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Aortic isthmus blood flow in fetuses of diabetic mothers

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Objective To test the hypothesis that the aortic isthmus flow index (IFI) is lower in fetuses of diabetic mothers than in fetuses of nondiabetic mothers.

Study Design We performed a cross-sectional observational study to assess the IFI in fetuses, with ($n = 13$) and without ($n = 37$) myocardial hypertrophy, of mothers with diabetes mellitus and in fetuses of nondiabetic mothers ($n = 23$). Analysis of variance and Tukey test were used to assess differences among the groups.

Results There were no differences in maternal or gestational age among the groups. In fetuses of diabetic mothers, the mean IFI in fetuses with myocardial hypertrophy was 1.19 ± 0.06, and in fetuses without it was 1.18 ± 0.09. The mean IFI in fetuses of nondiabetic mothers was 1.32 ± 0.07 ($P < 0.001$).

Conclusions The IFI in fetuses of diabetic mothers is lower than in fetuses of nondiabetic mothers, possibly as a result of a decreased left ventricular compliance. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS: fetal myocardial hypertrophy; maternal diabetes; fetal diastolic function; isthmus blood flow index

INTRODUCTION

Improvements in healthcare for pregnant diabetic women and adequate management have led to reductions in associated morbidity and mortality; however, neonatal complications remain more frequent in these women than in women in the general population (Oberhoffer *et al*., 1997; Kim *et al*., 2002). Fetal myocardial hypertrophy is found in about one-third of fetuses of diabetic mothers (Weiner *et al*., 1999).

Echocardiography is the primary tool used to assess fetal cardiac function (Danford *et al*., 1986; Allan, 2000). Fetal left ventricular diastolic dysfunction is highly prevalent in maternal diabetes, even before the appearance of myocardial hypertrophy. Various echocardiographic parameters have been used to assess fetal diastolic function abnormalities (Nishimura *et al*., 1989; Weber, 1996; Miyague *et al*., 1997; Little *et al*., 1998; Macklon *et al*., 1998; Firpo and Zielinsky, 2003; Zielinsky *et al*., 2003, 2004; Hatem *et al*., 2008). The aortic isthmus, the only true arterial shunt of fetal circulation, directs fetal blood flow to the cephalic part of the body and to the descending aorta and the umbilical artery (Fouron, 2003; Acharya, 2009). Normally, there is anterograde flow through the aortic isthmus during both systole and diastole (Del Rio *et al*., 2008; Figueras *et al*., 2009; Fouron *et al*., 2009) (Figure 1), even though there is also a normal short duration low velocity retrograde flow at end systole (Acharya, 2009) (Figure 1A). The aortic isthmus blood flow index (IFI), described by Fouron (2003) is obtained by adding the systolic and diastolic velocity–time integrals and dividing the sum by the systolic velocity–time integral. This index represents the contributions of both ventricles to ejection, in relation to load conditions and cerebroplacental balance. Thus, IFI values can be altered when this balance is affected by hypoxia, increased placental resistance, decreased cerebral circulation resistance, or changes in cardiac preload and afterload. Therefore, a decrease in the aortic isthmus flow is an indication of functional impairment (Del Rio *et al*., 2008; Acharya, 2009; Figueras *et al*., 2009; Fouron *et al*., 2009; Hernandez-Andrade *et al*., 2009; Vimpeli *et al*., 2009). Changes in left ventricular diastolic function in fetuses of diabetic mothers may interfere with left atrial dynamics and with the antegrade flow to the descending aorta, potentially affecting aortic isthmus blood flow and the IFI.

This study tested the hypothesis that the IFI in fetuses (with or without myocardial hypertrophy) of diabetic mothers is lower than that in fetuses of nondiabetic mothers.

MATERIALS AND METHODS

Consecutive fetuses (gestational age: 25 weeks to term) of mothers with pregestational or gestational diabetes mellitus were included in the study. The fetuses were examined by obstetrical ultrasound and fetal echocardiography during a period of two years. Mothers had been referred to the Fetal Cardiology Unit of the Institute of Cardiology of Rio Grande do Sul by several prenatal services in the city.

The sample of fetuses from diabetic mothers comprised 13 fetuses with myocardial hypertrophy and 37 fetuses without myocardial hypertrophy. The control group comprised normal fetuses of similar gestational age from

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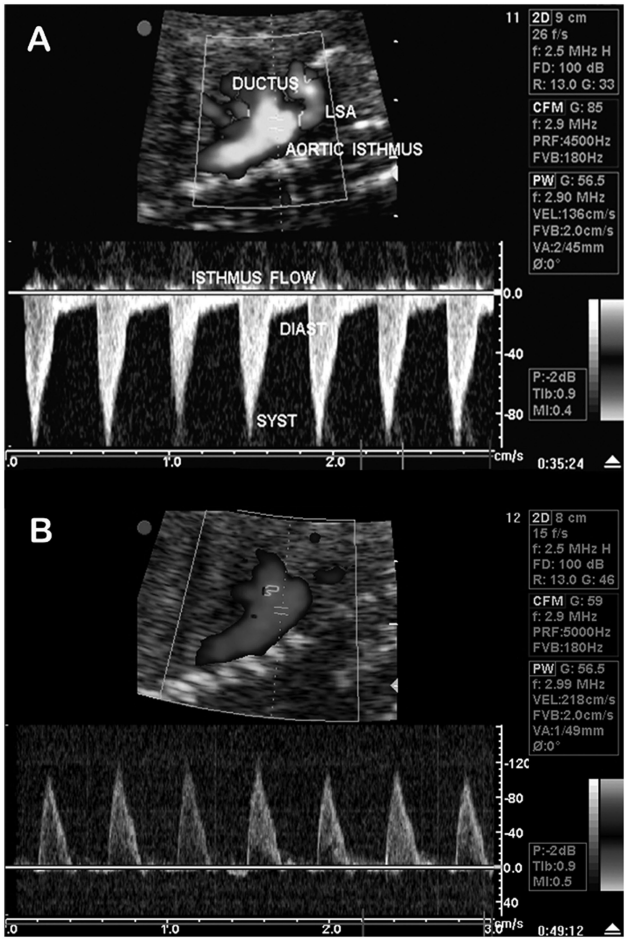

Figure 1A—32 weeks fetus from a nondiabetic mother. Flow through the aortic isthmus, located between the origin of the left subclavian artery and the aortic end of the ductus. Both antegrade systolic and diastolic flow are present. Figure 1B—33 weeks fetus from a diabetic mother with septal hypertrophy. The diastolic antegrade isthmical flow has a decreased velocity

disease-free mothers who were examined by routine fetal echocardiography to screen for cardiac abnormalities. None of the fetuses showed Doppler changes in the uterine, umbilical, or middle cerebral arteries.

Fetuses were excluded if they were outside of the gestational age range or had any morphological or functional cardiac abnormality, with the exception of septal hypertrophy.

Diabetes during pregnancy was diagnosed according to the Coustan and Carpenter criteria (Coustan *et al*., 1993). Data about gestational age, confirmed by measurements of biparietal diameter and femur length, were collected during obstetric ultrasound.

Fetal echocardiography was performed using Acuson ASPEN equipment with 4–7 MHz curved-array transducers or 2.25–4 MHz phased array transducers. Myocardial hypertrophy was established when septal thickness was greater than two standard deviations of the mean by M mode or two-dimensional image, according to the accepted nomogram (Zielinsky *et al*., 1997). Interobserver and intraobserver variability of septal thickness measurements were tested by Bland–Altman plots.

Aortic isthmus flow waveforms were recorded from the long aortic arch view or, alternatively, from the three-vessel trachea view (Rizzo *et al*., 2008). The IFI was obtained by the technique described by Fouron in 2003, using pulsed-wave Doppler flow analysis. IFI was calculated as the ratio between the sum of systolic and diastolic velocity–time integrals and the systolic velocity–time integral ([svi + dvi]/svi).

Nominal and continuous data are presented as means $\pm$ standard deviations. Analysis of variance (ANOVA) and Tukey test were used to assess differences among the three groups, with < 0.05 considered significant. Data were analyzed using the statistical package SPSS 15.0. Reproducibility of IFI Doppler measurement was tested. Intraobserver variability was assessed in 12 nonconsecutive fetuses (all from the control group) by repeating the measurements on two occasions (2 days apart) under the same basal conditions. Interobserver variability was performed with measurements of ten nonselected cases in the same day consecutively by a second observer who was unaware of the results of the first examination. Intraclass correlation coefficients were calculated to measure the strength of the agreement between the two sets of measurements. Bland–Altman charts were created to show the mean of differences between the measurements.

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RESULTS

Fetuses of 73 pregnant women were examined: 50 mothers (68.5%) had gestational or pregestational diabetes and 23 (31.5%) did not have diabetes and were included in the control group. Thirteen of the fetuses (26%) of diabetic mothers had septal hypertrophy and 37 (74%) did not. Mean interventricular septum thickness in fetuses with myocardial hypertrophy was 5.1 ± 0.7 (range: 3.5–5.8) mm, in those without hypertrophy it was 3.1 ± 0.4 (range: 2.0–4.4) mm and in fetuses of mothers without diabetes it was 3.0 ± 0.2 (range: 2.5–3.8) mm ($P = 0.001$). Interobserver variability of the interventricular septal thickness measurement was less than 10% of the average in 22 out of 25 cases and intraobserver variability was less than 20% of the average in 12 out of 15 cases.

Table 1 displays the demographic and echocardiographic characteristics of the study population. Mean maternal age was 30.9 ± 6.5 years (range: 15 to 43 years). There was no statistically significant difference in mean maternal age among the three groups ($P = 0.20$). Mean gestational age was 31.59 ± 0.03 weeks (range: 25 to 39 weeks (Table 1). Gestational age at echocardiography did not differ among the three groups ($P = 0.95$). In the diabetic mothers there were no significant differences in insulin or drug usage between those with and without fetal myocardial hypertrophy. Pregestational diabetes was present in six mothers (46%) of fetuses with myocardial hypertrophy and in seven (19%) of fetuses without myocardial hypertrophy ($P = 0.04$). Diabetes was well controlled by diet alone or by insulin administration in all patients, and their HbA1c levels were within normal limits.

Of the 73 fetuses examined, none showed increased resistance in the uterine arteries, nor did they show changes in the resistance indices in the umbilical and middle cerebral arteries (Table 2).

All fetuses showed the typical aortic isthmus flow pattern, with antegrade systolic and diastolic waveforms. A narrow low velocity retrograde flow at end systole was recorded in 44 fetuses from diabetic mothers and in 19 control fetuses. There were no significant differences in the mean systolic velocity–time integrals among the three groups ($P = 0.58$; Table 1 and Figure 2). Comparing the mean diastolic velocity–time integrals among the three groups, there was a significant lower velocity–time integral in fetuses of diabetic mothers, regardless of the presence or absence of myocardial hypertrophy ($P = 0.001$; Figure 3). Intraclass correlation coefficients of interobserver and intraobserver variations for Doppler IFI measurements were 0.89 (95% confidence interval: 0.78–0.95) and 0.92 (95% confidence interval: 0.82–0.96), respectively. Similarly, the mean IFI of fetuses (with and without hypertrophy) of diabetic mothers was significantly lower than the mean IFI of the control fetuses ($P = 0.001$; Figure 4).

DISCUSSION

Impairment of fetal left ventricle diastolic function in maternal diabetes have been demonstrated in many studies (Nishimura *et al*., 1989; Weber, 1996; Miyague *et al*., 1997; Little *et al*., 1998; Macklon *et al*., 1998; Firpo and Zielinsky, 2003; Zielinsky *et al*., 2003, 2004; Hatem *et al*., 2008). This study compared the dynamics of flow through the aortic isthmus in fetuses of mothers with those of fetuses of nondiabetic mothers. Fetuses of diabetic mothers, regardless of the presence of myocardial hypertrophy, had lower velocity–time integrals, and, as a result, lower IFIs than fetuses of mothers with normal glucose levels, confirming our initial hypothesis. Aortic isthmus flow is easy to record, both from the long aortic arch view or the three-vessel trachea view (Rizzo *et al*., 2008), and we did not have any losses from unsuccessful recordings.

The classical approach to the study of ventricular function is the analysis of atrioventricular flow velocities (Little *et al*., 1998; Macklon *et al*., 1998). Studies of alternative parameters to assess left ventricular diastolic function in fetuses of mothers with diabetes (Danford *et al*., 1986; Nishimura *et al*., 1989; Weber, 1996) have demonstrated alterations in the septum primum excursion index (Firpo and Zielinsky, 2003) and pulmonary vein impedance (Zielinsky *et al*., 2003). These studies have shown that fetuses of diabetic mothers have a higher preload than fetuses of normal mothers.

During diastole, when the two semilunar valves are closed, the downstream direction of the isthmus blood flow will be affected by the vascular impedances in the brain and in the placenta. Doppler flow velocity in the aortic isthmus in normal fetuses is antegrade in both

Table 1—Characteristics of the three study groups: fetuses with myocardial hypertrophy from diabetic mothers, fetuses without myocardial hypertrophy from diabetic mothers, and fetuses of nondiabetic mothers

	Total	D + MH	D w/o MH	Controls	*P*
n	73	13	37	23	
Age (years)	30.9 ± 6.5	33.0 ± 7.3	29.6 ± 7.3	31.8 ± 3.9	0.201
GA (weeks)	31.6 ± 2.9	31.9 ± 3.5	31.5 ± 3.2	31.6 ± 2.2	0.948
Systolic VTI (m)	0.093 ± 0.025	0.087 ± 0.022	0.095 ± 0.031	0.095 ± 0.016	0.582
Diastolic VTI (m)	0.021 ± 0.010	0.016 ± 0.006^{a}	0.017 ± 0.009^{b}	$0.029^{ab} \pm 0.006$	< 0.001*
Calculated IFI	1.228 ± 0.098	1.193 ± 0.063^{a}	1.185 ± 0.088^{b}	$1.315^{ab} \pm 0.069$	< 0.001*

D, diabetes; MH, myocardial hypertrophy; GA, gestational age; VTI, velocity–time integral; IFI, aortic isthmus flow index.
[a, b, ab]Tukey multiple comparison test. Mean values marked with the same letter differ significantly ($P < 0.05$).
*ANOVA.

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Table 2—Results of Doppler analysis of uterine, umbilical, and cerebral arteries

	Total	D + MH	D w/o MH	Controls	*P*
n	73	13	37	23	
Age (years)	31.6 ± 2.9	31.9 ± 3.5	31.5 ± 3.2	31.6 ± 2.2	0.948
UA RI	0.58 ± 0.15	0.50 ± 0.11	0.49 ± 0.06	0.61 ± 0.16	0.901
MCA RI	0.70 ± 0.20	0.77 ± 0.21	0.60 ± 0.30	0.75 ± 0.14	0.843
UA PI	0.97 ± 0.65	0.95 ± 0.55	0.90 ± 0.57	0.88 ± 0.40	0.774
MCA PI	2.33 ± 0.25	2.48 ± 0.21	2.60 ± 0.20	2.20 ± 0.22	0.555
S/D UtA	1.9 ± 0.13	1.7 ± 0.16	1.8 ± 0.16	1.6 ± 0.19	0.932

UA RI, umbilical artery resistance index; MCA RI, middle cerebral artery resistance index; UA PI, umbilical artery pulsatility index; MCA PI, middle cerebral artery pulsatility index; S/D UtA, mean systolic/diastolic velocities ratio in uterine arteries; D, diabetes; MH, myocardial hypertrophy.

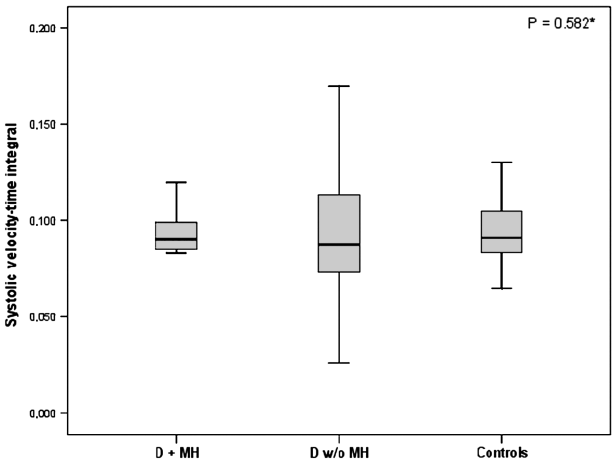

Figure 2—The systolic velocity time integrals of fetuses (with and without myocardial hypertrophy) of diabetic mothers and fetuses of nondiabetic mothers: * ANOVA; D; diabetes; MH, myocardial hypertrophy

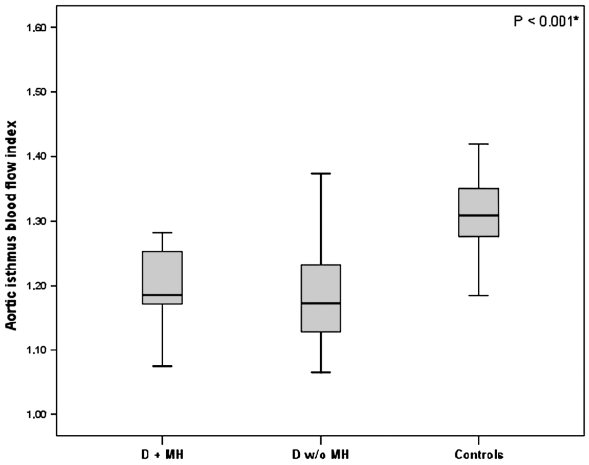

Figure 4—Aortic isthmus flow indices of fetuses (with or without myocardial hypertrophy) of diabetic mothers and fetuses of nondiabetic mothers: * Tukey test; D, diabetes; MH, myocardial hypertrophy

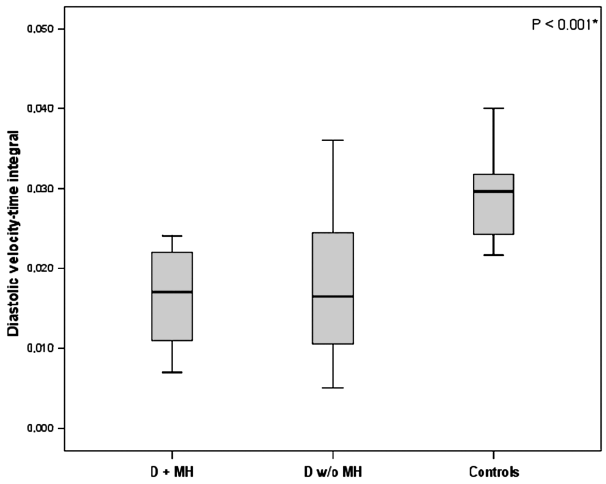

Figure 3—The diastolic velocity-time integrals (VTIs) of fetuses (with and without myocardial hypertrophy) of diabetic mothers and fetuses of nondiabetic mothers: * Tukey test; D, diabetes; MH, myocardial hypertrophy

systole and in diastole because of the low vascular impedance of the placenta. In this study, impedances to cerebral and placentary flows were not altered. Alterations in diastolic function of the left ventricle, with a decrease in distensibility and compliance, lead to changes in left atrial dynamics, even without myocardial hypertrophy. This, in turn, would lead to a higher flow impedance through the pulmonary veins and the foramen ovale, and to a decreased mobility of the septum primum. It is possible that the flow to the left ventricle could be affected. A compensatory increase in flow from the right ventricle to the ductus (higher right ventricular output) could interfere with antegrade flow through the isthmus even after diastolic closing of semilunar valves, thus affecting the IFI. An ongoing study designed to demonstrate that the fetal right ventricular output is increased in maternal diabetes could strenghten this explanation.

More sensitive parameters for assessing diastolic dysfunction might be able to detect its presence earlier, even before evidences of myocardial hypertrophy (Hatem *et al*., 2008), and the IFI could show early changes. Reliability of IFI measurements was shown to be high, confirming reports from the literature (Ruskamp *et al*., 2003). Moreover, maternal diabetes may cause other intrinsic alterations in the fetal heart that could affect ventricular distensibility regardless of an increase in myocardial mass. Fetal myocardial hypertrophy in maternal diabetes is a continuous variable, not a categorical variable, and functional changes may take place at earlier phases than those traditionally used as cut-off points for diagnosing hypertrophy (two standard deviations of the mean).

A limitation of this study is that a postnatal follow-up of babies with impaired IFI is not yet available. An ongoing project aims to assess several parameters in a scoring system to establish a risk protocol to be tested prenatally and postnatally.

Fetuses (with or without myocardial hypertrophy) of diabetic mothers had altered IFIs by Doppler echocardiography as compared with fetuses of disease-free mothers. This finding may help to advance our knowledge about the pathophysiology of fetal cardiovascular impact of maternal diabetes.

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