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Characterization of fetal cardiac structure and function detected by echocardiography in women with normal pregnancy and gestational diabetes mellitus†

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Objectives To assess fetal cardiac structure and function in normal pregnancy and in the presence of gestational diabetes mellitus (GDM) using echocardiography measurements.

Material and methods We studied fetal cardiac structure and function in 169 uncomplicated singleton pregnancies and in 92 complicated by GDM. Maternal glycemic control was deemed adequate in 75 women and inadequate in 17. Fetal two-dimensional ultrasound, pulsed wave Doppler and tissue Doppler imaging (TDI) were used to assess cardiac walls thickness and cardiac function, both systolic [with ejection fraction (EF)] and diastolic [using early diastolic peak flow velocity (E)/late peak of diastolic velocity (A) and early diastolic peak velocity at the annulus (Ea)/late diastolic peak velocity at the annulus (Aa) ratios].

Results In normal pregnancies, fetal ventricular walls and interventricular septum thickness increased progressively with advancing gestation and were significantly thicker in the presence of GDM ($P < 0.001$) independently of maternal glycemic control. Fetal cardiac systolic function indicated by EF did not change during normal pregnancy, but was significantly increased ($P < 0.001$) in the presence of GDM independently of maternal glycemic control. Both pulsed wave Doppler and TDI indicators of fetal diastolic cardiac function increased during normal pregnancy, reaching a maximum at 36 to 40 weeks of gestation ($P < 0.001$). The presence of GDM did not affect pulsed wave Doppler indicators of diastolic function [ratio of early/late diastolic peak flow velocity (E/A ratio)], whereas TDI indices [ratio of early/late diastolic peak velocity at the annulus (Ea/Aa ratio)] were significantly lower after adjustment for gestational age and estimated fetal weight (EFW); and such changes were independent of maternal diabetic control ($P < 0.001$).

Conclusions Fetal cardiac wall thickness, cardiac systolic and diastolic functions are affected by GDM independently of glycemic control. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS: gestational diabetes mellitus; echocardiography; tissue Doppler imaging; diastolic cardiac function

INTRODUCTION

Gestational diabetes mellitus (GDM) affects up to 4% of pregnancies (Karcaaltincaba *et al*., 2009) and is associated with a fourfold increased risk of perinatal morbidity and mortality than normal pregnancy (Russell *et al*., 2008a). Myocardial hypertrophy and diastolic dysfunction are frequent in fetuses of diabetic mothers (Sardesai *et al*., 2001; Ullmo, 2007; Russell *et al*., 2008b), and they are thought to be secondary to maternal and fetal hyperglycemia (Rosenn, 2002). Some studies have also demonstrated that good diabetic control in women with GDM during pregnancy may lower the risk of such cardiac changes (Bung, 1993; Reece and Homko, 1994; Lindegaard and Nielsen, 2008); other studies have suggested the presence of some bias accounting for the increased risk (Russell *et al*., 2008a; Corrigan *et al*., 2009). However, it remains difficult to assess the effect of maternal glycemic levels on fetal cardiac development.

Fetal two-dimensional ultrasonography (US) and pulsed wave Doppler are viewed as excellent screening and ongoing evaluation tools, and are widely used for evaluation of cardiac anatomy and function during pregnancy(Bhat and Sahn, 2004; Davey *et al*., 2009). Indeed, fetal echocardiography performed at an adequate timing in pregnancy and by operators with specific expertise and skills achieves a high rate of diagnostic efficacy for fetal congenital heart defects(Bhat and Sahn, 2004; Small and Copel, 2004). Less clear is the value of echocardiography in fetuses with cardiac dysfunction (Srinivasan, 2000).

Tissue Doppler imaging (TDI) can supplement echocardiography (Lindegaard and Nielsen, 2008): It allows the measurement of high intensity and low velocity echoes of the myocardium, recognizing systolic

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and diastolic interdependency (Lindegaard and Nielsen, 2008; Corrigan *et al*., 2009) and can be applied to detect velocities of normal and abnormal cardiac structures during cardiac cycle (Huhta *et al*., 2003) independently from heart load and heart rate. TDI is thought to be a powerful and independent predictor of death in adults with diabetes, hypertension, ischemic heart diseases (Corrigan *et al*., 2009) and in the general adult population (Lindegaard and Nielsen, 2008). In addition, TDI has been shown to be a useful imaging tool for fetal cardiac assessment in intrauterine fetal growth restriction and fetal hydrops (Bhat and Sahn, 2004). However, to our knowledge, fetal TDI has not been applied to fetal cardiac functional assessment in the presence of GDM.

In this study, we have used two-dimensional US, pulsed wave Doppler and TDI to characterize the fetal cardiac structure and function in normal pregnancies as well as in pregnancies complicated by GDM, and we have evaluated the effect of glycemic control on the findings.

MATERIALS AND METHODS

Patients

This cross-sectional study was conducted between November 2006 and January 2009 and it included 210 women with uncomplicated singleton pregnancies attending routine prenatal care between 20 and 40 weeks of gestation (controls) and 92 women with GDM (GDM group). GDM was treated with dietary changes in 25 women and required insulin therapy in 67. Gestational age was determined by the last menstrual period or by the first trimester ultrasound. All women underwent fetal cardiac functional examination by two-dimensional US, pulsed wave Doppler and TDI. Data were acquired and recorded during the course of each scan. If some of the participants were examined more than once during pregnancy, the latest echocardiography data were included for the purpose of analysis. All patients signed a written informed consent. This study was approved by the Ethics Committee of the Obstetrics and Gynecology Hospital affiliated to Fudan University.

According to the classification system of the American Diabetes Association, GDM was defined as any degree of glucose intolerance with onset or first recognition during pregnancy, regardless of whether glucose intolerance began at an unknown time and went unrecognized before pregnancy, or developed during pregnancy. GDM was confirmed when two or more of the venous plasma concentrations met or exceeded the following thresholds after a 100-g oral glucose tolerance test: fasting blood glucose $\geq$95 mg/dL (5.3 mmol/L), 1 h blood glucose $\geq$180 mg/dL (10.0 mmol/L), 2 h blood glucose $\geq$155 mg/dL (8.6 mmol/L) and 3 h blood glucose $\geq$140 mg/dL (7.8 mmol/L) (American Diabetes Association, 2007). All women with GDM received nutritional counseling, and if needed pharmacologic therapy (insulin) according to the American Diabetes Association guidelines (American Diabetes Association, 2007). Blood glucose levels were recorded and valued 30 min before and 2 h after eating and at 22 : 00 h every night. Criteria for uncontrolled GDM in our study were as follows: fasting blood glucose $>$104 mg/dL ($>$5.8 mmol/L); postprandial blood glucose $>$140 mg/dL ($>$7.8 mmol/L). Exclusion criteria for all women were preeclampsia, pre-existing hypertension treated with antihypertensive drugs, renal disease, liver disease and hematologic diseases.

Fetal echocardiography measurements

Two-dimensional US and pulsed wave Doppler were performed with Voluson 730 Expert (GE Medical Systems, Kretztechnik, Zipf, Austria) using a 4 to 8-MHz curved linear array transabdominal transducers. A systematic two-dimensional fetal echocardiography scan was performed to record fetal parameters, including head circumference, biparietal diameter, abdominal circumference and femur length. Estimated fetal weight (EFW) was calculated using the Hadlock formula based on head circumference, biparietal diameter, abdominal circumference and femur length (Hadlock, 1985).

Under maternal voluntary suspended respiration without fetal movement or fetal breathing movement, the thickness of fetal intraventricular septum (IVS) and of ventricular walls was measured in a transverse four-chamber view with the cursor perpendicular to the IVS. Measurements were taken in triplicate at the middle of IVS or ventricular wall (Allan, 2004) at end-diastolic phase using cine loop (Figure 1A), stored for later offline evaluation by 4D view software (4D view Version 2.1; GE Medical Systems, Kretztechnik, Zipf, Austria). The average of three measurements was used for analysis. Transvalve inflow measurements, including mitral and tricuspid early diastolic peak flow velocity (E)/late peak of diastolic velocity (A) ratio, were recorded in the mode of valve leaflets in an apical four-chamber view (DeVore, 2005). Ejection fraction (EF) was measured as end-diastolic ventricular internal dimension (EDVID)$-$end-systolic ventricular internal dimension (ESVID)/EDVID. The transducer ultrasound beam was maintained at an angle of $<$20° to the direction of blood flow. The peak systolic velocity (PSV) of aorta (Ao) and pulmonary artery (PA) involved left ventricular and right ventricular outflow tract views with the Doppler sampling volume beneath Ao or pulmonary valve.

TDI was performed at the mitral and tricuspid annulus in apical four-chamber plane. The ultrasound beam was aligned parallel ($<$10°) to the intraventricular septum in the four-chamber view. Fetal systolic [early systolic peak velocity of annulus/late diastolic peak velocity of annulus (Sa)] and diastolic peak [early diastolic peak velocity at the annulus (Ea), late diastolic peak velocity at the annulus (Aa)] tissue velocity values of the annulus of atrioventricular valves were measured as the mean over three consecutive heart cycles with a 2-mm sample area fixed to the basal part of the left and right free wall (Figure 1B). All the obstetric ultrasound examinations were performed by one of the researchers (Y.R.).

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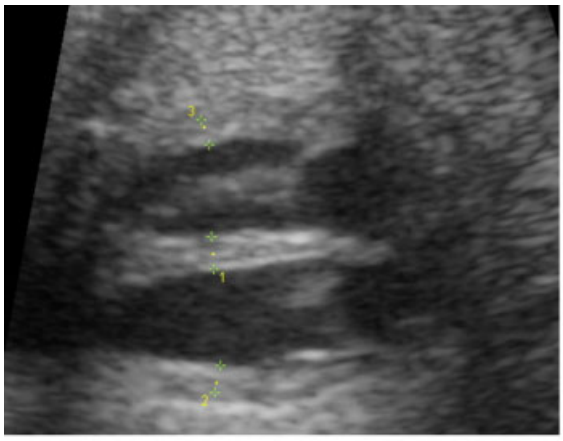
(A)



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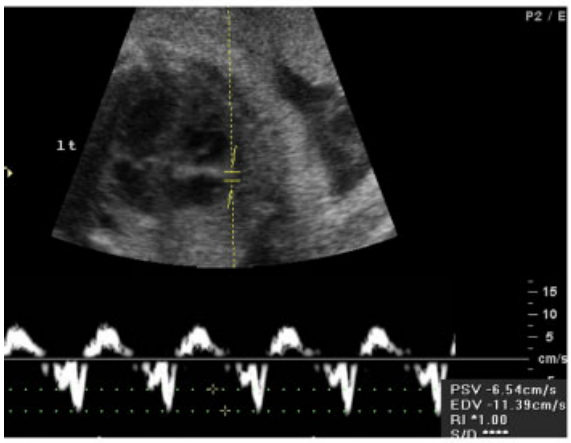

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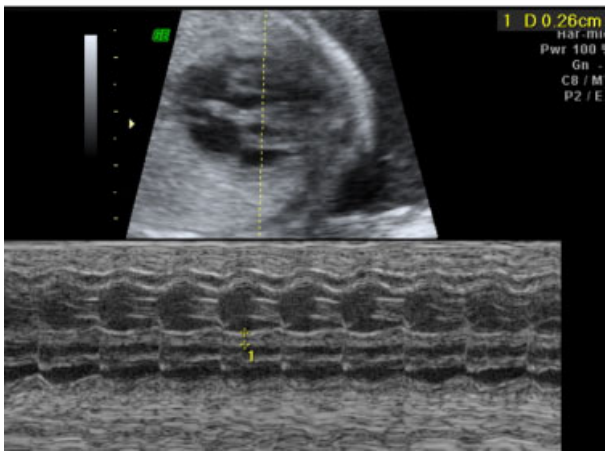

Figure 1—(A) Transverse four-chamber view at two-dimensional US, in which the thickness of intraventricular septum (IVS), right ventricular wall and left ventricular wall at end-diastolic phase are measured using cine loop, representing 1, 2 and 3 relatively. (B) Apical four-chamber view showing Doppler waveform at tricuspid annulus. The waveform above the baseline in uniphasic and bicuspid shape represented early systolic peak velocity of annulus/late diastolic peak velocity of annulus (Sa) and diastolic velocity of tricuspid annulus, relatively. Early diastolic peak velocity of annulus (Ea) wave and late diastolic peak velocity of annulus (Aa) wave corresponded to early ventricular filling of diastole and arterial systole, relatively. (C) Apical four-chamber view with M-mode scanning waveform. The appropriate measurement of thickness of IVS is represented by the number 1

Statistical analysis

Statistical analysis was performed using SPSS statistical software version 14.0 (SPSS, System for Windows, Chicago, IL, USA). Continuous variables were compared using either the *t*-test or one-way analysis of variance with Bonferroni correction, and correlations were calculated using Pearson's coefficient. Linear regression analysis was used to control for the effect of confounders. $P < 0.05$ was considered to be statistically significant.

RESULTS

Demographic characteristic of the patients

Among the 92 women with GDM, 75 had good blood glucose control and 17 had uncontrolled diabetes. Table 1 displays the population demographic and obstetric characteristics. Women with GDM were significantly older than women without GDM; they delivered at a lower gestational age and their newborns had heavier birth weight (Table 1; all $P < 0.001$). Neonates of women with uncontrolled GDM had higher rates of low Apgar's score at 5 min than those of women with well-controlled GDM or controls.

Fetal cardiac characteristic of women with normal pregnancy

As shown in Figure 2, in normal pregnancies, fetal cardiac structural indices, including fetal left ventricular posterior wall thickness at end diastole (LVPWD), right ventricular anterior wall thickness at end diastole (RVAWD), interventricular septal thickness at end diastole (IVSD), left ventricular posterior wall thickness at end systole (LVPWS), right ventricular anterior wall thickness at end systole (RVAWS) and interventricular septal thickness at end systole (IVSS) were significantly correlated with gestational age ($P < 0.001$). On the other hand, in cardiac diastolic function measurement, fetal E, ratio of early/late diastolic peak flow velocity (E/A ratio), Ea and ratio of early/late diastolic peak velocity at the annulus (Ea/Aa ratio) increased gradually toward term and reached a maximum at 36 to 40 weeks of gestation (Table 2; $P < 0.001$), together with gradually elevating fetal E between 20 and 32 weeks of gestation. Besides, there was no difference in fetal cardiac systolic function indicated by EF during pregnancy ($P > 0.05$).

Fetal cardiac characteristic of women with GDM

After adjustment for gestational age and EFW, fetal LVPWD, RVAWD, LVPWS, RVAWS, IVSD and IVSS were significantly thicker in pregnancies with GDM with or without good diabetic control than in normal pregnancies (Table 3; $P < 0.001$).

Table 1—Demographic and obstetric characteristics of women with normal pregnancy and gestational diabetes mellitus (GDM)

	Normal pregnancy ($n = 169$	Controlled GDM ($n = 75$)	Uncontrolled GDM ($n = 17$)
Maternal age (years)	27.6 ± 3.6	31.4 ± 4.1*	31.0 ± 4.1*
Gestational week at latest scan	29.2 ± 4.4	32.4 ± 4.4*	29.2 ± 3.4**
Primipara (%)	138/169 (82.2)	60/75 (80.0)	13/17 (76.5)
Delivery week	39.3 ± 1.4	38.1 ± 1.2*	37.8 ± 1.5*
Birth weight (g)	3323 ± 384	3446 ± 459*	3497 ± 664*
Cesarean section rate (%)	116/169 (68.6)	54/75 (72.0)	12/17 (70.2)
5 min Apgar's score ≤ 7 (%)	4/169 (1.8)	1/75 (1.4)	2/17(11.8) *,**

Values were presented as mean $\pm$ SD or n (%).
* $P < 0.001$ when compared with normal pregnancy.
** $P < 0.001$ when compared with women with controlled GDM.

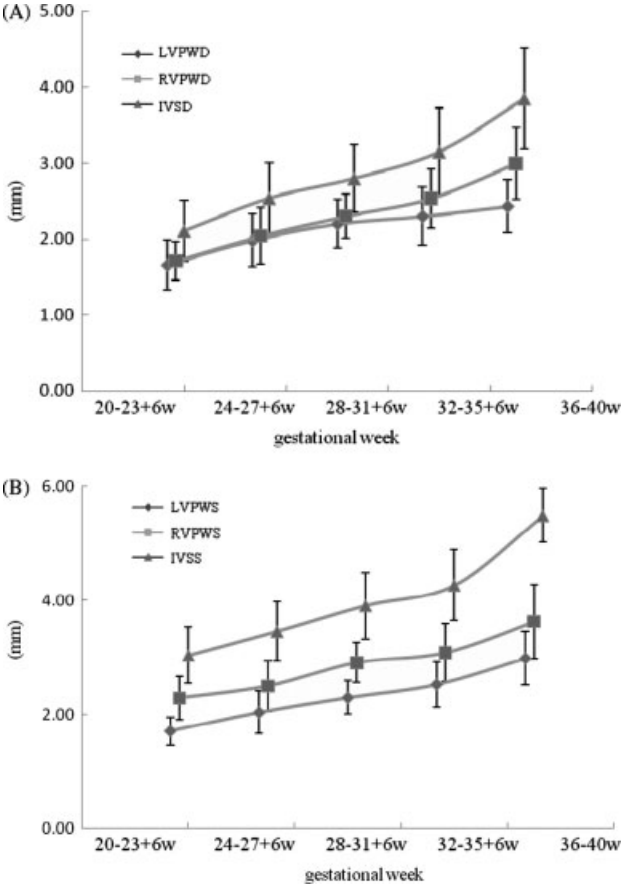

Figure 2—Cardiac structural evaluations of normal pregnant women by gestational age. (A) Evaluation at the end of diastole. (B) Evaluation at the end of systole. Left ventricular posterior wall thickness at end diastole (LVPWD), right ventricular anterior wall thickness at end diastole (RVAWD), interventricular septal thickness at end diastole (IVSD), left ventricular posterior wall thickness at end systole (LVPWS), right ventricular anterior wall thickness at end systole (RVAWS), interventricular septal thickness at end systole (IVSS)

In addition, fetal EF, Ao PSV and PA PSV were greater, and fetal Ea and Ea/Aa ratio were lower in pregnancies with GDM compared with controls after adjustment for gestational age, EFW, ventricular wall thickness at end diastole (VWD) and IVS ($P < 0.001$). There was no significant difference in any of the above measurements between fetuses of controlled versus uncontrolled diabetic pregnancies. Both, fetal E values and E/A ratio, indicating fetal cardiac diastolic function, were significantly lower in pregnancies with uncontrolled GDM ($P < 0.001$) than controlled GDM. There was no difference in Sa values among the three groups.

DISCUSSION

During normal pregnancy, the fetal heart underwent a continuous development of diastolic function, as detected by TDI, together with increased cardiac wall thickness at two-dimensional US and pulsed wave Doppler detection. We have found that fetal cardiac wall thickness was increased in pregnancies complicated by GDM, and the increase was independent of glycemic control. Moreover, diastolic fetal cardiac function, as measured by Maya (Sardesai *et al*., 2001), was impaired in GDM and this effect was independent of IVS.

Firstly, in normal pregnancies, we have found that fetal Ea and Ea/Aa ratios using TDI increased progressively throughout gestation and reached a maximum at 36 to 40 weeks of gestation; similar increases were present in other echocardiography parameters, including fetal cardiac walls and septum thickness as well as E and E/A ratio, partly in agreement with previous studies (Jaeggi *et al*., 2001). Our study covered the second half of pregnancy, providing a clue that fetal cardiac diastolic function and structural development are gradual and progressive through the entire pregnancy.

Secondly, we have shown that GDM was associated with a significant increase in the thickness of all cardiac walls compared with normal pregnancies, confirming in part the results of previous studies (Jaeggi *et al*., 2001). Distinguishing itself from other published studies that have focused on populations of women with pre-existing diabetes (Penney *et al*., 2003) or GDM (Zielinsky, 2004, 2009) without controlling for gestational age and fetal size, our results show that changes in cardiac wall thickness persisted after adjustment for gestational age and EFW. We hypothesize that maternal hyperglycemia may underlie the structural changes we observed as it can lead to fetal hyperinsulinism (Greco, 2003), hyperplasia and hypertrophy of myocardial cells by increasing fat and protein synthesis (Mehta and Hussain, 2003).

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Table 2—Cardiac functional evaluations of normal pregnant women by gestational age

	20 to 23^{+6} weeks		24 to 27^{+6} weeks		28 to 31^{+6} weeks		32 to 35^{+6} weeks		36 to 40 weeks	
	LV	RV	LV	RV	LV	RV	LV	RV	LV	RV
EF	0.28 ± 0.04	0.27 ± 0.02	0.33 ± 0.06	0.30 ± 0.05	0.28 ± 0.04	0.27 ± 0.05	0.32 ± 0.04	0.31 ± 0.03	—	—
E (cm/s)	32.04 ± 5.57	35.86 ± 4.02	34.71 ± 5.33	38.63 ± 5.47	37.98 ± 5.70	40.66 ± 7.81	37.70 ± 5.77	40.74 ± 8.02	35.69 ± 4.25	40.79 ± 7.21
E/A ratio*	0.62 ± 0.15	0.65 ± 0.10	0.71 ± 0.09	0.71 ± 0.11	0.76 ± 0.80	0.75 ± 0.15	0.76 ± 0.87	0.76 ± 0.14	0.81 ± 0.13	0.77 ± 0.27
Ea (cm/s) *	4.84 ± 0.86	5.90 ± 1.49	5.31 ± 0.95	6.52 ± 1.68	6.40 ± 1.51	7.73 ± 1.50	6.88 ± 0.96	8.37 ± 1.45	7.36 ± 1.40	9.71 ± 1.93
Ea/Aa ratio*	0.61 ± 0.01	0.57 ± 0.11	0.68 ± 0.15	0.64 ± 0.22	0.72 ± 0.14	0.71 ± 0.09	0.78 ± 0.16	0.74 ± 0.08	0.80 ± 0.10	0.76 ± 0.13

Values are presented as mean ± SD or *n* (%).
EF, ejection fraction; E, early diastolic peak flow velocity; E/A ratio, early/late diastolic peak flow velocity; Ea, early diastolic peak velocity of annulus; Ea/Aa ratio, early/late diastolic peak velocity of annulus; LV, left ventricular; RV, right ventricular.
* Pearson's correlation: $P < 0.001$.

Thirdly, we have demonstrated that fetal cardiac diastolic function was impaired in women with GDM, independent of the thickness of ventricular wall and IVS, as indicated by parameters for fetal cardiac diastolic function, including Ea, Ea/Aa ratio using TDI, as well as the traditional E/A obtained with pulsed wave Doppler. In addition, there were differences in fetal Ao PSV and PA PSV among the three groups, reflecting possible differences in ventricular contractility, arterial pressure and cardiac after-load (Abuhamad, 2004). Therefore, regardless of the E/A atrioventricular ratio as an index of ventricular diastolic function dependent on ventricular preload and compliance influenced by fetal hypoxemic of GDM (Abuhamad, 2004; Costa *et al*., 2009), TDI is a potential tool for fetal cardiac diastolic functional evaluation which is relatively independent of heart rate and heart load(Huhta *et al*., 2003). Tricuspid E/A ratio in GDM decreased more than mitral E/A ratio, possibly due to the fact that fetal right ventricular function exhibits greater sensitivity to changes in after-load (Rychik, 2004; Watanabe, 2009), as well as the fact that the increased placenta vascular resistance in GDM (Aoki *et al*., 2004; Madazlı *et al*., 2008) may induce diastolic dysfunction in the right ventricle. Because our postnatal follow-up is not yet completed, the underlying mechanisms for our findings remain speculative.

In addition, we have used two-dimensional US for the measurement of the thickness of IVS and ventricular wall instead of M-mode examination as Lacombe (Lacombe *et al*., 2007). M-mode scanning is an alternative that is widely used for infant heart measurements (Veille *et al*., 1996). We have found that observed values in M-mode scanning were comparatively higher than those obtained using two-dimensional US, possibly due to impermanent fetal position (Figure 1C); the latter may thus be a preferable alternative for the vertical visualization of heart structure, avoiding the deviation caused by fetal position.

Some limitations of our study deserve comment. Annular movements of the fetal heart were evaluated in apical four-chamber plane, and measured the so-called subendocardial longitudinal fiber velocities, which are different from radial velocities obtained from anterior and posterior wall movements. Longitudinal fiber velocities are of a greater magnitude and easier to obtain; further studies are needed to explore the differences among modalities of TDI evaluation.

In conclusion, fetal cardiac wall thickness was increased in women with controlled or uncontrolled GDM, and diastolic function (indicated by Ea and Ea/Aa ratios at TDI) was impaired, independent of IVS. Hence, Ea and Ea/Aa ratio may be promising TDI parameters for fetal cardiac diastolic functional evaluation. The role of TDI in the detection of fetal cardiac dysfunction in GDM needs further research.

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Table 3—Cardiac evaluations among women with normal pregnancy, controlled gestational diabetes mellitus (GDM) and uncontrolled GDM

	Normal pregnancy		Controlled GDM		Uncontrolled GDM	
	LV	RV	LV	RV	LV	RV
Two-dimension						
VWD (mm)	2.23 ± 0.51	2.31 ± 0.52	2.96 ± 0.79*	3.05 ± 0.71*	2.75 ± 0.64*	2.85 ± 0.61*
VWS (mm)	2.77 ± 0.48	2.85 ± 0.66	3.62 ± 0.89*	3.68 ± 0.86*	3.48 ± 0.99*	3.52 ± 0.79*
IVSD (mm)	2.85 ± 0.73		3.96 ± 1.16*		4.00 ± 1.04*	
IVSS (mm)	3.96 ± 0.83		5.17 ± 1.22*		5.34 ± 1.78*	
EF	0.28 ± 0.25	0.24 ± 0.04	0.31 ± 0.08*	0.25 ± 0.08*	0.30 ± 0.06*	0.25 ± 0.07*
Pulsed wave Doppler						
Ao PSV (cm/s)	86.68 ± 0.77		92.57 ± 1.15*		93.46 ± 2.12*	
PA PSV (cm/s)	68.16 ± 0.70		71.88 ± 1.06*		71.63 ± 1.95*	
E (cm/s)	36.08 ± 5.70	39.56 ± 6.79	36.31 ± 5.62	38.84 ± 7.87	39.31 ± 7.68*,**	38.94 ± 7.94
E/A ratio	0.73 ± 0.10	0.72 ± 0.09	0.74 ± 0.12	0.67 ± 0.28	0.69 ± 0.11*,**	0.67 ± 0.24
TDI						
Mitral Sa (cm/s)	5.17 ± 0.068		5.74 ± 0.103*		5.48 ± 0.190	
Tricuspid Sa (cm/s)	6.48 ± 0.072		6.65 ± 0.110		6.14 ± 0.200*,**	
Ea (cm/s)	6.13 ± 1.32	5.36 ± 1.09	5.96 ± 1.32	5.16 ± 0.89	5.68 ± 1.21*,**	4.94 ± 1.03*
Ea/Aa ratio	0.71 ± 0.14	0.72 ± 0.22	0.66 ± 0.38*	0.67 ± 0.18*	0.62 ± 0.12*	0.64 ± 0.16*,**

Values are presented as mean ± SD after multivariate general linear model adjusted by gestational age, EFW, VWD and IVS. Covariates appearing in the model were evaluated at the following values: gestational age = 30.44 weeks, EFW = 1687.24 g, LVPWD = 2.49 mm, RVAWD = 2.58 mm and IVSS = 3.28 mm.

VWD, ventricular wall thickness at end diastole; IVSD, interventricular septal thickness at end diastole; VWS, ventricular wall thickness at end systole; IVSS, interventricular septal thickness at end systole; EF, ejection fraction; E, early diastolic peak flow velocity; E/A ratio, early/late diastolic peak flow velocity; Ea, early diastolic peak velocity of annulus; Sa, early systolic peak velocity of annulus/late diastolic peak velocity of annulus; Ea/Aa ratio, early diastolic peak velocity of annulus/late diastolic peak velocity of annulus; Ao PSV, aorta peak systolic velocity; PA PSV, pulmonary artery peak systolic velocity; TDI, tissue Doppler imaging.

* $P < 0.001$ when compared with normal pregnancy.

** $P < 0.001$ when compared with women with controlled GDM.

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REFERENCES

Abuhamad A. 2004. Color and pulsed Doppler in fetal echocardiography. *Ultrasound Obstet Gynecol* **24**(1): 1–9.

Allan L. 2004. Technique of fetal echocardiography. *Pediatr Cardiol* **25**(3): 223–233.

American Diabetes Association. 2007. Gestational diabetes mellitus. *Diabetes Care* **26**: s103–s105.

Aoki M, Harada K, Ogawa M. 2004. Quantitative assessment of right ventricular function using doppler tissue imaging in fetuses with and without heart failure. *J Am Soc Echocardiogr* **17**(1): 28–35.

Bhat AH, Sahn DJ. 2004. Latest advances and topics in fetal echocardiography. *Curr Opin Cardiol* **19**(2): 97–103.

Bung P. 1993. Therapeutic exercise for insulin-requiring gestational diabetics: effects on the fetus results of a randomized prospective longitudinal study. *J Perinat Med* **21**(2): 125–137.

Corrigan N, Brazil DP, McAuliffe F. 2009. Fetal cardiac effects of maternal hyperglycemia during pregnancy. *Birth Defects Res A Clin Mol Teratol* **85**(6): 523–530.

Costa VN, Nomura RM, Reynolds KS, Miyadahira S, Zugaib M. 2009. Effects of maternal glycemia on fetal heart rate in pregnancies complicated by pregestational diabetes mellitus. *Eur J Obstet Gynecol Reprod Biol* **143**(1): 14–17.

Davey BT, Seubert DE, Phoon CK. 2009. Indications for fetal echocardiography high referral, low yield? *Obstet Gynecol Surv* **64**(6): 405–415.

DeVore GR. 2005. Assessing fetal cardiac ventricular function. *Semin Fetal Neonatal Med* **10**(6): 515–541.

Greco P. 2003. Timing of fetal growth acceleration in women with insulin-dependent diabetes. *Fetal Diagn Ther* **18**(6): 437–441.

Hadlock FP. 1985. Estimation of fetal weight with the use of head, body, and femur measurements–a prospective study. *Am J Obstet Gynecol* **151**(3): 333–337.

Huhta JC, Kales E, Casbohm A. 2003. Fetal tissue Doppler–a new technique for perinatal cardiology. *Curr Opin Pediatr* **15**(5): 472–474.

Jaeggi ET, Fouron JC, Proulx F. 2001. Fetal cardiac performance in uncomplicated and well-controlled maternal type I diabetes. *Ultrasound Obstet Gynecol* **17**(4): 311–315.

Karcaaltincaba D, Kandemir O, Yalvac S, Guvendag-Guven S, Haberal A. 2009. Prevalence of gestational diabetes mellitus and gestational impaired glucose tolerance in pregnant women evaluated by National Diabetes Data Group and Carpenter and Coustan criteria. *Int J Gynaecol Obstet* **106**(3): 246–249.

Lacombe VA, Viatchenko-Karpinski S, Terentyev D, *et al*. 2007. Mechanisms of impaired calcium handling underlying subclinical diastolic dysfunction in diabetes. *Am J Physiol Regul Intergr Comp Physiol* **293**: 1787–1797.

Lindegaard ML, Nielsen LB. 2008. Maternal diabetes causes coordinated down-regulation of genes involved with lipid metabolism in the murine fetal heart. *Metabolism* **57**(6): 766–773.

Madazlı R, Tuten A, Calay Z, Uzun H, Uludag S, Ocak V. 2008. The incidence of placental abnormalities, maternal and cord plasma malondialdehyde and vascular endothelial growth factor levels in women with gestational diabetes mellitus and nondiabetic controls. *Gynecol Obstet Invest* **65**(4): 227–232.

Mehta A, Hussain K. 2003. Transient hyperinsulinism associated with macrosomia, hypertrophic obstructive cardiomyopathy, hepatomegaly, and nephromegaly. *Arch Dis Child* **88**(9): 822–824.

Penney GC, Mair G, Pearson DW. 2003. Outcomes of pregnancies in women with type 1 diabetes in Scotland: a national population-based study. *BJOG* **110**(3): 315–318.

Reece EA, Homko CJ. 1994. Assessment and management of pregnancies complicated by pregestational and gestational diabetes mellitus. *J Assoc Acad Minor Phys* **5**(3): 87–97.

Rosenn BM. 2002. Antenatal fetal testing in pregnancies complicated by gestational diabetes mellitus. *Semin Perinatol* **26**(3): 210–214.

Russell NE, Foley M, Kinsley BT, Firth RG, Coffey M, McAuliffe FM. 2008a. Effect of pregestational diabetes mellitus on fetal cardiac function and structure. *Am J Obstet Gynecol* **199**(3): 312 e1–e7.

Russell NE, Holloway P, Quinn S, Foley M, Kelehan P, McAuliffe FM. 2008b. Cardiomyopathy and cardiomegaly in stillborn infants of diabetic mothers. *Pediatr Dev Pathol* **11**(1): 10–14.

Rychik J. 2004. Fetal cardiovascular physiology. *Pediatr Cardiol* **25**(3): 201–209.

Sardesai MG, Gray AA, McGrath MM, Ford SE. 2001. Fatal hypertrophic cardiomyopathy in the fetus of a woman with diabetes. *Obstet Gynecol* **98**: 925–927.

Small M, Copel J, 2004. Indications for fetal echocardiography. *Pediatr Cardiol* **25**: 210–222.

Srinivasan S. 2000. Fetal echocardiography. *Indian J Pediatr* **67**(Suppl 3): S20–S25.

Ullmo S. 2007. Pathologic ventricular hypertrophy in the offspring of diabetic mothers: a retrospective study. *Eur Heart J* **28**(11): 1319–1325.

Veille JC, Hanson R, Steele L, Tatum K. 1996. M-mode echocardiographic evaluation of fetal and infant hearts: longitudinal follow-up study from intrauterine life to year one. *Am J Obstet Gynecol* **175**(4): 922–928.

Watanabe S. 2009. Characterization of ventricular myocardial performance in the fetus by tissue Doppler imaging. *Circ J* **73**(5): 943–947.

Zielinsky P. 2004. Study of global left atrial shortening in fetuses of diabetic mothers. *Arq Bras Cardiol* **83**(6): 473–475.

Zielinsky P. 2009. Left atrial shortening fraction in fetuses with and without myocardial hypertrophy in diabetic pregnancies. *Ultrasound Obstet Gynecol* **33**(2): 182–187.