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Decreased fetal cardiac performance in the first trimester correlates with hyperglycemia in pregestational maternal diabetes

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KEYWORDS: cardiac function; first trimester; pregestational diabetes mellitus

ABSTRACT

Objective In-vitro *animal studies suggest that high glucose levels impair fetal cardiac function early in gestation. We aimed to study whether evidence of first-trimester myocardial dysfunction can be detected in fetuses of women with pregestational diabetes mellitus.*

Methods *Women with diabetes mellitus underwent fetal echocardiography at 11–14 weeks' gestational age. In fetuses with normal anatomy, the cardiac preload, diastolic function, global myocardial performance and placental afterload were studied by Doppler of the ductus venosus (DV), mitral and tricuspid early/atrial (E/A) ratios, left and right ventricular myocardial performance index (MPI) and umbilical artery (UA) Doppler, respectively. Cases were matched for gestational age and UA and DV Doppler with controls that had no diabetes mellitus.*

Results *Sixty-three singleton diabetic pregnancies were matched with 63 controls. Mean gestational age at enrollment was 12.6 (range, 11.1–13.6) weeks. Diabetic mothers had moderate to poor glycemic control (median (range) glycosylated hemoglobin A1 (HbA1c), 7.5 (5.1–12.7)%, and the HbA1c level was* $\geq 7\%$ *in 37 (59%)). Fetuses of diabetic mothers exhibited worse measures of diastolic dysfunction: the isovolumetric relaxation time (IRT) was significantly prolonged (left ventricle:* 36.9 ± 7.4 *ms vs.* 45.8 ± 6.8 *ms; right ventricle:* 35.6 ± 8 *ms vs.* 46.4 ± 7.3 *ms,* $P < 0.0001$ *for both). The mitral E/A ratio was lower in diabetics (*0.55 ± 0.06 *vs.* 0.51 ± 0.08, $P = 0.03$*), and the global myocardial performance was lower in both ventricles (left ventricle MPI:* 0.5 ± 0.08*; right ventricle MPI:* 0.52 ± 0.08, $P = 0.03$ *and* $P < 0.0001$*, respectively). This lower global myocardial performance was caused by a prolonged myocardial relaxation time, which was most marked in diabetics with an HbA1c of* $\geq 7\%$ *(*$P < 0.001$ *vs. controls for both ventricles). There were no significant correlations between cardiac Doppler parameters and DV, UA indices and fetal heart rate (*$P > 0.05$ *for all).*

Conclusions *Fetuses of poorly controlled diabetic mothers demonstrate significant differences in first-trimester diastolic myocardial function compared with non-diabetic controls. The decrease in myocardial performance is more marked with increasing HbA1c and appears to be independent of preload and afterload. The ability to document these cardiac functional changes this early in pregnancy opens potential new avenues to understand the consequences of maternal glycemic status.* Copyright © 2011 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Normal fetal cardiovascular development is an important prerequisite for successful pregnancy outcome and has effects all the way into adult life[1]. Normal pregnancy poses a challenge to the maternal glycemic status and maternal hyperglycemia can have several important impacts on fetal cardiovascular development. The timing and severity of hyperglycemia in relation to gestational age is a critical factor that determines these effects. In pregestational diabetes, first-trimester hyperglycemia exerts its effects on organogenesis and can lead to the typical conotruncal cardiac defects by interfering with neural crest migration[2,3]. In contrast, from the second trimester onwards, hyperglycemia puts the fetus at risk for myocardial hypertrophy and subsequent myocardial dysfunction. These fetuses

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have a risk of stillbirth five times greater than that of the normal population[4]. Recently it has been suggested that sonographic evidence of altered cardiac function is apparent before ultrasound evidence of cardiac structural changes[5].

The study of fetal cardiac function is complex as both preload and afterload can affect cardiac performance parameters[6]. While the Doppler techniques for first-trimester cardiac function assessment have been previously published[7], prior studies in diabetic women examined cardiac performance parameters in isolation without considering parameters of afterload and preload. Some other studies evaluated cardiac performance in the second trimester[5,8], which is too late to draw conclusions about the impact of maternal glucose status on first-trimester cardiac function. Accordingly, it was our aim to study first-trimester fetal cardiac function in fetuses of pregestational diabetic mothers with normal fetal cardiac anatomy. We specifically aimed to evaluate the relationship of cardiac performance parameters with the degree of hyperglycemia, accounting for possible compounding effects of preload and afterload.

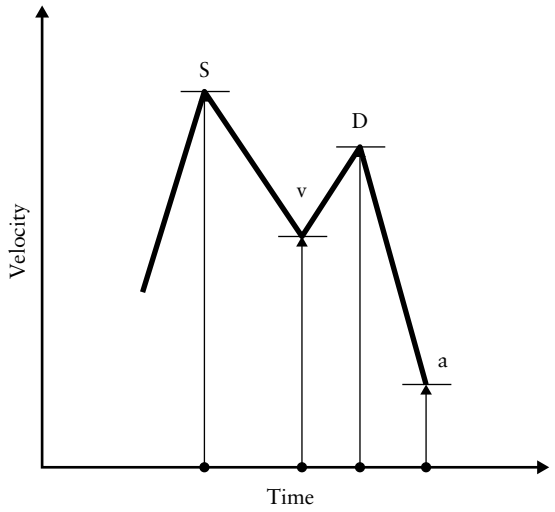

Figure 1 Components of the ductus venosus (DV) waveform and cursor placement for the measurement of velocities. Ventricular systolic ejection corresponds to the S-wave. Ascent of the closed atrioventricular valves in late systole corresponds to the v-trough (v-descent) that precedes passive diastolic ventricular flow (D-wave). Contraction of the atria during atrial systole produces the readily recognizable a-wave that corresponds to active diastolic ventricular filling. S/D, S/v, S/a, v/D, v/a and D/a ratios were calculated.

PATIENTS AND METHODS

This was a prospective observational study of women with insulin-dependent pregestational diabetes mellitus presenting for first-trimester screening at $11+0$ to $13+6$ weeks' gestation. The study was approved by the Institutional Review Board of the University of Maryland School of Medicine and was conducted between 2006 and 2010. All patients gave informed written consent for participation in the study.

Patients underwent integrated first-trimester assessment for fetal aneuploidy risk and early anatomy screening according to Fetal Medicine Foundation guidelines[9]. All women with pregestational diabetes and those with a normal ultrasound screening result received standardized first-trimester fetal echocardiography[10] for exclusion of major congenital heart disease. Study inclusion criteria were based on first-trimester variables only. These included a crown–rump length of 45–84 mm, a normal nuchal translucency thickness below the 95th centile, normal fetal anatomy and normal ductus venosus (DV) and tricuspid valve Doppler waveforms. Exclusion criteria were fetal cardiac anomalies diagnosed at the first-trimester echocardiogram, a reversed a-wave in the DV and the presence of tricuspid regurgitation and extracardiac fetal anomalies. In patients meeting the inclusion criteria the following integrated cardiovascular assessment was performed in two steps.

Step 1: vascular assessment

(a) Cardiac preload was quantified by measurement of the pulsatility index for veins (PIV) in the DV[11] and by calculating individual velocity ratios for the four phases of the venous waveform (Figure 1). The DV was identified in a sagittal or cross-sectional view of the upper abdomen using gray-scale and color Doppler imaging[6].

(b) As the placenta contributes to the majority of afterload in the human fetus, afterload was quantified using the umbilical artery (UA) pulsatility index (PI) by examining a free floating segment of the umbilical cord.

Step 2: cardiac function assessment

Once a satisfactory four-chamber view had been obtained, a 1- to 3-mm Doppler gate was placed immediately inferior to the atrioventricular (AV) valve to encompass inflow and outflow tracts throughout the entire cardiac cycle. Whenever possible these intervals were measured when diastolic filling and systolic ejection were seen in three to five consecutive cardiac cycles. Because of the small size of the fetal ventricles at this gestation, we found that we were able to demonstrate tricuspid valve and pulmonary valve clicks in the right ventricle without difficulty, allowing measurement of the time intervals. The same method was used for both ventricles (Figure 2).

(a) Systolic function was measured by assessment of the isovolumetric contraction time (ICT) (i.e. the interval of time between AV valve closure and aortic and pulmonary valve opening).

(b) Diastolic function was measured by assessment of isovolumetric relaxation time (IRT) (i.e. the interval of time between valve closure in the outflow tracts and opening of the AV valves) and the ratio between passive and active ventricular filling (early/atrial (E/A) ratio) in both ventricles, as previously described[12].

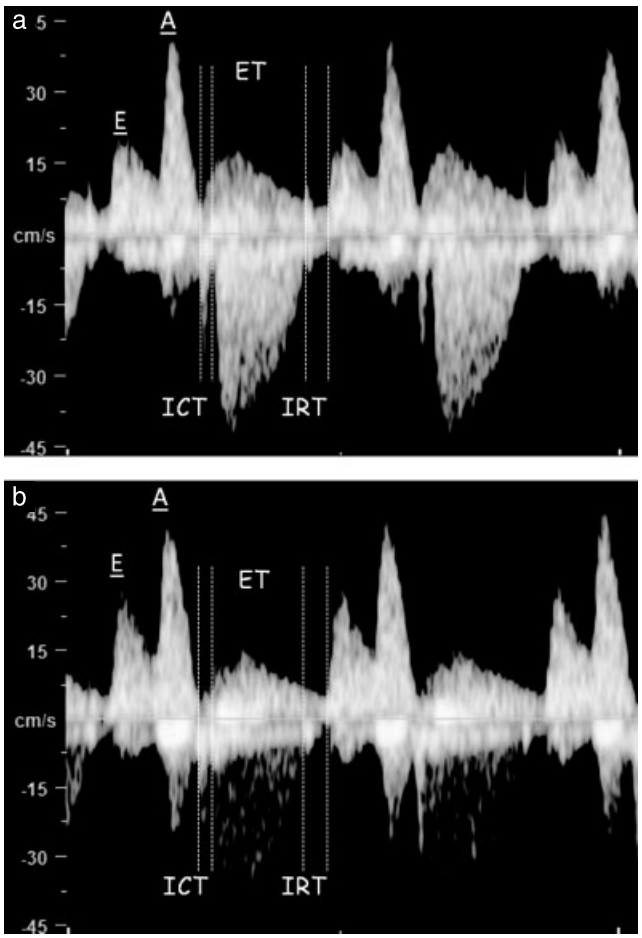

Figure 2 Spectral Doppler images of ventricular inflow and outflow obtained from the left (a) and right (b) ventricles, respectively. Utilizing the technique described by Hernandez-Andrade *et al.*[13], time intervals can be measured by placing the cursors on the valve clicks (bars). On the left side of the heart the interval between the closure of the mitral valve and the opening of the aortic valve marks the isovolumetric contraction time (ICT). The ejection time (ET) is the interval between aortic valve opening to closure, and the isovolumetric relaxation time (IRT) is the time interval between aortic valve closure and mitral valve opening (a). On the right side of the heart the same intervals can be determined utilizing the tricuspid and pulmonary valves (b). The myocardial performance index for the left and right ventricles was calculated using the formula (ICT + IRT)/ET. The same views were utilized to calculate the early/atrial (E/A) ratios between early passive ventricular filling.

(c) Global cardiac function was assessed using the modified myocardial performance index (MPI) according to the technique described by Hernandez-Andrade *et al.*[13]. Measurement of the time intervals for ICT, systolic ejection time (ET) and IRT were used to calculate the ratio of (ICT + IRT)/ET[13]. The average of two consecutive measurements was utilized in the analysis.

Ultrasound examinations were performed transabdominally or transvaginally, depending on the degree of visualization, using the Voluson E8 (GE Healthcare, Wauwatosa, WI, USA) with 4–8-MHz transabdominal or 5–9-MHz transvaginal transducers. For all Doppler examinations the lowest possible intensity of Doppler energy was used, and the duration of the entire ultrasound examination was limited to 30 min. Mechanical and thermal indices never exceeded 1.0 because the first-trimester setup of the ultrasound machine is preset to keep output power below these levels.

Based on the variance of Doppler measurements and the addition of peripheral Doppler studies, a sample size of 60 cases was estimated. In order to exclude independent impacts of preload and afterload, cases were matched for gestational age and for UA-PI and DV-PIV categories with controls that had no diabetes mellitus. These patients were selected from a group of women with normal pregnancy outcome whose first-trimester Doppler studies had been analyzed to construct reference values as part of a separate study. The average preconceptional glycemic control was assessed by the glycosylated hemoglobin A1 (HbA1c) levels. Good glucose control was defined as an HbA1c of $< 7\%$ and poor glycemic control was defined as an HbA1c of $\geq 7\%$.

E/A ratio and MPI calculation parameters (ICT, ET and IRT) were measured twice for mitral and tricuspid valves. The mean of two consecutive measurements was used for the final analysis. Intraobserver variability was calculated using Bland–Altman analysis[14]. Differences between the two consecutive measurements were calculated and expressed as a percentage of the mean of the two, with these values summarized as the mean ± SD percent difference. The coefficient of repeatability for each variable was calculated and expressed as a percentage. The coefficient of repeatability is 2 SD, with the difference between two repeated measurements expected to be within this percentage for 95% of subjects[14]. For an ideal method, the standard deviation must be close to zero.

Normality of data was tested for all continuous variables using the Kolmogorov–Smirnov test. Normally distributed parameters are presented as mean ± SD, and non-normally distributed values are presented as median (range). Parametric (the Student's *t*-test) or non-parametric (the Mann–Whitney *U*-test) comparisons were used based on the distribution of variables. Analysis of variance (ANOVA) was used for multiple variable analyses. Categorical variables were compared using the chi-square or Fisher's exact test according to cell size. A $P < 0.05$ was accepted as statistically significant. SPSS 13 (SPSS Inc., Chicago, IL, USA) and Microsoft Excel were used for statistical analysis.

RESULTS

Sixty-three diabetic women were enrolled and successfully matched with 63 controls. Exclusion criteria were not detected in any of the enrolled pregnancies and accordingly all prospectively enrolled pregestational diabetic women were retained for the final analysis.

The mean gestational age at examination was 12.6 (11.1–13.6) weeks. Diabetic women had higher body mass index values than controls and required transvaginal ultrasound examinations more frequently to achieve adequate fetal visualization. The demographics of the

Table 1 Demographics and ultrasound characteristics of the study population

Characteristic	*Controls* (n = 63)	*Diabetics* (n = 63)	P
Maternal			
Age (years)	32.1 ± 6.03	32.5 ± 6.68	NS
BMI (kg/m^2)	25.0 (17–42)	32.6 (19–61)	< 0.0001
Parity	0 (0–5)	1 (0–4)	NS
Race			NS
Black	45 (71.4)	37 (58.7)	
Caucasian	14 (22.2)	19 (30.2)	
Asian	3 (4.8)	4 (6.3)	
Hispanic	1 (1.6)	2 (3.2)	
Other	0 (0)	1 (1.6)	
HbA1c (%)	—	7.5 (5.1–12.7)	
Sonographic			
GA (weeks)	12.6 ± 0.55	12.5 ± 0.59	NS
NT (mm)	1.55 ± 0.39	1.66 ± 0.38	NS
FHR (bpm)	159 ± 7.7	160 ± 7.2	NS
Ultrasound type			0.028
TAS	63 (100)	57 (90.5)	
TVS	0	6 (9.5)	

Data are given as mean ± SD, median (range) or *n* (%). BMI, body mass index; bpm, beats per min; FHR, fetal heart rate; GA, gestational age; HbA1c, glycosylated hemoglobin A1; NS, not significant; NT, nuchal translucency thickness; TAS, transabdominal sonography; TVS, transvaginal sonography.

study population are presented in Table 1. In our patient population of diabetic mothers, first-trimester glycemic control was poor, based on HbA1c levels (median, 7.5 (range, 5.1–12.7)%) which were ≥ 7 in 37 (59%) patients. Adequate matching for diabetes and control groups was verified by similar gestational age and UA and DV Doppler indices. There were no significant differences in UA-PI, DV-PIV and individual velocity ratios (S/v, S/D, S/a, v/D, v/a and D/a) between the two groups (ANOVA; $P > 0.05$ for all).

Significant differences in diastolic function and myocardial performance parameters were observed between diabetics and controls. The E/A ratios were lower in diabetic pregnancies for the left ventricle, but no significant difference was observed for the right ventricle (left E/A: 0.55 ± 0.06 vs. 0.51 ± 0.08, $P = 0.03$; right E/A: 0.57 ± 0.07 vs. 0.56 ± 0.08, $P > 0.05$; for controls vs. diabetics; Figure 3).

The IRT was statistically significantly prolonged in both the left ventricle (36.9 ± 7.4 vs. 45.8 ± 6.8 ms) and the right ventricle (35.6 ± 8.0 vs. 46.4 ± 7.3 ms) in diabetic compared with control fetuses ($P < 0.0001$ for both, Figure 4). The ICT was significantly shorter for the left ventricle in the diabetic group ($P = 0.03$), but no significant difference was observed for the right ventricle ($P > 0.05$). Based on the variance of measurements, our study was powered to detect differences in the E/A ratio of 0.05 ($\alpha = 0.05$; $\beta = 0.10$; minimal sample size = 44) and differences in IRT of 5 ms ($\alpha = 0.05$; $\beta = 0.10$; minimal sample size = 43).

The observed differences in isovolumetric times translated into significant differences in MPI for both ventricles

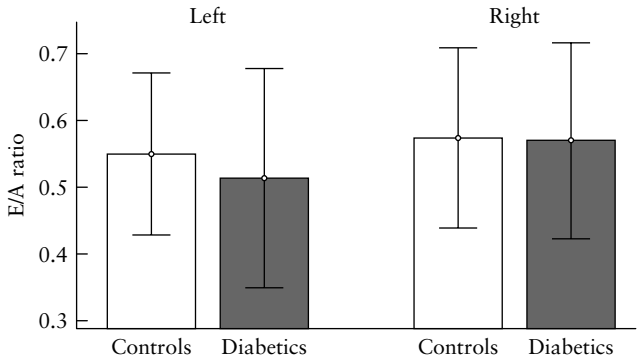

Figure 3 Early/atrial (E/A) ratios on left and right sides of the heart in control subjects (□) and diabetic patients (■). Bars represent mean values and vertical lines represent 2 SD.

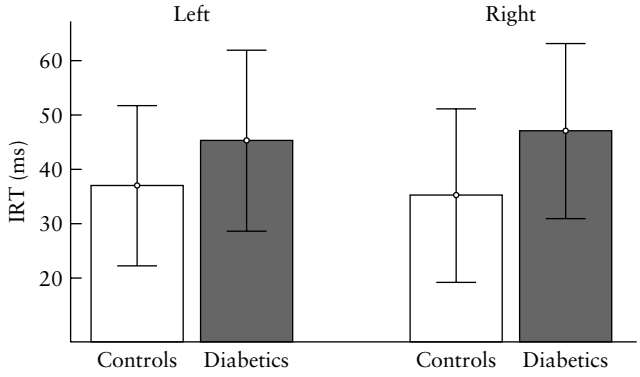

Figure 4 Isovolumetric relaxation time (IRT) on left and right sides of the heart in control subjects (□) and diabetic patients (■). Bars represent mean values and vertical lines represent 2 SD.

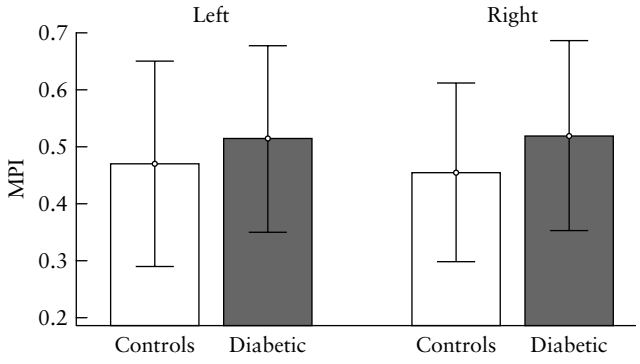

Figure 5 Myocardial performance index (MPI) on left and right sides of the heart in control subjects (□) and diabetic patients (■). Bars represent mean values and vertical lines represent 2 SD.

(left ventricle: 0.47 ± 0.09 vs. 0.5 ± 0.08, $P = 0.03$; right ventricle: 0.45 ± 0.08 vs. 0.52 ± 0.08, $P < 0.0001$; controls and diabetics, respectively; Figure 5 and Table 2). This lower global myocardial performance was the result of a prolonged myocardial relaxation time that was most marked in diabetics with an HbA1c of ≥ 7% ($P < 0.001$ vs. controls for both ventricles) (Figure 6, Table 2). There were no significant correlations between cardiac Doppler parameters and DV, UA indices and fetal heart rate ($P > 0.05$ for all).

In the intraobserver variability analysis, the mean ± SD difference for the left E/A ratio, ICT, IRT and

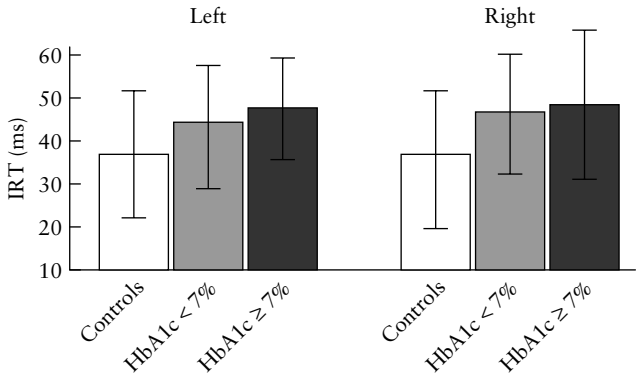

Figure 6 Isovolumetric relaxation time (IRT) on left and right sides of the heart in controls (□) and in diabetic patients with glycosylated hemoglobin A (HbA1c) either < 7% (▒) or ≥ 7% (■). Bars represent mean values and vertical lines represent 2 SD.

MPI were $0.3 \pm 6.5\%$, $9.0 \pm 8.2\%$, $-6 \pm 9.3\%$ and $1.4 \pm 4.8\%$, respectively. The mean ± SD difference for the right E/A ratio, ICT, IRT and MPI were $0.5 \pm 6.2\%$, $-5.1 \pm 9.9\%$, $4.9 \pm 9\%$ and $-3.5 \pm 4.5\%$, respectively. Standard deviations of the differences between paired measurements for each of the variables ranged from 4.5% to 9.9%. The corresponding coefficients of repeatability were acceptable, ranging between 9 and 19.8%.

DISCUSSION

Fetal cardiovascular development in women with diabetes mellitus can be affected by maternal hyperglycemia. Although associations between first-trimester hyperglycemia and cardiac defects are recognized, the effects of first-trimester hyperglycemia on cardiac performance have been less well studied. We evaluated the relationship between maternal hyperglycemia and first-trimester fetal cardiac performance parameters. In order to minimize potential confounding effects, cases and controls were matched for parameters of afterload and preload.

Our results, in a moderate- to high-risk population of diabetics, demonstrate an impact of hyperglycemia on fetal cardiac performance parameters, even in the absence of cardiac defects. Fetuses of diabetic mothers have slower postsystolic ventricular relaxation. Accordingly, diastolic ventricular filling relies more on atrial systole. These differences compared with controls are independent of placental blood flow resistance and preload, and are responsible for a decreased E/A ratio and a higher MPI. Although reduction in ventricular relaxation was apparent for both ventricles, the effect on filling appeared to be more prominent for the left ventricle. The degree of these abnormalities is related to first-trimester glycemic control and is most marked in women with a higher HbA1c.

Our findings are consistent with previous studies evaluating fetal cardiac functional impacts of maternal diabetes. Fetuses of diabetic mothers have been shown to have an accelerated increase in maximum and mean temporal velocities across AV valves through gestation compared with normal pregnancies[15]. Rizzo and coworkers demonstrated lower E/A ratios and abnormal precordial venous Doppler related to hyperglycemia, suggesting a relationship with impaired diastolic function and ventricular filling[8,16]. By controlling for peripheral vascular parameters, we were able to show that these observations are caused by cardiac effects rather than

Table 2 Cardiac function parameters in controls and diabetic pregnancies, overall and according to glycosylated hemoglobin A1 (HbA1c) levels

		Diabetic pregnancies (n = 63)					
	Controls (n = 63)	*All*		*HbA1c < 7%* (n = 26)		*HbA1c ≥ 7%* (n = 37)	
Parameter	*Mean ± SD*	*Mean ± SD*	P	*Mean ± SD*	P	*Mean ± SD*	P
Left ventricle							
Diastolic parameters							
E/A ratio	0.55 ± 0.06	0.51 ± 0.08	0.03	0.52 ± 0.07	NS	0.52 ± 0.09	< 0.05
IRT (ms)*	36.9 ± 7.41	45.8 ± 6.79	< 0.0001	43.3 ± 7.20	< 0.0001	47.6 ± 6.0	< 0.0001
Systolic parameter							
ICT (ms)	41.5 ± 8.81	38.3 ± 8.03	0.03	38.1 ± 7.49	NS	38.5 ± 8.49	NS
Global function parameter							
MPI	0.47 ± 0.09	0.5 ± 0.08	0.03	0.48 ± 0.05	NS	0.52 ± 0.09	< 0.05
Right ventricle							
Diastolic parameters							
E/A ratio	0.57 ± 0.07	0.56 ± 0.08	NS	0.57 ± 0.06	NS	0.56 ± 0.08	NS
IRT (ms)	35.6 ± 7.99	46.4 ± 7.32	< 0.0001	45.0 ± 6.3	< 0.0001	47.4 ± 7.9	< 0.0001
Systolic parameter							
ICT (ms)	39.0 ± 9.97	38.9 ± 8.0	NS	40.4 ± 8.5	NS	37.8 ± 7.6	NS
Global function parameter							
MPI	0.45 ± 0.08	0.52 ± 0.08	< 0.0001	0.51 ± 0.09	0.004	0.52 ± 0.08	0.001

P-values calculated vs control group. *HbA1c < 7 vs. HbA1c ≥ 7: $P = 0.053$. E/A ratio, ratio of peak velocities during early and late diastolic ventricular filling; ICT, isovolumetric contraction time; IRT, isovolumetric relaxation time; MPI, myocardial performance index; NS, not significant.

by alterations in preload and afterload. Russell and coworkers also confirmed decreased diastolic function and demonstrated a decline in global myocardial performance, predominantly as a result of significant prolongation of end-systolic ventricular relaxation[5]. Based on second-trimester follow-up examinations, their study further suggests that these abnormalities are confined to the first trimester. Hatem and coworkers, using tissue Doppler, suggested that diabetes mellitus is associated with alterations in fetal left-ventricular diastolic function[17]. Similarly to our findings, these previous investigations also documented a predominant effect of hyperglycemia on left-ventricular diastolic function. There are several possible explanations for these findings.

Fetal hypertrophic cardiomyopathy with impaired cardiac function complicates maternal diabetes independently of the degree of glycemic control[18,19]. The myocardial hypertrophy characteristically affects the interventricular septum, and to a lesser extent the ventricular free walls, and is associated with increased ventricular stiffness with a measurable impact on diastolic filling and systolic ejection[20]. While septal thickening may have already developed before 20 weeks' gestation[21], fetal hypertrophic cardiomyopathy and subsequent hemodynamic alterations generally become fully established in the second and third trimesters[22]. Russell *et al.* demonstrated altered diastolic function in patients with type 1 diabetes mellitus in the first trimester but could not demonstrate persistence of this finding[5]. These differences in timing, as well as the resolution of first-trimester cardiac-function abnormalities, may suggest an alternate underlying mechanism.

One of the experimentally documented first-trimester effects of hyperglycemia is altered gene expression of embryonic cardiac neural crest cells, leading to disturbed cell migration and differentiation with subsequent development of conotruncal cardiac abnormalities, typical of first-trimester diabetic fetopathy[2].

During neural crest ablation experiments it was also noted that decreased cardiac contractility and a significant reduction in the ejection fraction, consistent with cardiomyopathy, occurred before cardiac anomalies were established[23,24]. In the absence of any structural explanatory factors it was demonstrated that the underlying abnormalities were depressed L-type calcium current, decreased calcium transport, excitation–contraction coupling and calcium insensitivity of the contractile apparatus[25,26]. It was subsequently established that neural crest cells have two distinct functions in early cardiac development.

Migration is a well-recognized mechanism by which neural crest cells populate the conotruncus and complete the formation of the outflow tracts. Signaling is a second distinct function by which neural crest cells regulate contractile properties of the adjacent cardiac myocytes[27,28]. Accordingly, first-trimester fetal cardiac dysfunction observed with maternal hyperglycemia could result from abnormal neural crest signaling[23]. This would provide a plausible mechanism (distinct from the second-trimester structural myocardial changes) that has a sufficiently early onset to produce first-trimester findings which resolve as the role of the neural crest in the regulation of cardiac contractility declines.

A second possibility is that early embryonic cardiac contractile proteins respond differently to hyperglycemia. It has been established that there is a switch of myocardial contractile protein isoforms which is generally completed by the early second trimester[29]. Greater sensitivity of earlier isoforms to high glucose could theoretically explain why myocardial dysfunction can be observed in the first trimester but is no longer seen later as the adult forms of contractile proteins predominate in the myocardium.

Our study design was non-blinded and the measurements were performed by a single investigator (S.T.). While this may affect ascertainment bias and reproducibility, our findings are consistent with several previous studies. Both intraobserver variability and measures of repeatability were acceptable. We did not perform longitudinal follow-up throughout the trimesters and the neonatal period, and therefore cannot provide information about the persistence of cardiac functional abnormalities. Given the limitations of prenatal cardiac function assessment, the strengths of our study include the prospective case–control design. In addition, patients were matched for UA and venous Doppler indices to control for preload and afterload. Our statistical power was adequate to demonstrate differences in study parameters. While we cannot provide an anatomic correlate, our findings and the proposed underlying mechanism raise several important possibilities for future research. Experimental studies are necessary to evaluate further the differential impact of hyperglycemia on neural crest migration and signaling. It remains to be clarified whether the fate to develop conotruncal defects or early cardiac dysfunction is determined by a threshold of hyperglycemia or by blood glucose fluctuation. In addition, the predominance of left ventricular dysfunction observed in several studies requires further explanation. Finally, the distinction of resolving first-trimester cardiac dysfunction from newly developing second-trimester cardiomyopathy requires longitudinal follow-up studies initiated in the first trimester. Addressing these questions can potentially further clarify the timing, extent and long-term fetal cardiovascular impacts of maternal diabetes.

In conclusion, fetuses of diabetic mothers exhibited evidence of first-trimester diastolic myocardial dysfunction with worsening glycemic control. These findings are consistent with experimental models linking abnormal neural crest function and myocardial dysfunction[30]. It remains to be demonstrated whether hyperglycemia can induce neural crest dysfunction, even in the anatomically normal heart. The ability to document cardiac functional changes this early in pregnancy potentially opens new avenues to understand the range of fetal developmental consequences of maternal glycemic status.

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