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Comparison of Fetal Cardiac Function between Pregnancies with Diabetes Mellitus and Normal Controls

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ABSTRACT

Objectives: The purpose of this study was to compare fetal cardiac function (systolic, diastolic and global) in patients with maternal diabetes mellitus during 35-37 weeks of gestation and to evaluate the association between cardiac function and adverse perinatal outcomes.

Materials and Methods: In this prospective observational cross-sectional study, 138 pregnant women with diabetes and 149 healthy pregnant women underwent fetal echocardiography to evaluate fetal cardiac function. The perinatal outcomes were evaluated after delivery.

Results: This study found that the mean modified myocardial performance index (mod-MPI) was significantly raised in fetuses of diabetic mothers (0.53 ± 0.06 vs. 0.49 ± 0.05, $p < 0.001$) while the mean E/A ratio ratio and cardiac output (CO) were similar in the diabetes and control groups. A subgroup analysis showed that mitral E/A and tricuspid E/A ratios, Mod-MPI, right, left, and combined CO were similar in women with gestational diabetes (GDM) with diet control and those with GDM or pre-gestational diabetes (PDM) with insulin usage. The neonatal outcomes (Apgar score at 1 min, Apgar score at 5 min, Apgar score ≤ 6 at 5-min, cesarean delivery due to fetal non-reassuring, neonatal intensive care unit admission, stillbirth, and perinatal death) were similar in the two groups. No correlation was observed between the fetal cardiac function and adverse perinatal outcomes.

Conclusion: Mod-MPI in the diabetic group was the only fetal cardiac function that was significantly higher than in the healthy pregnant women. No significant correlation was observed between fetal cardiac function and adverse perinatal outcomes.

Keywords: cardiac function, fetal echocardiography, diabetes mellitus, myocardial performance index, tei index.

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การเปรียบเทียบการทำงานหัวใจทารกในครรภ์ระหว่างหญิงตั้งครรภ์ที่เป็นเบาหวานกับหญิงตั้งครรภ์ปกติ

พจนีย์ ผดุงเกียรติวัฒนา, ลัลธพร พัฒนาวิจารย์

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบการทำงานหัวใจทารกในครรภ์ (ช่วงบีบตัว, ช่วงคลายตัว และการทำงานหัวใจรวม)ในช่วงอายุครรภ์ 35-37 สัปดาห์ ของการตั้งครรภ์ในมารดาที่เป็นเบาหวาน และศึกษาความสัมพันธ์ระหว่างการทำงานหัวใจทารกในครรภ์กับผลลัพธ์ไม่พึงประสงค์ช่วงปริกำเนิด*

วัสดุและวิธีการ: *เป็นการศึกษาเชิงสังเกตไปข้างหน้าแบบภาคตัดขวางโดยกลุ่มศึกษาได้แก่ ทารกในครรภ์มารดาที่เป็นเบาหวานจำนวน 138 คน เปรียบเทียบกับทารกในครรภ์มารดาปกติ ไม่เป็นเบาหวานจำนวน 149 คน ได้รับการตรวจหัวใจทารกเพื่อประเมินการทำงานหัวใจ และประเมินผลลัพธ์การตั้งครรภ์ช่วงปริกำเนิด*

ผลการศึกษา: *จากการศึกษาพบว่า ค่าเฉลี่ย modified myocardial performance index (mod-MPI) ทารกในครรภ์มารดาที่เป็นเบาหวานมีค่าสูงกว่าอย่างมีนัยสำคัญ (0.53 ± 0.06 vs. 0.49 ± 0.05, p < 0.001) ในขณะที่ค่าเฉลี่ย E/A ratio และปริมาณเลือดที่ส่งออกจากหัวใจต่อนาที ไม่แตกต่างกันอย่างมีนัยสำคัญ เมื่อศึกษากลุ่มย่อยพบว่า mitral E/A, tricuspid E/A ratio, Mod-MPI, ปริมาณเลือดที่ส่งออกจากหัวใจต่อนาที เมื่อวัดหัวใจห้องขวา ห้องซ้าย และ ค่ารวมห้องขวาและซ้าย ไม่แตกต่างกันในกลุ่มที่มารดาเป็นเบาหวานชนิดควบคุมอาหาร กับกลุ่มมารดาที่เป็นเบาหวานชนิดฉีดอินซูลิน ผลลัพธ์ทารกแรกเกิด (คะแนน Apgar ที่ 1 นาที, 5 นาที และคะแนน Apgar score น้อยกว่าหรือเท่ากับ 6 ที่ 5 นาที, การผ่าตัดคลอดเนื่องจากแพทย์ไม่มั่นใจความปลอดภัยของทารก, การเข้านอนหอผู้ป่วยทารกแรกเกิดระยะวิกฤต, ทารกแรกเกิดเสียชีวิต หรือทารกเสียชีวิตในช่วงปริกำเนิด) ไม่แตกต่างกันอย่างมีนัยสำคัญ และไม่พบความสัมพันธ์ระหว่างการทำงานหัวใจทารกในครรภ์กับผลลัพธ์ไม่พึงประสงค์ช่วงปริกำเนิด*

สรุป: *Mod-MPI เป็นการทำงานหัวใจทารกในครรภ์เพียงค่าเดียวที่พบว่ามีความแตกต่างอย่างมีนัยสำคัญระหว่างมารดาที่เป็นเบาหวานเมื่อเปรียบเทียบกับมารดาปกติที่ไม่เป็นเบาหวาน และไม่พบความสัมพันธ์ระหว่างการทำงานหัวใจทารกในครรภ์กับผลลัพธ์ไม่พึงประสงค์ช่วงปริกำเนิด*

คำสำคัญ: *การทำงานหัวใจ, การตรวจหัวใจทารกในครรภ์, เบาหวาน, myocardial performance index, tei index.*

Introduction

Diabetic mothers have increased risk of fetal heart disease. Pregestational diabetes (PDM) mainly affects structural heart disease[1-3], and people with PDM and gestational diabetes (GDM) carry a higher risk of developing fetal hypertrophic cardiomyopathy[4, 5]. Fetal cardiac function may also be impaired, but this can also occur independently of hypertrophic cardiomyopathy[6, 7]. Many studies have found greater cardiac dysfunction in fetuses of diabetic mothers compared to those of healthy controls[6, 8-10], but other research investigations have been unable to identify any such differences[11-13].

Diabetes mellitus during pregnancy can increase the risk of perinatal mortality and morbidity due to such factors as intrapartum fetal compromise, perinatal death, and admission to the neonatal intensive care unit (NICU) [14-16]. During labor, the fetus is exposed to oxygenation compromise as a result of myometrium contractions and birth canal compression, so that the fetus exhibits adaptive cardiovascular responses via increased fetal heart rate and cardiac output. Because of this, if the fetus of a mother with diabetes has impaired fetal cardiac function, it cannot compensate for the asphyxia process. Therefore, the hypothesis is that cardiac function abnormality may be associated with adverse perinatal outcomes.

The primary aim of this study was to compare the fetal cardiac function (systolic, diastolic and global) in maternal diabetes mellitus during 35-37 weeks of gestation with normal controls. The secondary objectives were to find the correlation between cardiac function and adverse perinatal outcomes.

Materials and Methods

A prospective observational cross-sectional study was conducted from September 2018 to August 2019 at Rajavithi Hospital. This study was approved by the local Ethics Committee, and informed consent for the study was obtained from all patients. The study group consisted of 138 pregnant women with diabetes and a control group of 149 healthy pregnant women. The pregnant women with PDM were selected from their medical records. The risk screening for GDM was used in our hospital based on the Fifth International Workshop-Conference on Gestational Diabetes and the diagnosis was made before 28 weeks of gestation with one or more of the glucose levels meeting the following thresholds after a 75-gram two-hour oral glucose tolerance test (75-g OGTT): fasting glucose ≥ 92 mg/dL, 1 hour ≥ 180 mg/dL, 2 hour v 153 mg/dL. All pregnant women in the control group passed a 50-gram glucose challenge test or 75-g OGTT.

The following criteria were used for exclusion: maternal smoking, maternal age < 18-years, cardiovascular disease, connective tissue disease, renal disease, multiple pregnancies, fetal congenital anomalies, and fetal growth restriction.

All participants underwent a 2-D ultrasound examination between their 35th and 37th weeks of gestation. GE Voluson S8 or E6 (GE Medical Systems, CT, USA) equipment with 5-2 MHz curved arrays was used to perform fetal echocardiography where there was absence of fetal body and respiratory movements, and fetal heart rate was within the range of 120-160 beats/min. All examinations were performed by a single maternal fetal medicine specialist, and a detailed anatomy survey was performed in the second trimester. The fetal cardiac function parameters consisted of:

(1) E/A ratio, which represents fetal diastolic function. The mitral and tricuspid inflow velocities were recorded from the four-chamber view. The sample volume of pulsed Doppler (2–3 mm) was positioned in each ventricle immediately distal to the atrioventricular valves at an insonation angle of less than 20°.

(2) cardiac output (CO), which represents fetal systolic function. The diameters of aortic (Ao) and pulmonary (Po) valves and the velocities of flow across the valves were measured. In measurement of the velocity-time integral (VTI), the sample volume of pulsed Doppler (2–3 mm) was made immediately distal to the semilunar valves at an insonation angle of less than 20°. Stroke volume of the left or right ventricle was calculated by multiplying the VTI of the aorta or pulmonary artery by the corresponding vessel area. The left cardiac output (LCO) and right cardiac output (RCO) were calculated

by multiplying the corresponding stroke volume and the heart rate (HR). The formula for CO was 3.14 × (semilunar valve diameter/2)^2 × VTI × HR. The combined cardiac output (CCO) was calculated as the sum of LCO and RCO.

(3) modified myocardial performance index (mod-MPI). The mod-MPI, representing global cardiac function, was calculated in the fetal left ventricle as described by Hernandez-Andrade et al[17]. The mod-MPI was calculated by the following formula: (ICT + IRT)/ET where ICT = isovolumetric contraction time, IRT = isovolumetric relaxation time, and ET = ejection time.

Three values of each fetal cardiac parameter were taken and the average of the measurements was used.

In addition to the echocardiography data, sonographic data were recorded, including estimated weight, amniotic fluid index, ratio of the pulsatility index (PI) in the middle cerebral artery to the umbilical artery or cerebroplacental ratio (CPR).

Both participants and obstetricians were blinded to the ultrasound results. The only exceptions for disclosure of ultrasound findings were estimated fetal weight, oligohydramnios (amniotic fluid index < 5 cm), non-vertex presentation, absent or reversed umbilical artery flow velocity waveforms. Labor and delivery were managed according to local protocols.

The demographic data and perinatal outcomes were recorded. Obesity was defined as body mass index (BMI) ≥ 30 kg/m^2. Fetuses and neonates were classified as large for gestational age (LGA) according to estimated fetal weight and birth weight > 90th centile based on the King Chulalongkorn Memorial Hospital's nomogram[18]. Polyhydramnios was defined as amniotic fluid index > 24 cm. Adverse perinatal outcomes were defined as follows: cesarean delivery due to fetal non-reassuring, Apgar score at 5-min ≤ 6, NICU admission, stillbirth, and perinatal death.

Sample size calculation was based on the formula for testing two independent means by using a reference number that was a mean (SD) of myocardial performance index (MPI) from Bhorat's study[19], as an MPI of 0.38 ± 0.20 for control and 0.56 ± 0.21 for GDM group, and set type I error at 0.05 with a power of 80%. The calculated sample size was 21 persons per group. When combined with dropout 20%, a total of at least 26 subjects were required per group.

Data were exported and analyzed using SPSS version 22.0 (SPSS Inc., III., USA). The normality of distribution was determined using the Kolmogorov-Smirnov test. Descriptive statistics for continuous variables were shown in means and standard deviations (SD) or median and interquartile ranges (IQR) while categorical variables were shown as the number of cases and percentages. The difference between the groups in terms of mean values was compared by student's t-test and the difference between the groups in terms of median values was compared by Mann–Whitney U test. Categorical variables were tested using Pearson's chi-square or Fisher's exact tests. A p value of < 0.05 was considered statistically significant.

Results

A total of 287 pregnant women, 138 diabetic and 149 healthy pregnant females, were analyzed. Of the 138 participants in the diabetes group (DM), 92 had GDM with diet control while the remaining 46 had PDM or gestational diabetes mellitus with insulin usage. The median insulin dosage (with interquartile range, IQR) was 32 units (13.75-67.00) and median hemoglobin A1C (IQR) was 5.8 % (5.3-6.3) in diabetic mothers with insulin usage. Baseline data of the patients in this study are summarized in Table 1. The mean (± SD) maternal age (33.8 ± 5.4 years vs 29.0 ± 6.0 years, p < 0.001), multiparous (65.2% vs 47%, p = 0.002), previous cesarean delivery (18.8% vs 8.7%, p = 0.012), pregestational BMI (25.35 ± 5.10 kg/m^2 vs 22.64 ± 3.72 kg/m^2, p < 0.001), obesity (15.9% vs 5.4%, p = 0.003), gestational age at birth (38.33 ± 1.08 vs 38.78 ± 1.1, p = 0.001), cesarean section rate (51.4% vs 32.2%, p = 0.001), birth weight (3187.3 ± 427.7 vs 3161.5 ± 354.1, p = 0.001) were significant higher in the diabetic group.

On fetal ultrasound, the ICT, the IRT and the mod-MPI were statistically higher in fetuses in the diabetic group than in the controls (39.27 ± 5.79 vs 36.69 ± 4.95, p < 0.001), (47.15 ± 4.42 vs 43.93 ± 4.8, p < 0.001), and (0.53 ± 0.06 vs 0.49 ± 0.05, p < 0.001) respectively (Table 2). Intra-observer analysis of mod-MPI found good agreement, with an intra-class

correlation coefficient of 0.731 (95% confidence interval 0.682-0.775, p < 0.001).

Table 1. Demographic characteristics of groups.

Characteristics	DM N = 138	Control N = 149	p value
Maternal age (years)	33.8 ± 5.4	29.0 ± 6.0	< 0.001
Thai	82 (59.4%)	84 (56.4%)	0.60
Multiparous	90 (65.2%)	70 (47%)	0.002
Previous Cesarean delivery	26 (18.8%)	13 (8.7%)	0.012
Pregestational BMI (kg/m^2)	25.35 ± 5.10	22.64 ± 3.72	< 0.001
Obesity	22 (15.9%)	8 (5.4%)	0.003
Gestational age at US (weeks)	36.05 ± 0.8	36.23 ± 0.76	0.056
Gestational age at birth(weeks)	38.33 ± 1.08	38.78 ± 1.1	0.001
Interval from US to birth (weeks)	2.28 ± 1.3	2.55 ± 1.3	0.081
Cesarean section rate	71 (51.4%)	48 (32.2%)	0.001
Fetal male sex	79 (57.2%)	83 (55.7%)	0.792
Birth weight (grams)	3,187.3 ± 427.7	3,161.5 ± 354.1	0.001
Fetal LGA	26 (18.8%)	20 (13.4%)	0.21

Data are presented as mean ± standard deviation or number (percentage).
DM: diabetes mellitus, BMI: body mass index, US: ultrasound, LGA: large for gestational age

Table 2. Fetal parameters from ultrasound in the two groups.

	DM N = 138	Control N = 149	p value
Estimated fetal weight (grams)	2,718 .62 ± 380.63	2,687.33 ± 354.44	0.471
AFI (cm)	15.80 ± 6.5	14.61 ± 4.91	0.083
Polyhydramnios	14 (10.1%)	7 (4.7%)	0.077
Fetal heart rate	143.4 ± 7.9	144.2 ± 7.8	0.37
Umbilical artery PI	0.89 ± 0.17	0.90 ± 0.18	0.80
Middle cerebral artery PI	1.50 ± 0.37	1.49 ± 0.29	0.839
Cerebroplacental ratio	1.72 ± 0.49	1.73 ± 0.48	0.80
ICT (ms)	39.27 ± 5.79	36.69 ± 4.95	< 0.001
IRT (ms)	47.15 ± 4.42	43.93 ± 4.8	< 0.001
ET (ms)	165.04 ± 11.2	166.33 ± 10.7	0.319
Mod-MPI	0.53 ± 0.06	0.49 ± 0.05	< 0.001
Mitral E/A ratio	0.78 ± 0.07	0.78 ± 0.08	0.914
Tricuspid E/A ratio	0.78 ± 0.07	0.78 ± 0.07	0.432
RCO (mL/min)	992.61 ± 287.30	1005 ± 263.58	0.69
LCO (mL/min)	512.53 ± 139.90	539.78 ± 125.84	0.088
CCO (mL/min)	1,505.33 ± 355.88	1,551.76 ± 311.57	0.255

Data are presented as mean ± standard deviation or number (percentage).
DM: diabetes mellitus, AFI: amniotic fluid index, PI: pulsatility index, ICT: isovolumetric contraction time, IRT: isovolumetric relaxation time, ET: ejection time, Mod-MPI: modified myocardial performance index, RCO: right-sided cardiac output, LCO: left-sided cardiac output, CCO: combined cardiac output

Subgroup analysis in the diabetes group found that the mitral and tricuspid E/A ratios, Mod-MPI, RCO, LCO, and CCO were similar in patients with GDM with diet control and those with GDM or PDM

with insulin usage (Table 3).

Neonatal outcomes including Apgar score at 1 min, Apgar score at 5 min, Apgar score < 6 at 5 min, cesarean delivery due to fetal non-reassuring, NICU admission, stillbirth, and perinatal death were similar in the two groups (Table 4).

The composite of adverse outcomes was noted in 24 of 287 fetuses, 11 in the diabetic group and 13 in the controls. The Mitral and Tricuspid E/A ratios, Mod-MPI, RCO, LCO, and CCO were similar in the adverse outcomes and normal outcomes groups (Table 5).

Table 3. Fetal cardiac function in the study group subdivided by diet control and insulin usage.

	diet control N = 92	Insulin usage N = 46	p value
Mitral E/A ratio	0.77 ± 0.07	0.79 ± 0.05	0.106
Tricuspid E/A ratio	0.79 ± 0.06	0.80 ± 0.06	0.595
Mod-MPI	0.53 ± 0.06	0.53 ± 0.06	0.255
RCO (mL/min)	997.00 ± 268.12	984.12 ± 324.30	0.810
LCO (mL/min)	520.9 ± 146.8	495.6 ± 124.68	0.329
CCO (mL/min)	1,518.58 ± 335.56	1,479.73 ± 395.0	0.559

Data are presented as mean ± standard deviation or number (percentage).

Mod-MPI: modified myocardial performance index, RCO: right-sided cardiac output, LCO: left-sided cardiac output, CCO: combined cardiac output

Table 4. Neonatal outcomes in the two groups.

Variable	DM N = 138	Control N = 149	p value
Apgar score at 1 min	8.71 ± 0.92	8.5 ± 1.25	0.310
Apgar score at 5 min	9.79 ± 0.55	9.68 ± 0.8	0.167
Apgar score ≤ 6 at 5-min	1 (0.7%)	2 (1.3%)	0.60
CS due to fetal non-reassuring	10 (7.2%)	11(7.4%)	0.965
NICU admission	1(0.7%)	1 (0.7%)	0.96
Stillbirth	0	0	-
Perinatal death	0	0	-

Data are presented as mean ± standard deviation or number (percentage).

DM: diabetes mellitus, CS: Cesarean section, NICU: neonatal intensive care unit

Table 5. Comparison of fetal cardiac functions with adverse fetal outcomes.

	Adverse outcome N = 24	Normal outcome N = 263	p value
Mitral E/A ratio	0.78 + 0.06	0.77 + 0.07	0.825
Tricuspid E/A ratio	0.78 + 0.06	0.80 + 0.06	0.067
Mod-MPI	0.51 + 0.05	0.51 + 0.06	0.884
RCO (mL/min)	1008.49 + 276.36	998.78 + 275.19	0.874
LCO (mL/min)	535.30 + 122.46	526.0 + 134.29	0.754
CCO (mL/min)	1,543.79 + 317.06	1,528.22 + 335.77	0.834
Perinatal death	0	0	-

Data are presented as mean ± standard deviation or number (percentage).

DM: diabetes mellitus, CS: Cesarean section, NICU: neonatal intensive care unit

Discussion

This study demonstrated that mean mod-MPI was significantly raised in fetuses of diabetic mothers (0.53 ± 0.06 vs 0.49 ± 0.05, p < 0.001) while mean E/A ratio and CO were similar in the diabetes and control groups. Likewise, the authors of many studies[6, 9, 10, 19, 20], have found that fetuses of diabetic mothers had higher values of mod-MPI compared with those of healthy mothers. Fetal cardiac function, represented by mod-MPI is increased among fetuses of diabetic mothers. This implies that the heart of affected fetuses works harder than the control, though the function is still within normal limits. Increased fetal insulin with the effect of hyperglycemia in fetuses of diabetic mothers are hypothesized as being the primary cause implicated in impaired fetal cardiac function. However, the underlying pathophysiology appears to be multifactorial and is still not completely explain[7].

In contrast with a previous study by Figueroa et al[9], which reported a relationship between mod-MPI and insulin usage, we did not find any such association in our study. This may be due to the fact that in our study, mothers with insulin usage had well-controlled diabetes with median hemoglobin A1C (IQR) of 5.8% (5.3-6.3) or that there was no association between the status of glycemic control and mod-MPI or other fetal cardiac function parameters; Russel et al[21] and Garcia et al[22] also found no correlation between the status of glycemic control and mod-MPI.

In our study, perinatal outcomes including Apgar score at 1 min, Apgar score at 5 min, Apgar score ≤ 6 at 5 min, cesarean delivery due to fetal non-reassuring, NICU admission, stillbirth, and perinatal death were not significantly different in the diabetes and control groups. There are several possible explanations for this: first, our hospital is a tertiary center and diabetic mothers are cared by maternal fetal medicine specialist; secondly, diabetic mothers in our study had well-controlled blood glucose with amniotic fluid index, rate of polyhydramnios, and rate of fetal LGA similar to the controls and with median hemoglobin A1C in diabetics with insulin usage of 5.8%; thirdly, even though mean mod-MPI (0.53 ± 0.06 vs 0.49 ± 0.05, p < 0.001) was the only fetal cardiac function that was statistically significantly higher in the diabetic group, there was no clinical significance because the normal range of MPI in Thai women between 35 and 37 weeks of gestation was 0.46-0.65 (10^{th} centile to 90^{th} centile)[23]; therefore our study showed that fetal cardiac function and adverse perinatal outcomes in the diabetic and control groups were not significantly different.

Furthermore, we demonstrated that fetal cardiac function was not correlated with composite of adverse perinatal outcomes, including Apgar score ≤ 6 at 5 min, cesarean delivery due to fetal non-reassuring, or NICU admission. A previous study by Bhorat et al[20] observed a correlation between mod-MPI and adverse perinatal outcomes in diabetic groups, but our study found no such relationship. This may be because the incidence of adverse perinatal outcomes in our study was lower than that in Bhorat's investigation; thus, the women included in this study may not truly reflect a diabetic population.

This study had several strengths. It comprehensively assessed fetal cardiac function (systolic, diastolic, global ventricle) and found an association between fetal cardiac function and perinatal outcomes; furthermore, fetal cardiac function was performed by a single operator, thus increasing internal validity.

Limitations of this study included the fact that hemoglobin A1C was not measured in the GDM with diet control group; however, we did measure fasting blood sugar and 1- hour postprandially in these patients. Patients with poorly controlled blood sugar levels were sent to an endocrinologist for insulin use monitoring. Lastly, the sample size was too small to determine any relationship between fetal cardiac function and adverse perinatal outcomes, especially for stillbirth or perinatal death. Further research in the form of large prospective studies may clarify the potential effectiveness of fetal cardiac function in terms of its clinical utility for the prediction of adverse perinatal outcomes.

Conclusion

The Mod-MPI in fetuses of pregnant women with

PDM and GDM was the only fetal cardiac function that was significantly higher than in healthy pregnant women; however, the Mod-MPI in the diabetic group was in the normal range. No significant correlation was observed between fetal cardiac function with maternal insulin usage and perinatal outcomes. Further research in the form of large prospective studies may verify the potential efficiency of fetal cardiac function in terms of its clinical utility in predicting adverse perinatal outcomes.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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