Comparing Ventricular Function in Fetuses of Diabetic and Non-Diabetic Mothers Using Tissue Doppler Imaging

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Abstract

Background: Maternal diabetes is associated with increased teratogenic effects on fetuses; it affects the structure and functions of fetal heart and alters the fetal-placental circulation. Although several articles have demonstrated fetal cardiac malformation and defects in diabetic mothers, ventricular systolic and diastolic function has not been properly investigated, particularly in Iran.

Objectives: The aim of this study was to assess ventricular function using tissue Doppler imaging (TDI) in fetuses of diabetic mothers compared with fetuses of non-diabetic mothers in the Iranian population.

Patients and Methods: Twenty-one diabetic pregnant women at 28 weeks’ gestation were enrolled as the case group, and 35 healthy pregnant women at the same gestation were considered as the control group. Fetal echocardiography, including TDI, was carried out for all cases. The variables measured by echocardiography were as follows: the systolic annular peak velocity (Sa), late-diastolic annular peak velocity (Aa), and diastolic annular peak velocity (Ea) waves on the lateral and septal walls of the left ventricle (LV) at the mitral valve annulus using TDI; mitral inflow E and A waves using pulse Doppler; and inter-ventricular septum thickness using two-dimensional (2D) echocardiography.

Results: According to cut-off value of 6.3% for hemoglobin A1C (HbA1c), only one patient with HbA1c = 8 had uncontrolled diabetes. In 20 other patients with controlled diabetes, the mean HbA1c was 4.78 ± 1.22%. There was no significant difference between groups according to maternal age (29.24 ± 5.86 in the case group vs. 28.58 ± 4.42 in the control group, P = 0.6). No significant difference was found in the septal thicknesses between the two groups (P = 0.39). Moreover, there were no statistically significant differences between groups in terms of other echocardiography variables (P > 0.05).

Conclusions: We did not find significant differences in ventricular function or ventricular septal thickness in the fetuses of mothers who were referred to our hospital with a previous diagnosis of diabetes mellitus compared with the fetuses of non-diabetic mothers. This could be due to early identification, appropriate treatment, and tightly controlled diabetes in our study population. It should be noted that only pregnant women who were being closely monitored by their gynecologist were referred to us, so there may be some bias in our case selection; moreover, only patients who have taken steps to control their diabetes, so that only one of them had an abnormal HbA1c level. Other possible reasons for our results are over-diagnosis of gestational diabetes by gynecologists and an inadequate number of participants in our study.

Keywords: Maternal Diabetes Mellitus, Fetal Ventricular Function, Tissue Doppler Imaging

1. Background

Maternal diabetes mellitus (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. 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 cardiomyocyte gene expression and subsequent structural and functional malformation in the fetal heart. Some studies have shown that fluctuations in glucose values during pregnancy make these fetuses prone to hypertrophic cardiomyopathy and thickening of the interventricular septum. Also, researchers have reported an inverse relationship between hemoglobin A1C (HbA1c) and fetal cardiac function (1, 2).

Insulin-dependent DM (IDDM) occurs in nearly 0.1% of the pregnant population (3). Maternal diabetes is associated with increased teratogenic effects on fetuses. Cardiomegaly is an extremely common malformations in fe-
tuses of diabetic mothers (30%), and heart failure occurs in 5% - 10% of these cases. The incidence of asymmetric septal hypertrophy is 30% - 38% of cases, specifically, 50% in fetuses of mothers with IDDM and 25% in fetuses of mothers with insulin-independent DM (IIDM) (2).

The most common heart malformations in fetuses of diabetic mothers include the following: coarctation of the aorta (CoA), transposition of great arteries (TGA), Truncus arteriosus, double outlet right ventricle (DORV), ventricular septal defect (VSD), hypoplastic left heart syndrome (HLHS), and heterotaxy syndrome (4). Incidence of congenital heart defects among the newborns of diabetic mothers is five times greater than that of the general population (4). While improvements in perinatal management have led to a reduction in diabetes-related mortality, the incidence of associated congenital anomalies remains higher than in the general population (1).

Hyperglycemia in the first trimester can interfere with organogenesis and leads to conotruncal defects, and after that time, it increases the risk of cardiac dysfunction. Fetal echocardiography is a robust, noninvasive technique that has improved the diagnosis and management of fetal heart diseases. Conventionally, two-dimensional (2D) echocardiography and Doppler assessment of blood flow are used to evaluate fetal heart function. Changes in chamber size and flow velocities are measured and interpreted using these techniques. Tissue Doppler imaging (TDI) has the benefit of being less dependent on loading conditions, so it is more accurate for the assessment of cardiac function and can detect subclinical fetal cardiac dysfunction.

Fetal echocardiography shows the timing of development of the myocardial changes in the fetus of the diabetic mother with documentation of increased ventricular septal thickening and ventricular inflow and outflow velocities (5-7). Although several articles have demonstrated cardiac malformation and defects in fetuses of diabetic mothers, there is little information about their systolic and diastolic cardiac function.

2. Objectives

The aim of this study was to assess ventricular function using TDI in fetuses of diabetic mothers compared with fetuses of non-diabetic mothers in the Iranian population, which has not been studied before.

3. Patients and Methods

3.1. Study Design

This case-control study included 21 pregnant women who were diagnosed as diabetic by a gynecologist based on the American diabetes association (ADA) criteria at their 28th gestational week (8) as the case group and 35 healthy pregnant women at the same age of gestation as the control group. All participants were referred to the Rajaie cardiovascular medical and research center a tertiary care center for cardiovascular patient in Tehran, Iran for fetal echocardiography from 2014 to 2015. Only singleton pregnancies without any major malformation observed via ultrasound examination were enrolled in this study.

A full history was taken from all patients, including maternal age, number of pregnancies, parity, and history of any associated medical disorders or drug intake. In the case group, gestational DM (GDM) or pre-GDM was diagnosed based on the patients’ medical histories, and all of their HbA1C levels were checked. Participants with a family history of congenital heart disease; any other metabolic and endocrine disease, such as hypo- or hyperthyroidism; rheumatic diseases; and any medications that could affect the fetus’s left ventricular (LV) function, such as corticosteroids or anti-neoplastic drugs, were excluded from the study.

3.2. Echocardiography

All participants underwent complete 2D fetal echocardiography via segmental the sequential anatomic approach using a commercial GE Vivid system (Horten, Norway) equipped with a convex transducer with variable frequency (2 - 5.7 MHz). To improve the chance of finding any small anatomic defect, the highest frequency (5.7 MHz), a single acoustic focal zone, and a narrow image field were used. Interventricular septal thickness was measured during diastole just inferior to the atrioventricular valves.

Other sonographic techniques, including M-mode, Doppler, and color Doppler imaging, which are routinely used in our institute to detect any arrhythmia, dysfunction, abnormal flow pattern, and evaluation of blood flow velocity, were used for each participant. Color Doppler was employed to place the pulsed wave sample volume appropriately in the distal to mitral valve leaflets in the apical four chamber view. A sample volume of 2.0 to 3.0 mm was positioned in the direction of flow with an insonation angle of less than 20°. Multiple measurements (in at least three cardiac cycles) of diastolic E and A waves were obtained and an average was recorded. Following this, the E/A ratio was calculated offline. Myocardial velocities were obtained in the same view by adjusting a transducer capable of performing TDI. The sample volume (2 - 3 mm) was placed in the basal part of the interventricular septum and the LV free wall; again, the attempt was made to ensure that the insonation angle was less than 20°. Early diastolic annular peak velocity (Ea), late-diastolic annular peak velocity (Aa), and systolic annular peak velocity (Sa)
were recorded in at least three cardiac cycles and the average was calculated; the E/Ea ratio was also evaluated offline (Figure 1).

The study protocol was in accordance with the Helsinki declaration of the World medical association (2000) and was approved by the institutional review board and our local ethics committee; all patients signed an informed consent form authorizing the use of their data in this study.

3.3. Inter- and Intra-Observer Reliability
Twenty patients were randomly assessed to study the intra-observer reliability of the echocardiographic parameters. Echocardiographic data were determined twice by an expert cardiologist. The operator was blinded to other examination results. To reduce any inter-observer error, which is inherent in echocardiography, all examinations were performed by one person.

3.4. Statistics
All data were analyzed using SPSS software, version 11.0 (SPSS, Chicago, IL, USA). Quantitative data were expressed as mean ± standard deviation (SD) and qualitative data as number (%). All variables were tested for normal distribution using the Kolmogorov-Smirnov test. Participants’ characteristics were compared for the case and control groups using the independent T or Mann-Whitney U tests and the chi square or Fisher’s exact test. A value of P < 0.05 was considered statistically significant.

4. Results

4.1. Participants’ Characteristics
According to a cut-off value of 6.3% for HbAlc (9, 10), only one participant with HbAlc = 8 had uncontrolled diabetes. In the 20 other participants with controlled diabetes, the mean HbAlc was 4.78 ± 1.22%.

In the case group, 9 (42.9%) participants had diabetes before their pregnancy (pre-GDM), and 12 (57.1%) participants had GDM. The mean age of mothers in the case group was 29.24 ± 5.18 years, and in the control group it was 28.58 ± 4.42 years. There was no significant difference between groups according to maternal age (P = 0.6).

4.2. Echocardiographic Findings
Fetal echocardiography was performed at a mean gestational age of 28.19 ± 0.87 weeks in the case group and 28.03 ± 0.44 weeks in healthy participants. The echocardiographic parameters in the case and control groups at 28 weeks of pregnancy are shown in Table 1.

No significant difference was found regarding the septal thickness between two groups (P = 0.39). There were no statistically significant differences between the groups in terms of other echocardiography variables (P > 0.05).

The Bland and Altman method showed that there were no statistically differences between the two groups in terms of echocardiographic data (P = 0.44). The mean difference in echocardiographic parameters was 0.55 ± 9.67 (mean of differences ± 2 SD was -9.12 - 10.22, P = 0.44).

5. Discussion
Over the past two decades, advances in ultrasound have enabled the detection of structural and functional heart diseases in fetuses. The field of fetal echocardiography is developing rapidly, especially when it comes to detecting subtle cardiac dysfunction before end-stage heart failure and hydrops fetalis occur. Evaluation of the fetal heart is challenging because adequate imaging is necessary, but the restricted access to the fetus in the maternal abdomen, small heart size, and rapid heart rate increase the chance of suboptimal scanning. Different types of ultrasound techniques, including 2D imaging, M-mode, and conventional pulsed Doppler, have been applied to evaluate fetal heart function. Recently, TDI, color TDI, 2D speckle tracing (strain and strain rate), 4D spatiotemporal correlation (4D-STIC), and velocity vector imaging (VVI) have been used for fetal cardiac function evaluation (11).

TDI can measure myocardial velocities by calculating frequency shifts. It is less dependent on loading conditions, and recently, it has been applied more frequently for cardiac evaluation in fetuses. The other mentioned techniques require special software to perform complex analysis, providing information about myocardial function and have not yet been validated in fetal cardiology. It should be kept in mind that electrocardiogram (ECG) is required for offline processing in these techniques, as this cannot be acquired easily during intrauterine life (12).

The present study aimed to assess fetal echocardiography indices in pregnant diabetic women compared with non-diabetic ones in the Iranian population. All participants were referred to our hospital with the previous diagnosis of diabetes and treatment either just diet or diet with insulin was started by their gynecologist. Complete echocardiography assessment, including M-mode, 2D, conventional pulsed Doppler, color Doppler, and tissue Doppler were performed at 28 weeks in two groups of...
women with GDM or pre-GDM and non-diabetic pregnant women. This gestational age was selected because ventricular dysfunction occurs in the second and third trimester of pregnancy; moreover, muscle mass of the heart, especially ventricular septal thickening (hypertrophic cardiomyopathy), happens in the third trimester in fetuses (13, 14). Many studies have shown increased ventricular wall thickness, especially in the interventricular septum, when diabetes is not appropriately controlled (10, 13-16). In our study there was no significant difference between the two groups in terms of ventricular septal thickness. According to Hornberger, thickening of the interventricular septum would occur in infants of diabetic mothers regardless of whether the diabetes is under control (1).
During fetal life, the sarcoplasmic reticulum and calcium handling in the myocytes is immature. Myocardial immaturity produces an impaired relaxation pattern, and Doppler analysis of the mitral and tricuspid valves’ flows shows an E/A ratio less than 1, which is due to stiff myocardium during fetal life and the early neonatal period. The role of atrial contraction (A wave in Doppler study), which is used as an additional pump after birth, is more obvious during fetal life. The maturation of myocytes with the ageing of the fetus will be reflected in Doppler signals as increasing E wave velocity, relatively constant A wave velocity, and an increasing E/A ratio during gestational life; gradually, the ventricular relaxation matures (17).

Different studies have confirmed the same findings in tissue Doppler study of the myocardium (13, 14). Investigations have shown altered fetal myocardial function in maternal diabetes and the tendency of diastolic dysfunction to occur earlier than systolic dysfunction. Previous studies using 2D and conventional Doppler echocardiography have shown an accelerated increase in the maximum and mean temporal velocities across the atrioventricular valves in the fetuses of diabetic mothers, which have been attributed to a compensatory mechanism and a reaction to chronic hypoxemia (1, 18). Hatem et al. used TDI and observed significantly higher diastolic myocardial velocities in fetuses of diabetic mothers in comparison with non-diabetics ones. They also showed that the E/Em ratio in normal pregnancies is significantly higher than in diabetic ones, demonstrating impaired cardiac function. These researchers consider that the decreased relaxation and compliance of the ventricle in fetuses of diabetic mother prompt the increment of myocardial velocities to counter this limitation, which is prioritized over the proper formation of the ventricle (14).

In their study, Walther et al. showed enhancement in the left ventricular mass and contractility and reduction in cardiac output. This was secondary to a reduced stroke volume due to septal hypertrophy that was an anabolic result of fetal hyperinsulinemia during the third trimester (18-21).

In the current study, echocardiography showed that fetal ventricular systolic and diastolic functional parameters were not significantly different in the two groups (P > 0.05). We did not observe any difference in atrioventricular valve inflow velocities (E, A, E/A ratio), tissue Doppler velocities (Em, Am, Em/Am ratio), or E/Em ratios. This could be due to early identification, proper treatment, and tightly controlled diabetes in our study population; we did not observe significant changes in ventricular function and ventricular septal thickness in fetuses of diabetic mothers.

HbA1C values as an indicator of maternal diabetic control was lower than 6.3% in all patients except one, which is considered to represent well-controlled blood glucose. However, the incongruities between our study and others in literature give rise to two important questions, as follows: Was there any over-diagnosis of diabetes in our study population? Was the sample size inadequate for analysis?

While several studies have reported a lack of correlation between fetal cardiac function and maternal blood glucose control, Gardiner et al. reported a significant inverse relationship between LV function and HbA1c values that can reflect the importance of the proper control of diabetes (18). Nashaat and Mansour found a positive correlation between HbA1c levels and septal thickness measurements in their study, a may reflect cumulative metabolic effect on septal thickness (10). In her article, Hornberger explained that tightly controlled diabetes will not relieve greater septal thickness (1).

The aim of our study was to compare the fetal cardiac function between pregnant diabetic and non-diabetic mothers. HbA1c in our study group was within normal limits except in one case. This may be due to either well-controlled diabetes or over-diagnosis (22, 23). All of the participants were referred to us for fetal cardiac evaluation with previous diagnosis of diabetes, but at the beginning of the study, we did not consider over-diagnosis, an issue which has been recently raised in the literature. Only after analyzing the data and finding inconsistencies with the previous literature did this question arise.

5.1. Conclusions

Careful management of blood glucose in pregnant diabetic women reduces the incidence or severity of fetal cardiac dysfunction. Our center is a tertiary referral heart center and we started fetal echocardiography as collateral for outpatients some years ago. Only pregnant women who are being carefully monitored by their gynecologists are referred to us, so there may have been some bias in our case selection. Moreover, it is clear that only patients who are actively controlling their diabetes come to our center, as just one of them had an abnormal HbA1c level. Some patients whose echo window was not suitable were omitted from the study. Because of these limitations, our case group was small, and the power of study was low; thus, our results did not show any meaningful differences. As a result, we plan to continue our study and try to extend our research by encouraging obstetric and gynecological centers to remain in close contact with us to follow their diabetic pregnant women with more concern about over-diagnosis. Further studies are needed with larger samples and uncontrolled diabetic pregnant mothers to determine the precise incidence of changes in the septal thickness and LV functional parameters in infants of diabetic mothers.

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Footnote

Authors’ Contribution: Maryam Moradian: conducting the study, management of the article; Avisa Tabib: conducting the study, manuscript revision; Nasrin Alaee: management of the article; Avisa Tabib: manuscript preparation, data collection; Zahra Akbarzadeh: data collection; Ahmad Ghasempour: manuscript preparation, data collection.

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