

# Fetal Cardiac Function in Late First Trimester of Pregnant Women with Abnormal Glucose Challenge Test

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## ABSTRACT

**Objective:** To compare fetal cardiac function during 12-14 weeks of gestation between normal pregnant women and pregnant women who have abnormal 50 gm glucose challenge test (GCT) including gestational diabetes mellitus (GDM).

**Methods:** Thai singleton pregnant women, 12-14 weeks of gestation, who have no clinical risk factors of GDM and those with abnormal 50 gm GCT including GDM were enrolled. Fetal cardiac function parameters were evaluated by Doppler ultrasonography.

**Results:** One hundred and thirteen women met the inclusion criteria. Sixty one women were the control group (no clinical risk factors of GDM), whereas 52 were the study group which was then divided into 2 subgroups: 37 women with abnormal 50 gm GCT, who did not meet the criteria for diagnosis of GDM confirmed by 100 gm OGTT and 15 women with GDM. In the control group, the average values (mean±standard deviation) of right E/A ratio, left E/A ratio, right myocardial performance index (MPI) and left MPI were 0.56±0.06, 0.53±0.06, 0.49±0.08 and 0.48±0.09, respectively. No significant differences of all fetal cardiac function parameters in the first trimester were observed between groups.

**Conclusion:** Fetal cardiac function in late first trimester of pregnant women who have abnormal 50 gm GCT including GDM appeared normal.

**Keywords:** Cardiac function, E/A ratio, gestational diabetes mellitus, myocardial performance index

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## INTRODUCTION

Pregnancy complicated by diabetes mellitus is a relatively common condition, affecting up to 0.5% of the pregnant population<sup>1</sup>. At Siriraj Hospital, we use our clinical practice guideline for diagnosis and management of gestational diabetes mellitus (GDM). All pregnant women who have clinical risk factors of GDM are screened by using 50 gm glucose challenge test (50 gm GCT) at the first visit of antenatal care. If the test result appears abnormal, then they are confirmed by using 100 gm oral glucose tolerance test (100 gm OGTT) and the criteria for interpretation of the result are referenced from the National Diabetes Data Group (NDDG).<sup>2</sup> Women

whose results of 100 gm OGTT are abnormal for at least two of four values, will be diagnosed as GDM and managed according to our guideline. Meanwhile, those women whose results do not meet the criteria for diagnosis of GDM (normal all values or only one abnormal value of 100 gm OGTT) are managed as normal and scheduled for repeat screenings at 26-28 weeks and 32 weeks of gestation. However, previous studies found that some pregnant women with one value abnormal of 100 gm OGTT, particularly the first value after glucose administration, have had many complications similar to GDM women. These pregnant women are advised about diet and weight gain control.<sup>3-6</sup>

Some previous studies reported that fetuses of diabetic mothers were at increased risk of perinatal morbidity and mortality<sup>7-8</sup>. It has been reported that hypertrophic cardiomyopathy was found in 40% of infants born to diabetic mothers and 5% of them might have symptoms postnatally. Furthermore, pregnancies with poor-controlled blood sugar might be complicated by

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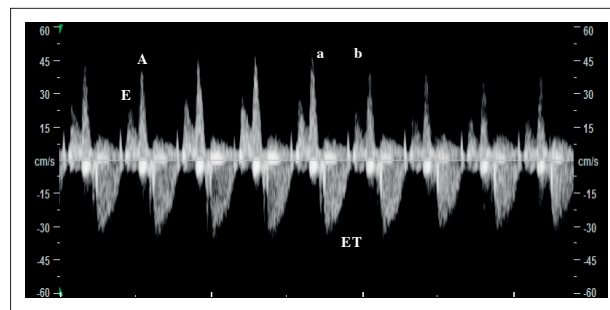
fetal congestive cardiac failure leading to a dead fetus in utero.<sup>9-10</sup> However, these previous studies mainly focused on maternal and fetal adverse events caused by pre-gestational diabetes mellitus and GDM.

So far, advancements in imaging technology particularly ultrasonography has led us to improve the feasibility of the evaluation of fetal cardiac structure and function in the first trimester with sensitivity of 70% and specificity of 98% for detection of cardiac defects.<sup>11</sup> In the aspect of cardiac function evaluation, the myocardial performance index (MPI) or Tei index and E/A ratio measured by using the Doppler application have been used to evaluate the systolic and diastolic function of fetal hearts. In addition to their usefulness for fetal cardiac function evaluation, these techniques are also informative and non-invasive methods.

The purpose of this study was to compare fetal cardiac function during 12-14 weeks of gestation between normal pregnant women and pregnant women who have risk factors of gestational diabetes mellitus (GDM) with abnormal 50 gm glucose challenge test (GCT) including GDM.

## MATERIALS AND METHODS

This cross-sectional study was conducted between June 2010 and February 2011 at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. This research was approved by the Institutional Review Board. All participants gave their informed consent before enrollment into the study. All eligible women were more than 18 years old, normal singleton pregnancy and booked for antenatal care before 14 weeks of gestation. Women with one of any clinical risk factors of GDM (age  $\geq 30$  years old, obesity (BMI  $> 30$  kg/m<sup>2</sup>), previous child's birth weight  $\geq 4,000$  gm, family history of DM, previous history of GDM and unexplained fetal death and/or fetal anomaly in previous pregnancy) were screened for GDM by using 50 gm GCT. If the result was positive (blood sugar level  $\geq 140$  mg/dl), they were assigned to be the study group. Then they were confirmed for diagnosis of GDM by 100 gm OGTT and divided into 2 subgroups: GDM group (abnormal blood sugar level  $\geq 2$  of 4 values) and normal 100 gm OGTT group (abnormal 1 value or normal all values). Meanwhile, those without any clinical risk factors of GDM were assigned as the control group. If abnormal fetal cardiac structure, which was detected by fetal echocardiography, had anomalous scan, and finally appeared in this group, these women were excluded. Gestational age of each case, calculated by the last menstrual period, was then confirmed by ultrasonography (Voluson E-8, GE Medical, USA). Fetal cardiac function evaluation including the crown-rump length (CRL) and nuchal translucency measurement were scheduled and performed during 12-14 weeks of gestation by one operator (1<sup>st</sup> author). All women were in supine position, and then transabdominal ultrasonography was introduced by using a curvilinear 2-7 MHz probe. After the four-chamber view of each fetal heart was obtained, the Pulsed wave Doppler mode was applied with 1-2 mm



**Fig 1.** The Doppler waveform of left ventricle: The Doppler gate was placed inferior to the mitral valve, with ventricular inflow above the line and ventricular outflow below the line. E, early passive ventricular filling; A, active ventricular filling; ET, ejection time; a, isovolumetric contraction time (IVCT) and b, isovolumetric relaxation time (IVRT). MPI was computed as (a+b)/ET.

sampling volume placed immediately inferior to the AV valve and slightly tilted the probe toward the outflow tract of each side of the fetal heart.<sup>12</sup> The lowest intensities of the Doppler energy were used, and the duration of the examination was limited to 30 minutes. The mechanical and thermal indices never exceeded 1 and the angle of insonation was less than 30 degrees.<sup>13</sup> Three to five waveforms were established and finally, 3 discrete waveforms were analyzed. Each average value was then obtained. All analyses were performed firstly at the time of the scan, and then the data was collected in the hard disk of the ultrasound machine for further analysis. Time intervals were measured when the diastolic filling wave and systolic ejection wave were seen simultaneously. Intra-cardiac maximum velocities of both ventricles were measured with electronic calipers to determine the E- and A-wave peak velocities (Fig 1). The E wave represented the early passive ventricular filling, whereas the A wave represented the active ventricular filling secondary to atrial contraction. Finally, the E/A ratio was obtained for assessment of diastolic ventricular function.

Myocardial performance index (MPI) or Tei index, as previously described by Tei et al.<sup>14</sup>, individually assessed the isovolumetric contraction time (IVCT) and isovolumetric relaxation time (IVRT). The IVCT is the fraction of time between the end of ventricular diastolic filling (A wave) and the commencement of ventricular ejection. The IVRT is the fraction of time between the end of ventricular ejection and the recommencement of the passive ventricular filling (E wave) as shown in Fig 1. Both IVCT and IVRT were also measured in the left and right ventricle. Finally, MPI, which was used to assess the systolic and diastolic function of cardiac ventricle, was calculated by the formula:  $MPI = (IVCT + IVRT) / \text{Ejection time}$ .

To evaluate the reproducibility of the results, the intra-observer reliability was tested by repeating the cardiac function measurements as described in 20 randomly selected women whose data was collected in the same ultrasound machine at 1 month later. In addition, the inter-observer reliability was evaluated by the 2 observers (1<sup>st</sup> and 2<sup>nd</sup> author) who independently analyzed the fetal

cardiac function in the same 20 randomly selected women. Each observer independently performed the measurements without knowledge of the results obtained by the other.

Statistical analysis was performed by SPSS for Windows version 13 (SPSS Inc, Chicago, IL, USA). The reproducibility was determined by intra-class correlation coefficient (ICC). An ICC more than 0.7 demonstrates good reproducibility. The results are expressed as mean values  $\pm$  standard deviations (SD). The Fisher's exact and Mann-Whitney U tests were used for differentiation between the two groups. *P* value < 0.05 was used for statistically significant difference. The Kruskal-Wallis test for unpaired data was also used to compare the results.

## RESULTS

One hundred and thirteen women were enrolled in this trial. Sixty one women (54%) were the control group. For the study group, 15 (13.3%) were GDM women whereas 37 (32.7%) were pregnant women with abnormal 50 gm GCT, but normal 100 gm OGTT (26 women with all values normal and 11 women with one value abnormal). The demographic characteristics of the control and study groups have been shown in Table 1. No significant dif-

ferences occurred between these three groups in the aspect of maternal height, body weight, body mass index, gestational age, crown-rump length, and nuchal translucency. However, only maternal age showed a significant difference, and this was unlikely to affect the fetal cardiac function.

Clinical risk factors of GDM in the study group have been shown in Table 2. Family history of diabetes mellitus in first degree relative was significantly more common in GDM women than in the group of abnormal 50 gm GCT with normal or abnormal 1 value of 100 gm OGTT. However, the other factors demonstrated no significant differences between groups.

Table 3 showed the results of blood sugar levels of 50 gm GCT and 100 gm OGTT determined by mean and standard deviation. The result showed that the GDM group had significantly higher blood sugar level of 50 gm GCT and 100 gm OGTT than others.

Table 4 demonstrated the mean values  $\pm$  standard deviation of E/A ratio, isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT) and myocardial performance index (MPI) of each cardiac ventricle between the control and study groups. No significant differences were demonstrated in all parameters of cardiac function.

**TABLE 1.** Maternal characteristic (Mean  $\pm$  SD).

	Control group (N = 61)	Study group (N = 52)		<i>P</i>
		Abnormal 50 gm GCT and normal 100 gm OGTT/or abnormal 1 value of 100 gm OGTT (N = 37)	Gestational diabetes Mellitus (N = 15)	
Age	25.7 $\pm$ 5.7	33.8 $\pm$ 5.2	34.07 $\pm$ 4.5	< 0.001*
Height (cm.)	159.3 $\pm$ 5.6	159.0 $\pm$ 5.4	157.7 $\pm$ 5.5	0.62*
Weight (kg.)	54.22 $\pm$ 9.5	55.8 $\pm$ 10.4	57.5 $\pm$ 12.4	0.49*
Body mass index, [BMI (kg/m <sup>2</sup> )]	21.3 $\pm$ 3.3	22.0 $\pm$ 64.1	23.1 $\pm$ 4.7	0.23*
Gestational age (days)	92 $\pm$ 3	92 $\pm$ 3	91 $\pm$ 5	0.575‡
Crown-rump length (mm.)	70 $\pm$ 7	70 $\pm$ 7	67 $\pm$ 10	0.506‡
Nuchal translucency (mm.)	1.5 $\pm$ 0.6	1.5 $\pm$ 0.5	1.5 $\pm$ 0.7	0.972‡

\* 1-way ANOVA test ‡ Kruskal-Wallis test

**TABLE 2.** Clinical risk factors of gestational diabetes mellitus in the study group (number, %).

	Abnormal 50 gm GCT and normal 100 gm OGTT/or abnormal 100 gm OGTT 1 value (N = 37)	Gestational diabetes Mellitus (N = 15)	<i>P</i>
Age $\geq$ 30 years old	31(83.8)	13(83.7)	1.00
Obesity (BMI $\geq$ 30 kg/m <sup>2</sup> )	2 (5.4)	2 (13.3)	0.569
Family history of diabetes mellitus in first degree relative	8 (21.6)	8 (53.3)	0.044
History of macrosomia (birth weight >4,000 gm)	0	0	-
History of previous gestational diabetes mellitus	2 (5.4)	1 (6.7)	1.00
History of unexplained fetal demise	1 (2.7)	1(6.7)	0.498
History of unknown cause of fetal deformity	0	0	-

Fisher's exact test

**TABLE 3.** Results of 50 gm GCT and 100 gm OGTT in the study group (Mean ± SD).

	Abnormal 50 gm GCT and normal 100 gm OGTT/abnormal 100 gm OGTT 1 value (N = 37)	Gestational diabetes Mellitus (N = 15)	P
50 gm GCT	160.97 ± 20	192.73 ± 33	< 0.001
Fasting blood sugar	78.08 ± 8	93.52 ± 19	< 0.001
100 gm OGTT 1 hr.	151.39 ± 34	211.05 ± 26	< 0.001
100 gm OGTT 2 hr.	133.85 ± 29	198.22 ± 34	< 0.001
100 gm OGTT 3 hr.	101.5 ± 27	174.24 ± 71	< 0.001

Mann-Whitney U test

**TABLE 4.** Data demonstrated each fetal cardiac function parameter (Mean ± SD).

	Control group (N = 61)	Abnormal 50 gm GCT and normal 100 gm OGTT/ abnormal 100 gm OGTT 1 value (N = 37)	Gestational diabetes Mellitus (N = 15)	P
Right E/A ratio	0.56 ± 0.06	0.57 ± 0.05	0.56 ± 0.07	0.815
Right isovolumetric contraction time (IVCT) (ms.)	0.039 ± 0.006	0.038 ± 0.005	0.035 ± 0.005	0.054
Right isovolumetric relaxation time (IVRT) (ms.)	0.041 ± 0.006	0.038 ± 0.009	0.041 ± 0.005	0.053
Right myocardial performance index (MPI)	0.49 ± 0.08	0.46 ± 0.10	0.51 ± 0.11	0.086
Left E/A ratio	0.53 ± 0.06	0.54 ± 0.06	0.52 ± 0.06	0.359
Left isovolumetric contraction time (IVCT) (ms.)	0.038 ± 0.006	0.037 ± 0.005	0.035 ± 0.008	0.386
Left isovolumetric relaxation time (IVRT) (ms.)	0.041 ± 0.008	0.039 ± 0.007	0.042 ± 0.006	0.438
Left myocardial performance index (MPI)	0.48 ± 0.09	0.45 ± 0.10	0.50 ± 0.09	0.284

Kruskal-Wallis test

For intraclass correlation coefficient (ICC) of inter- and intra-observer reliability, all values of this study were more than 0.9 which also demonstrated the reproducibility of the results.

## DISCUSSION

So far, there are many techniques used for evaluation of fetal cardiac function. A non-invasive technique especially fetal echocardiography including the Doppler modality has clearly shown important roles to evaluate both structural and functional aspects of a fetal heart. In this study, the authors decided to choose the measurement of E/A ratio to evaluate the ventricular diastolic function and myocardial performance index (MPI) or Tei index for both systolic and diastolic ventricular function. We found that the evaluation of fetal cardiac function can be successful during the late first trimester whereas cardiac structure survey seems to be more difficult. Additionally, these measurements demonstrated the reproducibility of the technique as shown in our results.

To our knowledge, no existing research study has addressed about the comparison of fetal cardiac function in late first trimester between normal pregnant women and pregnant women with clinical risk factors of GDM

along with abnormal 50 gm GCT including GDM. As mentioned before, diabetes mellitus, either pre gestational or gestational DM, causes many adverse effects to pregnancy outcomes including fetal cardiac structure and function. However, many previous studies mainly focused on the problematic women and did not study in women with clinical risk factors, which did not meet the criteria for diagnosis of GDM. These women may be proposed to be impaired glucose tolerance and still have trends to be disease as gestation advances. The authors firstly hypothesized that fetuses of mothers with clinical risk factors of GDM along with abnormal 50 gm GCT including GDM might have had alterations of cardiac structure and function during their early lives. In addition, we interestingly considered to study during this gestation because of the organogenesis period of fetal organ development. Many adverse events can influence this process. Owing to the small size of fetal heart in the first trimester, it was an important obstacle to thoroughly examine and to demonstrate fetal cardiac structure and abnormalities. Therefore, it should be better to evaluate fetal cardiac function only by using the Doppler mode of ultrasonography. Furthermore, abnormal fetal cardiac function might also affect to change fetal cardiac structure later.

From our results, there were no statistically signifi-

cant differences of cardiac function parameters during 12-14 weeks of gestation compared between groups. In the previous study by Russell NE., et al<sup>15</sup>, they found that fetuses of pregnant women with insulin dependent diabetes mellitus (IDDM) or DM type 1 appeared to have decreasing ventricular diastolic function at the first trimester compared to normal pregnant women. Additionally, this previous study also demonstrated the decrease of E/A ratio, prolonged isovolumetric relaxation time (IVRT) and abnormal left myocardial performance index (MPI) in pregnant women with IDDM.<sup>15</sup> However, these previous reports focused on pre gestational DM which might have more severe adverse effects than our subjects.

Because of the limitation of this cross sectional study, our results could not demonstrate any significant differences during late first trimester. However, this did not inform us about the alteration which might occur with advancing gestation. Further longitudinal study should be warranted.

Although no effect to fetal cardiac function in early fetal life was observed in GDM women, these women should be advised for good control of blood sugar until term to reduce any adverse effects which might occur later. In women that had clinical risk factors of GDM and abnormal screening test obtained in the first trimester, these women still had the trends to be GDM later. Therefore, we propose that counseling about diet control similar to GDM women might also have benefits to their pregnancy outcomes.

Additionally, this study also reported the normal values of Thai fetal cardiac function parameters, such as right E/A ratio =  $0.56 \pm 0.06$ , left E/A ratio =  $0.53 \pm 0.06$ , right MPI =  $0.49 \pm 0.08$  and left MPI =  $0.48 \pm 0.09$ , which were similar to the study of Russell NE., et al.<sup>15</sup>

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