Original Article

Evaluation of Ventricular Dyssynchrony Measured by Tissue Doppler Indices in Fetuses of Diabetic Mothers: A Case-Control Study

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Received 08 February 2024; Accepted 12 September 2024

Abstract

Background: *This study aimed to evaluate the effects of overt maternal diabetes on fetal cardiac function.*

Methods: *In this case-control study, 26 pregnant women with overt diabetes (the case group) and 26 women with uncomplicated pregnancies (the control group) were examined using tissue Doppler echocardiography. Cardiac function was assessed twice in the fetal period (18–22 weeks and 28 weeks of gestation) and once in the neonatal period (1 week postnatal). Fetal cardiac function was assessed using early-diastolic maximum velocity index (Em), end-diastolic maximum velocity index (Am), Em/Am, left ventricular myocardial function index (LVMPI), and interventricular mechanical delay index (IVMDI).*

Results: *The case and control groups were not significantly different in maternal and gestational age in fetal Doppler evaluation. Em (P=0.007), Am (P<0.001), LVMPI (P=0.003), and IVMDI (P=0.026) were significantly higher in the case group than in the control group, while there was no significant difference in Em/Am (P=0.264). Eight fetuses (30.8%) of diabetic mothers had dyssynchrony, while no cases of dyssynchrony were seen in fetuses of non-diabetic mothers (P=0.004). Infants of diabetic mothers were 8.8 times more likely to develop adverse neonatal outcomes than infants of healthy mothers (RR: 8.8, 95% CI: 1.71 to 45.31, P=0.009).*

Conclusion: *The findings of the current study revealed significant cardiac dysfunction and dyssynchrony in fetuses of diabetic pregnant women. Additionally, IVMDI and LVMPI can be used to predict adverse neonatal outcomes in pregnancies complicated with overt diabetes.*

J Teh Univ Heart Ctr 2024;19(4):276-282

This paper should be cited as: Kalai Moghadam M, Hemmatian MN, Mirmohammadkhani M, Rahmanian M. Evaluation of Ventricular Dyssynchrony Measured by Tissue Doppler Indices in Fetuses of Diabetic Mothers: A Case-Control Study. J Teh Univ Heart Ctr 2024;19(4):276-282.

Keywords: *Pregnancy; Diabetes mellitus; Fetus*

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Introduction

Maternal diabetes mellitus (DM) can impact the structure and function of the fetal heart and alter fetal-placental circulation from the embryonic stage through the second and third trimesters of pregnancy.[1] Hyperglycemia can affect every stage of heart development, including cardiac morphogenesis, placental formation, and fetal circulation.[2] Studies have indicated that fluctuations in maternal blood glucose levels during pregnancy increase the risk of hypertrophic cardiomyopathy and interventricular septal thickness in the fetus.[3, 4] Cardiomegaly is the most common malformation in fetuses of diabetic mothers, occurring in approximately 30% of cases, with heart failure observed in 5%–10% of them.[5-7] Dyssynchrony examination has been established as a reliable parameter for evaluating cardiac function in adults and children. Recent studies have indicated that ventricular dyssynchrony may serve as an independent risk factor for exacerbating fetal heart failure,[8, 9] leading to diastolic dysfunction in early stages and systolic dysfunction in later stages. Therefore, a practical, simple, and sensitive diagnostic technique is required for early identification and monitoring of myocardial dysfunction, allowing for preventative measures before clinical evidence of cardiac dysfunction is apparent.[10-12] While numerous studies have investigated dyssynchrony in cardiac dysfunction assessment for children and adults, research on fetal dyssynchrony examination remains limited. Tissue Doppler imaging (TDI) serves as a sensitive approach for quantitative evaluation of myocardial function, allowing for the examination of cytological and diastolic dysfunction in early stages and the detection of dyssynchrony.[13-18] While multiple studies have investigated congenital malformations and congenital heart diseases in fetuses of diabetic mothers, limited research has focused on the assessment of systolic and diastolic function and dyssynchrony.

In this study, we aimed to assess interventricular dyssynchrony through fetal echocardiography, investigate its relationship with hemoglobin A1C levels, and evaluate neonatal outcomes, including Apgar scores and birth weight. Early identification of cardiac alterations resulting from maternal diabetes is crucial for better diabetes management and improved cardiac outcomes. Accordingly, the primary objective of this study was the early detection of dyssynchrony using fetal echocardiography, enabling timely intervention and enhanced maternal blood sugar monitoring to prevent adverse cardiac consequences and improve cardiac complications.

Methods

This case-control study included pregnant mothers referred for fetal echocardiography at 18–22 weeks of gestation at Amir Al-Momenin Hospital of the Semnan University of Medical Sciences. Inclusion criteria comprised overt diabetic mothers (diagnosed before or at the beginning of pregnancy), absence of fetal congenital heart defects, fetal arrhythmia, non-cardiac abnormalities, early-onset fetal growth restriction, and normal fetal ventricular function (ejection fraction ≥50%), as well as the absence of maternal hypertension, liver, kidney, thyroid, or heart disorders that could impact fetal heart function.

The study protocol was approved by the Ethics Committee of the Semnan University of Medical Sciences (IR.SEMUMS.REC.1398.228). The study participants' welfare was ensured by adherence to the ethical conduct standards of the Declaration of Helsinki.

For all participants, fetal echocardiography was performed at 18-20 weeks of gestation to assess cardiac function. Hemoglobin A1C values were measured during the first and second trimesters of pregnancy. Subsequently, at 28 weeks, patients underwent a second echocardiography to evaluate dyssynchrony and fetal cardiac function. After birth, neonatal outcomes, including birth weight and Apgar scores, as well as demographic characteristics of the case and control groups, were documented using a pre-designed checklist.

Echocardiographic examinations were performed one week after birth by an experienced fetal cardiologist using a Philips Affiniti 50 echocardiography device with a C6-2 MHz Convex probe and S8-3 MHz phased array probe. The purpose was to assess cardiac function and dyssynchrony and examine the structure and function of the fetal and neonatal heart, respectively. Mechanical interventricular dyssynchrony was assessed using the M-mode method with a long-axis or lateral 4-chamber view. The M-mode cursor was positioned at the level of atrioventricular valves crossing the interventricular septum. To ensure accuracy, peak systole of the right and left ventricles was identified, and their difference was determined by measuring the interval between the opening of the aortic and pulmonary valves. Additionally, left ventricular systolic and diastolic functions were evaluated using the Tei index method with TDI. Cardiac function was evaluated at 2 time points during the fetal period (18–22 weeks and 28 weeks of gestation) and once during the neonatal period (1 week after birth). As no signs of cardiac dysfunction were observed in fetuses during the 18–22 weeks' evaluation, all fetal heart function parameters reported in the results section correspond to the 28-week gestation assessment.

Sample size calculation was based on the study by Rolf et al.[19] Considering a maximum type I error of 5%, 90% power, and equal group sizes, the required sample size for each group was estimated to be 26 individuals. This resulted in a total sample size of 52 patients, composed of 26 pregnant women with pre-existing diabetes (the case group) and 26 healthy pregnant women (the control group). The sample

size calculation was performed using the formula to compare proportions between 2 independent groups.

Data were entered into SPSS version 16.0, a statistical software package for social sciences. Variables were represented as mean ± standard deviation. One-way ANOVA was employed for data analysis. When necessary, continuous variables were compared using either an independent t-test or the Mann-Whitney U test. For classified data, the χ^2 or Fisher exact probability test was utilized for comparisons when appropriate. A P value ≤0.05 was considered statistically significant in all analyses.

Results

There was no significant difference in maternal age between the case and control groups (33.40±5.70 y vs 31.50±0.60 y; *P*=0.250) (Table 1). In the case group, mean HbA1C levels at 6 and 28 weeks were 6.03±0.94 and 6.01±0.95, respectively.

Fetuses of diabetic mothers exhibited significantly higher early-diastolic maximum velocity index (Em) (*P*=0.007), end-diastolic maximum velocity index (Am) (*P*<0.001), left ventricular myocardial function index (LVMPI) (*P*=0.003), and interventricular mechanical delay index (IVMDI) (*P*=0.026) compared than fetuses of non-diabetic mothers (Table 2). Nonetheless, no significant difference in Em/Am was observed between the 2 groups (*P*=0.264). Moreover, the prevalence of dyssynchrony was significantly higher in fetuses of diabetic mothers (30.8%) than in fetuses of non-diabetic mothers, where no cases of dyssynchrony were detected (*P*=0.004).

No significant differences were found between the diabetic and non-diabetic groups concerning birth weight and first-minute Apgar scores of infants (Table 3). Nevertheless, the frequency of neonatal hospitalization (*P*=0.002) and abnormal echocardiography during the first postnatal week (*P*=0.004) was significantly higher in the diabetic group. The overall frequency of adverse neonatal outcomes was meaningfully greater in the diabetic group (*P*=0.002).

The risk ratio calculation revealed that infants of diabetic mothers had an 8.8 times higher risk for adverse outcomes than infants of healthy mothers (RR:8.80, 95% CI: 1.71 to 45.31, *P*=0.009).

Significant differences were observed among the diabetic subgroups with adequate and inadequate blood sugar control and the control group regarding Em (*P*=0.026), Am (*P*<0.001), LVMPI (*P*<0.001), and IVMDI (*P*<0.001). Post hoc tests revealed the following:

- Am (*P*<0.001) and Em (*P*=0.029) were significantly higher in the diabetic subgroup with adequate glycemic control than in the control group.
- Am (*P*<0.001), LVMPI (*P*<0.001), and IVMDI (*P*<0.001) were significantly higher in the diabetic subgroup with inadequate glycemic control than in the control group.
- Am (P<0.001), LVMPI (*P*<0.001), and IVMDI (*P*<0.001) were significantly higher in the diabetic subgroup with inadequate glycemic control than in the diabetic subgroup with adequate glycemic control.

Dyssynchrony was exclusively observed in the diabetic subgroup with inadequate glycemic control (*P*<0.001). The frequency of adverse neonatal outcomes was highest in the diabetic subgroup with inadequate glycemic control (87.5%), followed by the diabetic subgroup with adequate glycemic control (22.2%), and the control group (7.7%, *P*<0.001) (Table 4).

Among the fetal cardiac function parameters, only LVMPI (P=0.034) and IVMDI (P<0.001) demonstrated a statistically significant association with adverse neonatal outcomes. LVMPI and IVMDI values were significantly higher in the group with adverse neonatal outcomes (Table 5).

Receiver operating characteristic curve analysis revealed that IVMDI had good predictive power for adverse neonatal outcomes in diabetic mothers, with an area under the curve of 0.887 (95% CI: 0.75 to 1.00, *P*=0.001). Similarly, LVMPI also demonstrated good predictive power, with an area under the curve of 0.762 (95% CI: 0.57 to 0.95, *P*=0.024).

The optimal IVMDI cutoff point for predicting adverse neonatal outcomes in diabetic mothers was determined to be 6.5 milliseconds, which demonstrated 67% sensitivity and 100% specificity. An IVMDI value at or above this threshold increased the risk of adverse neonatal outcomes by 24.5-fold (RR:24.5, 95% CI: 2.28 to 262.53, *P*=0.008).

For LVMPI, the optimal cutoff point was 0.44, with 75% sensitivity and 79% specificity. An LVMPI value at or above this cutoff was associated with an 11-fold increased risk of adverse neonatal outcomes (RR:11, 95% CI: 1.770 to 68.350, *P*=0.010).

Table 1. Comparisons of demographic characteristics between the diabetic and non-diabetic groups*

Index	Group		P
	Case (diabetic)	Control (non-diabetic)	
Age (y)	33.40±5.70	31.51±0.62	0. 231
Average gestational age (18-22) (y)	20.00±0.10	21.00±1.30	0.202

*Data are presented as mean±SD.

Table 2. Comparisons of fetal heart function between the diabetic and non-diabetic groups*

Index	Group		P
	Case (diabetic)	Control (non-diabetic)	
Em	30.31±4.04	27.64±3.95	0.007†
Am	53.10±4.07	3.68±46.18	<0.001‡
Em/Am	0.57±0.08	0.60±0.09	0.264†
LVMPI	0.43±0.06	0.38±0.05	0.003‡
IVMDI	4.69±4.93	1.50±0.65	0.026*

*Data are presented as mean±SD.
†The Man-Whitney U test
‡The independent t-test
Em, Early-diastolic maximum velocity index; Am, End-diastolic maximum velocity index; Em/Am, Left ventricular myocardial function index; LVMPI, Interventricular mechanical delay index; IVMDI, Interventricular mechanical delay index.

Table 3. Comparisons of neonatal outcomes between the diabetic and non-diabetic groups*

Variable	Group		P
	Case (diabetic)	Control (non-diabetic)	
Birth weight (g)	2881.35±595.69	3124.42±365.79	0.124†
First-minute Apgar score	8.71±1.30	9.35±0.81	0.067†
Neonatal Hospitalization			0.002‡
Yes	9 (34.6)	0 (0)	
No	17 (65.4)	26 (100)	
First-week Echocardiography			0.004‡
Normal	18 (69.2)	36 (100)	
Aortic coarctation	1 (3.8)	0 (0)	
Interventricular wall defect	13.8))	0 (0)	
Left ventricular and interventricular septum hypertrophy	311.5))	0 (0)	
Minor interventricular wall defect	2 (7.7)	0 (0)	
Ventricular hypertrophy and left outlet obstruction	1 (3.8)	0 (0)	
Any Adverse Outcomes¶			0.002§
Yes	12 (46.2)	2 (7.7)	
No	14 (53.8)	24 (92.3)	

*Data are presented as mean±SD or n.(%)
†The Man-Whitney U test
‡The Fisher exact test
§The χ^2 test
¶Existence of at least 1 of the following: abnormal birth weight, Apgar scores of <7, hospitalization, and abnormal findings in the first-week echocardiography

Table 4. Comparisons of fetal heart function and neonatal outcomes between the diabetic subgroups with adequate and inadequate blood glucose and the non-diabetic subgroup

Variable	Diabetic Group		Control Group (non-diabetic)(n=26)	P
	Appropriate control (n=18)	Inappropriate control (n=8)		
Em	30.22±3.61	30.61± 5.12	27.64±3.91	0.026†
Am	51.32±1.92	57.41±4.32	46.13±3.62	<0.001‡
Em/Am	59.01±0.07	53.01±0.08	0.60±0.090	0.082†
LVMPI	41.00±0.05	0.48±0.05	0.38±0.04	<0.001‡
IVMDI	1.50±0.51	11.88±0.99	1.52±0.684	<0.001†
Dyssynchrony				
Yes	0	8 (100)	0	<0.001§
No	18 (100)	0	26 (100)	
Adverse Neonatal Outcomes				
Yes	4 (22.2)	7 (87.51)	2 (7.7)	<0.001§
No	14 (77.8)	1 (12.5)	24 (92.3)	

*Data are presented as mean±SD or n.(%)
†The Kruskal-Wallis test
‡Analysis of variance test
§The Fisher exact test
Em, Early-diastolic maximum velocity index; Am, End-diastolic maximum velocity index; Em/Am, Left ventricular myocardial function index; LVMPI, Interventricular mechanical delay index; IVMDI, Interventricular mechanical delay index

Table 5. Relationships between fetal heart function and adverse neonatal outcomes in the diabetic group*

Index	Adverse Neonatal Outcomes†		P
	Yes (n=12)	No (n=14)	
Em	4.62±31.26	3.40±29.52	0.527‡
Am	5.01±55.12	1.92±51.41	0.085‡
Em/Am	0.10±0.57	0.06±0.57	0.631‡
LVMPI	0.07±0.46	0.05±0.41	0.034§
IVMDI	5.05±8.50	0.51±10.43a	<0.001‡

*Data are presented as mean±SD.
†The presence of at least 1 of the following: abnormal birth weight, Apgar scores of <7, hospitalization, and abnormal findings in the first-week echocardiography
‡ The Man-Whitney test
§The independent t-test
Em, Early-diastolic maximum velocity index; Am, End-diastolic maximum velocity index; Em/Am, Left ventricular myocardial function index; LVMPI, Interventricular mechanical delay index.

Discussion

Fetal echocardiography was initially conducted at 18–22 weeks of gestation; however, cardiac dysfunction was not detected in fetuses at this stage. The second assessment was performed at 28 weeks of gestation, as ventricular dysfunction is known to occur during the second and third trimesters. Moreover, the development of hypertrophic cardiomyopathy, particularly thickening of the ventricular septum, typically occurs in the third trimester of pregnancy.[20, 21]

In the present study, fetuses of diabetic mothers demonstrated significantly higher Em and Am values than fetuses of non-diabetic mothers. Still, no significant differences were observed in Em/Am between the groups. The findings of Hatém et al[20] chime with the results of the present study, as they observed a significant increase in the maximum velocity of E and A waves in fetuses of diabetic mothers (types 1 and 2) compared with fetuses of mothers with normal pregnancies. Additionally, there was no significant difference in E/A between diabetic and non-diabetic groups in their study. In a study by Gaber et al,[22] fetuses of mothers with gestational diabetes were compared with fetuses of healthy mothers, yielding results consistent with our findings. The study by Alanyali et al[23] showed that the maximum E and A wave velocities in fetuses of diabetic mothers (preexisting diabetes) were significantly higher than those in a non-diabetic group, and the 2 groups differed in terms of E/A. This finding is in line with our results. It is noteworthy that Alanyali and colleagues attributed the similarity in E/A between the groups to the similar gestational age at the time of measurements.

Sanhal et al[24] found a significantly lower E/A in the diabetic group (comprising both gestational and pre-gestational diabetes) than in the control group, which contrasts with our findings. Several factors may contribute to the discrepancies between studies, including differences in study populations, gestational age at fetal evaluation, type of diabetes and its management, measurement tools, and other variables.

Overall, our study's results, in line with most research findings, demonstrated significantly higher maximum A and E wave velocities in the diabetic group, indicating diastolic dysfunction in fetuses of diabetic mothers.[25, 26] According to Zielinsky et al,[25] the increased maximum A and E wave velocities in the diabetic group may be attributable to increased septal thickness in fetuses of diabetic mothers, leading to left ventricular filling issues and abnormal flow through the mitral valve. Moreover, the present study showed significantly higher LVMPI values in fetuses of diabetic mothers than in fetuses of non-diabetic mothers.

Alanyali et al[23] demonstrated significantly higher MPI values in the diabetic group (preexisting diabetes) than in the non-diabetic group. Figueroa et al[26] also reported a significant increase in MPI in fetuses of diabetic mothers (both gestational and preexisting diabetes) compared with fetuses of mothers with normal pregnancies. Likewise, Bui et al[27] found a significant increase in MPI in fetuses of mothers with preexisting diabetes. The results of our study align with these findings, indicating global cardiac dysfunction in fetuses of diabetic mothers. Similarly, Sanhal et al[24] reported an optimal MPI cutoff point of 0.39 with 90.9% sensitivity and 47.7% specificity for predicting adverse perinatal outcomes (respiratory distress, cord pH <7.15, neonatal hospitalization, and hyperbilirubinemia) in infants of diabetic mothers (both gestational and preexisting diabetes). These findings suggest that global cardiac dysfunction may contribute to increased fetal complications in diabetic mothers.[15] Furthermore, they highlight the utility of MPI as a valuable tool for assessing overall fetal cardiac function and its potential role as a predictor of adverse neonatal outcomes in diabetic mothers.

Our study revealed significantly higher IVMDI values, indicating interventricular dyssynchrony, in fetuses of diabetic mothers compared with fetuses of non-diabetic mothers (mean: 4.69, range: 1–13 ms in the diabetic group vs mean: 1.50, range: 1–3 ms in the control group). Furthermore, IVMDI demonstrated a strong predictive capability for

adverse neonatal outcomes in diabetic mothers, with an area under the curve of 0.887 and a cutoff point of 6.5 ms (67% sensitivity and 100% specificity). These findings suggest that IVMDI may serve as a more powerful predictive marker than LVMPI for adverse neonatal outcomes in diabetic mothers.

Dyssynchrony is an established parameter for evaluating cardiac function in adults[28] and children,[29] with proven diagnostic utility for myocardial dysfunction, even in subclinical conditions.[30, 31] Despite its potential, fetal dyssynchrony assessment has not yet been widely adopted in clinical practice, and only a limited number of studies have examined its role in fetuses affected by maternal diabetes. A literature search yielded a single study by Rolf et al,[25] which found significantly higher dyssynchrony in fetuses of diabetic mothers (both gestational and preexisting diabetes) than in fetuses of healthy mothers, consistent with our results. They identified an optimal cutoff point of 10 milliseconds for interventricular dyssynchrony to distinguish between diabetic and non-diabetic pregnancies, with 74.5% sensitivity and 93.8% specificity.

Overall, our study revealed significantly increased interventricular dyssynchrony in fetuses of diabetic mothers. Moreover, we found a significant association between fetal interventricular dyssynchrony and adverse neonatal outcomes. These findings suggest that IVMDI may serve as a valuable tool for the early detection of myocardial functional changes in fetuses of diabetic mothers. Additionally, IVMDI holds promise as a potential predictive marker of adverse neonatal outcomes in diabetic pregnancies.

Our study investigated the association between maternal glycemic control and fetal heart function, revealing that the diabetic subgroup with adequate glycemic control fared significantly better than those with inadequate control. Notably, ventricular dyssynchrony was observed exclusively in the subgroup with inadequate glycemic control, and neonatal complications occurred more frequently in this group. Nonetheless, fetuses of diabetic mothers with good glycemic control exhibited significantly higher Em and Am values than the control group, indicating the presence of diastolic dysfunction in this group as well. Our findings align with previous research, which has demonstrated that improved glycemic control in mothers with diabetes can help prevent fetal heart dysfunction, although it may not eliminate the risk.[21] These results emphasize the importance of optimal glycemic control in significantly reducing complications associated with maternal diabetes. At the same time, they highlight that maternal diabetes, regardless of glycemic control, can have adverse effects on fetal heart function. Consequently, even in diabetic mothers with good glycemic control, potential risks should not be overlooked.

The presence of cardiac issues in the diabetic subgroup with good glycemic control suggests that the fetus may have been exposed to an abnormal metabolic environment (high blood sugar and hyperinsulinemia) for a prolonged period, potentially influencing fetal development from early pregnancy onward.

Lastly, it is essential to consider the limited sample size in this study, particularly in the subgroup with inadequate glycemic control. To draw more definitive conclusions on the impact of blood sugar regulation on heart complications related to gestational diabetes, further investigations with larger sample sizes are warranted.

Several limitations should be acknowledged in this study. Firstly, the relatively small sample size, particularly in the diabetic subgroup with inadequate glycemic control, may have influenced the results. Secondly, the inability to obtain fetal ECG data precluded the use of more precise methods such as TDI and speckle-tracking echocardiography (STE), which are commonly employed in children and adults.

Despite these limitations, the study benefits from a prospective design, ensuring a consistent type of diabetes among all mothers in the case group. Additionally, it is the first study to investigate the diagnostic value of fetal ventricular dyssynchrony in predicting adverse neonatal outcomes. Furthermore, the employed method does not necessitate an ECG and, in contrast to the STE approach, does not require the installation of costly software programs on the echocardiography device, making it more accessible for clinical use.

Conclusion

The present study revealed significant ventricular dysfunction and dyssynchrony in fetuses of diabetic mothers. Notably, IVMDI, as a marker of interventricular dyssynchrony, and LVMPI, as an indicator of global cardiac dysfunction, were found to be useful predictors of adverse neonatal outcomes in diabetic pregnancies.

Acknowledgments

This study received approval and support from the Semnan University of Medical Sciences, Semnan, Iran.

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