemoglobin, FBG: fasting blood glucose, 2HPP: 2 hours post prandial, FHR: fetal heart rate, IVS: interventricular septum, LV: left ventricular, LV FS: left ventricular fractional shortening.