

Maternal cardiac function in fetal growth-restricted and non-growth-restricted small-for-gestational age pregnancies

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KEYWORDS: echocardiography; fetal growth restriction; maternal cardiac function

ABSTRACT

Objective To compare maternal cardiac function in women with intrauterine growth restriction (IUGR) to those with small-for-gestational age (SGA) pregnancies (non-IUGR).

Methods This was a cross-sectional study involving maternal echocardiography and uterine, umbilical and fetal middle cerebral artery Doppler assessment in 52 normotensive women at 20–36 weeks' gestation with SGA fetuses (26 IUGR and 26 non-IUGR).

Results In the IUGR (compared to the non-IUGR) group, maternal cardiac output (CO) was lower (4.7 vs. 6.1 L/min, $P < 0.001$) and total vascular resistance (TVR) was higher (1444 vs. 1088 dynes/s/cm⁵, $P < 0.001$). The lower CO was due to a lower preload, demonstrated by a reduced stroke volume (59.9 vs. 73.6 mL, $P < 0.01$) and smaller left atrial diameter (LAD) (31.5 vs. 34.1 mm, $P = 0.01$). Mean arterial pressure and diastolic function were similar between the groups. Logistic regression and receiver–operating characteristics curve analysis for detection of IUGR demonstrated that a model using TVR, LAD, fetal middle cerebral artery pulsatility index and gestational age, had a sensitivity of 96.2% and a specificity of 84.6%.

Conclusions Maternal echocardiography can provide a very sensitive tool for identifying IUGR pregnancies. Copyright © 2007 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Maternal cardiovascular adaptation to normal pregnancy includes increase in cardiac output^{1,2}. Impaired

placentation is associated with altered maternal cardiovascular function, which can lead to pre-eclampsia and/or intrauterine growth restriction (IUGR)^{3,4}. In pregnancies with IUGR, compared to those with normal fetal growth, the maternal cardiac output is lower⁵. Duvekot *et al*⁶ examined 10 women, early in the first trimester, who subsequently had normal pregnancies and four women who subsequently developed IUGR. They found a suboptimal increase in cardiac output and smaller left atrial diameter, an index of preload and thus plasma volume expansion in pregnancies that subsequently developed fetal growth restriction⁶. Similarly, in pregnancies with pre-eclampsia, cardiac output is reduced; however, in the pre-clinical phase of the condition cardiac output is increased⁷. It is uncertain whether the low cardiac output in IUGR is the mere consequence of the small fetal size or the result of the impaired placenta *per se*. One previous study of pregnancies with small fetuses demonstrated an inverse correlation between birth weight centile and total vascular resistance. In this study, maternal cardiac output in the fetuses with high umbilical artery pulsatility index (PI), classified as IUGR, was lower than in those with normal Doppler results, classified as small-for-gestational age (SGA). However, the birth weight, corrected for gestation, in the SGA group was double that of the IUGR group, and it is therefore uncertain whether the maternal cardiac function findings are a mere reflection of the difference in fetal size rather than the consequence of impaired placentation⁸.

In the present study, we assessed maternal cardiac function in normotensive pregnancies with similarly sized SGA fetuses and investigated possible differences between those with indirect evidence of hypoxemia, including asymmetric growth deficit, oligohydramnios and Doppler evidence of redistribution in the fetal circulation (IUGR group) and those with normal fetal oxygenation (non-IUGR).

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METHODS

Patient selection

This was a cross-sectional study of maternal central hemodynamics in 52 women with singleton pregnancies, referred to our fetal medicine center for further assessment because ultrasound examination in their own hospitals demonstrated reduced fetal growth at 20–36 weeks. All women were normotensive non-smokers with no previous adverse medical history and were not on any medication. The fetal abdominal circumference was below the 5th centile of the normal range for gestational age⁹, which was calculated from the last menstrual period and was confirmed by ultrasound biometry in the first trimester. The exclusion criteria were: pregnancies with sonographically detectable fetal defects; chromosomal abnormalities; genetic syndromes; infections and pregnancies that subsequently developed pre-eclampsia or cardiovascular disease. All women gave written informed consent to participate in the study, which was approved by the Research Ethics Committee of King's College Hospital, London.

Fetal assessment

Transabdominal ultrasound examination was carried out for measurement of the fetal head circumference, abdominal circumference and femur length and color Doppler was used to measure the pulsatility index (PI) in the uterine, umbilical and fetal middle cerebral arteries, according to previously described methods^{10,11}.

Maternal assessment

The women were studied after a rest period of 15 min in the left lateral decubitus position. Recordings were made when three consecutive electrocardiographic measurements of the heart rate from the R–R interval demonstrated a variation below 10%. One examiner (J.B.) performed all measurements and in all parameters three cardiac cycles were averaged.

Imaging and Doppler echocardiography were performed using a 3.5-MHz transducer (Toshiba Aplio CV, Toshiba Corporation, Tokyo, Japan) according to the guidelines of the American Society of Echocardiography¹². Stroke volume (SV) was computed as the product of the cross-sectional area of the left ventricular outflow tract and the velocity time integral of the pulsed Doppler subaortic waveform, measured in the five-chamber view. Cardiac output (CO) was calculated as the product of heart rate and stroke volume. Total vascular resistance (TVR) was calculated as $TVR = \text{mean arterial pressure (MAP)} \times 80 / \text{cardiac output}$.

Long axis function of the left ventricle was evaluated by two-dimensionally guided M-mode recordings through the mitral valve annulus, using the apical four-chamber view for the lateral and septal sides². Diastolic function was assessed by measuring the left ventricular filling

dynamics in the apical four-chamber view. Transmitral flow velocities were recorded with the sample volume positioned adjacent to the tips of the mitral leaflets in diastole. Peak velocity of early atrial filling (*E*), peak velocity of late atrial filling (*A*) and peak *E*:*A* ratio were measured¹³. The mitral closing to opening time (*a*) was measured at the interval from the end to the onset of the mitral inflow velocity pattern. The left ventricular ejection time (*b*) was measured from the onset to the end of the Doppler subaortic waveform pattern. The interval between mitral valve closure and mitral valve opening was measured. The Tei index was calculated as $(a - b) / b$. The Tei index has been considered as a combined measure of systolic and diastolic function^{14,15}.

Doppler tissue imaging recordings were made using a 3.5-mm sample volume for the septal side and a 5-mm sample volume at the lateral sides of the mitral annulus in the four-chamber view, according to the guidelines of the American Society of Echocardiography¹⁶. The peak velocity of early (*E'*) and late (*A'*) diastolic filling, isovolumetric relaxation time (IVRT) and isovolumetric contraction time (IVCT) were obtained at each side. The transmitral *E*:*E'* ratio was derived for the septal and lateral annulus: this measurement has been shown to correlate with pulmonary capillary wedge pressure and left atrial pressure.

Blood pressure (BP) was measured using a mercury sphygmomanometer (Accoson Dekamet, AC Cossor & Son (Surgical) Ltd, London, UK) according to the recommendations of the British Hypertension Society¹⁷. Mean arterial pressure (MAP) was calculated from the equation: $MAP = (BP \text{ systolic} + (2 \times BP \text{ diastolic})) / 3$.

Demographic characteristics and the findings of our assessment were recorded prospectively into a database. The subsequent management of the patients was carried out either in their own hospital or in our unit.

Classification of IUGR and non-IUGR

At the completion of each pregnancy, the notes of the patients were reviewed by a doctor who was not aware of the findings of the initial assessment and they were assigned into an IUGR or a non-IUGR group on the basis of the following three criteria: (a) fetal asymmetry, defined as head circumference:abdominal circumference ratio above the 95th centile; (b) cerebral redistribution, defined as the ratio of umbilical artery PI:middle cerebral artery PI greater than the 95th centile; and (c) oligohydramnios, defined as amniotic fluid index below the fifth centile. In the IUGR group all three criteria were satisfied and in the non-IUGR none was present.

Statistical analysis

Unpaired *t*-tests or the χ^2 , where appropriate, were performed in order to examine the differences in the demographic characteristics between the examined populations. Univariate analyses, comparing the two groups non-IUGR SGA and IUGR in terms of the

cardiac variables, were performed with two-sample *t*-tests for continuous variables and with χ^2 tests for the categorical variables ethnicity and bilateral uterine artery notching. The correlations and associations between cardiac variables were assessed using multiple linear regression models and factor analysis. In the multiple regression we investigated the contribution of gestational age at presentation, maternal ethnicity, age and body surface area for those cardiac variables where there has been evidence in the literature that they are influenced by the above-mentioned parameters.

Logistic regression and receiver–operating characteristics (ROC) curve analysis were used in order to find the best predictors that are able to discriminate between the two groups IUGR and non-IUGR and determine the optimal discriminatory point with the best combination of sensitivity and specificity. The area under each of the ROC curves and the 95% confidence interval (CI) were calculated. After the final model was created, we compared three ROC curves: one with the combined fetal–maternal variables of the final model; one with only the fetal Doppler variables; and another with the maternal cardiac variables.

Reproducibility for a single examiner (J.B.) and between J.B. and a second examiner was analyzed in 10 non-pregnant women. Intraobserver variabilities of Doppler and tissue Doppler imaging measurements were in the range 3–5% and interobserver variabilities 3–7%. Statistical analysis was performed using MedCalc for Windows, version 8.1.00 (MedCalc Software, Mariakerke, Belgium).

RESULTS

The entry criteria were fulfilled by 52 pregnancies, which were subdivided into IUGR ($n = 26$) and non-IUGR

($n = 26$). In the IUGR group, the mean maternal age, and gestation at entry and at delivery were lower than in the non-IUGR group, but there were no significant differences in maternal ethnic origin, parity, height, pre-pregnancy weight, body surface area, abnormal uterine artery Doppler or birth weight centile (Table 1).

In the IUGR group, there were 23 live births at a mean gestation of 33 (range 27–38) weeks and three intrauterine deaths at 23, 26 and 29 weeks. The birth weight centiles of the babies who died were 0, 0.2 and 0.6, respectively. In the non-IUGR group, there were 24 live births at a mean gestation of 39 (range 35–42) weeks. In this group, there was one stillbirth at 41 weeks following poor antenatal care (birth weight centile 3.7), and one neonatal death due to abruption at 28 weeks (birth weight centile 6.3).

In the IUGR group, cardiac output, cardiac index, stroke volume and left atrial diameter were significantly lower than in the non-IUGR group by 23%, 24%, 19% and 7%, respectively, and total vascular resistance was higher by 33% (Table 2). Heart rate, ejection time and long axis function, mean arterial pressure, transmitral flow patterns and Doppler tissue parameters at the septal and lateral mitral annulus were not significantly different between the two groups. Although the purpose of the study was to compare the differences between the IUGR and non-IUGR groups, in order to facilitate appreciation of the deviation from the normal, we plotted the cardiac output, stroke volume and total vascular resistance of the studied populations against the reference ranges that we created from our ongoing maternal cardiovascular physiology studies (Figures 1–3).

In the IUGR group, the amniotic fluid index and middle cerebral artery PI were significantly lower and the umbilical artery PI was higher than in the non-IUGR group but there was no significant difference in uterine artery PI (Table 2).

Table 1 Demographic characteristics of the study populations

Parameter	Non-IUGR pregnancies ($n = 26$) (n (%) or mean (95% CI))	IUGR pregnancies ($n = 26$) (n (%) or mean (95% CI))	P
Maternal age (years)	30 (27–32)	26 (24–29)	0.042
Ethnicity			0.480
Afro-Caribbean	11 (42)	7 (27)	
Caucasian	11 (42)	13 (50)	
Other	4 (15)	6 (23)	
Parity			0.230
0	13 (50)	19 (73)	
1	8 (30)	7 (27)	
2	5 (19)	0 (0)	
3	13 (50)	17 (65)	
Maternal height (m)	1.6 (1.6–1.6)	1.6 (1.6–1.6)	0.880
Pre-pregnancy weight (kg)	59.7 (56.1–63.2)	61.3 (55.2–67.3)	0.640
Body surface area (m ²)	1.6 (1.6–1.7)	1.6 (1.6–1.7)	0.723
Gestation at entry (weeks)	30 (29–32)	28 (26–30)	0.021
Gestation at delivery (weeks)	39 (38–40)	33.0 (31–35)	< 0.001
Birth weight centile	3.7 (2.8–4.6)	2.6 (1.3–3.9)	0.280
Uterine artery PI > 95 th centile	14 (53)	16 (62)	0.500

IUGR, intrauterine growth restriction; PI, pulsatility index.

Table 2 Univariate analysis of maternal cardiovascular function and fetal variables

Variable	Non-IUGR (n = 26) Mean (95% CI)	IUGR (n = 26) Mean (95% CI)	P
Maternal cardiac systolic function			
Cardiac output (L/min)	6.1 (5.6–6.7)	4.7 (4.4–5.1)	< 0.001
Cardiac index (L/min/m ²)	3.8 (3.4–4.2)	2.9 (2.7–3.1)	< 0.001
Stroke volume (mL)	73.6 (67.0–80.2)	59.9 (56.3–63.4)	< 0.01
Heart rate (bpm.)	84.3 (79.5–89.1)	79.5 (75.8–83.2)	0.1
Left atrial diameter (mm)	34.1 (32.9–35.2)	31.5 (29.9–33.1)	0.011
Mean arterial pressure (mmHg)	79.5 (75.7–83.4)	83.6 (79.3–87.9)	0.15
Total vascular resistance (dynes/s/cm ⁵)	1088 (978–1197)	1443 (1328–1558)	< 0.001
Long axis shortening septal (mm)	13.1 (12.3–14)	12.7 (11.9–13.4)	0.36
Long axis shortening lateral (mm)	15.5 (14.7–16.22)	14.7 (13.8–15.6)	0.18
Maternal cardiac diastolic function			
Transmitral E:A ratio	1.4 (1.3–1.6)	1.4 (1.3–1.5)	0.88
Tei index	0.4 (0.3–0.4)	0.4 (0.3–0.4)	0.88
DTI E':A' ratio septal (cm/s)	1.5 (1.3–1.7)	1.5 (1.3–1.7)	0.99
Isovolumetric relaxation time septal (ms)	0.07 (0.06–0.08)	0.07 (0.06–0.07)	0.59
Isovolumetric contraction time septal (ms)	0.06 (0.06–0.07)	0.07 (0.06–0.07)	0.25
DTI E':A' ratio lateral	1.9 (1.61–2.27)	2.2 (1.82–2.51)	0.34
Isovolumetric relaxation time lateral (ms)	0.05 (0.05–0.06)	0.06 (0.05–0.06)	0.62
Isovolumetric contraction time lateral (ms)	0.06 (0.06–0.07)	0.06 (0.06–0.07)	0.77
Amniotic fluid index and Doppler studies			
Amniotic fluid index (cm)	12.7 (11.3–14.2)	9.8 (8.7–11.0)	0.02
Mean uterine artery PI	1.0 (0.8–1.1)	1.2 (1.0–1.4)	0.09
Umbilical artery PI	1.1 (1.0–1.2)	1.5 (1.3–1.8)	0.004
Middle cerebral artery PI	1.8 (1.7–1.9)	1.5 (1.4–1.7)	0.004

A, peak velocity of late atrial filling; DTI, Doppler tissue imaging; E, peak velocity of early atrial filling; IUGR, intrauterine growth restriction; PI, pulsatility index.

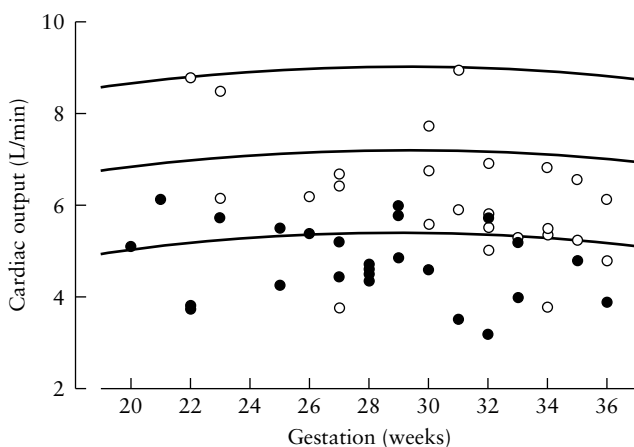


Figure 1 Changes in cardiac output with increasing gestation. Regression lines of uncomplicated pregnancies (5th, 50th and 95th centiles), and the individual values of the IUGR (closed circles) and non-IUGR pregnancies (open circles) are shown.

Multiple logistic regression demonstrated that significant independent contributors in distinguishing between IUGR and non-IUGR were TVR, left atrial diameter, middle cerebral artery PI and gestational age (Table 3). In the ROC analysis, the area under the curves for the combined fetal–maternal variables (0.95, 95% CI 0.86–0.1) was similar to that for maternal cardiac variables (0.93, 95% CI 0.83–0.98) and they were both significantly greater than for the fetal Doppler model (0.79, 95% CI 0.66–0.89) (Table 4 and Figure 4).

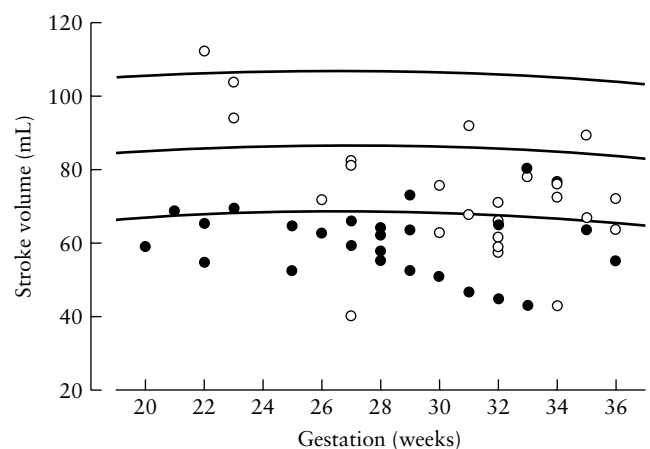


Figure 2 Changes in stroke volume with increasing gestation. Regression lines of uncomplicated pregnancies (5th, 50th and 95th centiles), and the individual values of the IUGR (closed circles) and non-IUGR pregnancies (open circles) are shown.

Total vascular resistance correlated to mean uterine artery PI ($r = 0.29$, $P = 0.03$), and to birth weight centile ($r = -0.30$, $P = 0.02$). Furthermore, birth weight centile correlated positively with maternal cardiac output ($r = 0.29$, $P = 0.03$).

DISCUSSION

The results of this study have shown that in normotensive IUGR pregnancies left ventricular systolic function, as

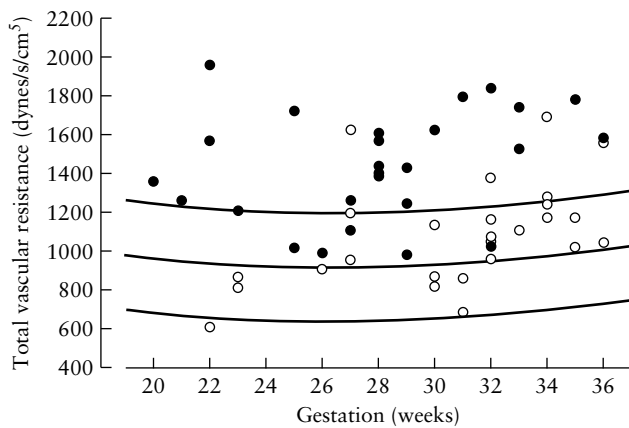


Figure 3 Changes in total vascular resistance with increasing gestation. Regression lines of uncomplicated pregnancies (5th, 50th and 95th centiles), and the individual values of the IUGR (closed circles) and the non-IUGR pregnancies (open circles) are shown.

Table 3 Logistic regression for the independent contributors in distinguishing between IUGR and non-IUGR (odds ratios and 95% confidence intervals)

Variables	Odds ratio	95% CI	P
Total vascular resistance (dynes/s/cm ⁵)	1.01	1.00–1.01	0.001
Left atrial diameter (mm)	0.67	0.45–0.99	0.04
Middle cerebral artery PI	0.03	0.001–0.69	0.02
Gestational age (weeks)	0.62	0.44–0.86	0.004

PI, pulsatility index.

assessed by maternal cardiac output, is substantially lower and total vascular resistance is higher than in pregnancies with equally small non-IUGR fetuses. These differences persist even after correction for maternal age, ethnic origin and body surface area. Mean arterial pressure, the long axis systolic function and the diastolic function of the left ventricle, as assessed by transmitral velocities and Doppler tissue imaging (DTI), were not different between the two groups.

Left ventricular systolic function depends on preload, afterload, and myocardial contractility. The most likely explanation for our findings is that in IUGR the preload is lower than in the non-IUGR group. Cardiac output is reduced in the IUGR group compared to the non-IUGR

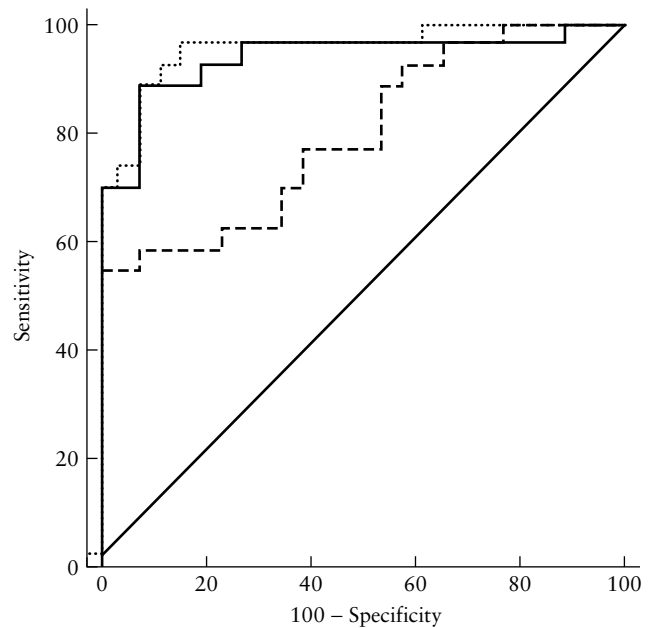


Figure 4 Receiver – operating characteristics curves of the models distinguishing between intrauterine growth restriction (IUGR) and non-IUGR using fetal (---), maternal (—) and maternal–fetal (.....) variables.

group, due to a reduction in stroke volume, and without a concomitant drop in heart rate. The reduced stroke volume is due to a reduction in preload, as evidenced by the lower left atrial diameter in the IUGR group. Afterload is assessed by TVR and is a function of vascular tone and blood viscosity. Although TVR was higher in the IUGR than in the non-IUGR group, mean arterial pressure, reflecting vascular tone, was not significantly different between the two groups. A low cardiac output in the presence of an elevated mean arterial pressure would be expected to increase TVR⁵. Thus, the finding of a high TVR in association with a normal mean arterial pressure implies reduced hemodilution due to reduced preload expansion. We could speculate that the high TVR may be a reflection of increased blood viscosity, which was previously reported in these pregnancies¹⁸. As far as myocardial contractility is concerned, we found no significant differences between the groups in myocardial long axis function, as assessed by the mitral valve annulus displacement. Whilst the increased TVR might be expected to increase left atrial size, in fact, we observed

Table 4 Comparison of the area under the curve for the three receiver-operating characteristics (ROC) curves

Variables	Comparison	Difference between the areas under the curve (95% CI)	P
ROC 1 TVR, LAD, MCA, GA	ROC 1 vs. ROC 2	0.01 (–0.02–0.06)	0.38
ROC 2 TVR, LAD, GA	ROC 1 vs. ROC 3	0.16 (0.04–0.27)	0.007
ROC 3 UMB, MCA	ROC 2 vs. ROC 3	0.14 (0.005–0.27)	0.042

GA, gestational age; LAD, left atrial diameter; MCA, fetal middle cerebral artery pulsatility index; TVR, total vascular resistance; UMB, umbilical artery pulsatility index.

a smaller left atrial diameter in the IUGR group, which implies that the lower cardiac output in the IUGR group is mainly due to a reduction in preload^{5,6} and is further suggestive of a reduced plasma volume expansion. In normal pregnancy, there is a 40% increase in plasma volume between 5 and 30 weeks and previous studies have demonstrated that this physiological expansion is impaired in pregnancies complicated by IUGR^{19,20}.

Left ventricular diastolic function, which relates to the left ventricular relaxation properties after contraction, was not different between the two groups. Diastolic function describes the ability of the left ventricle to maintain adequate filling volumes and maintain a good cardiac output without substantial increase in the intracavitary pressure²¹. It is assessed in diastole during the periods of (1) early rapid filling (E-wave velocity), (2) late filling (A-wave velocity) during atrial systole, and (3) isovolumetric relaxation. In normal pregnancy, E-wave velocity decreases, A-wave velocity increases and E:A ratio decreases as a result of increased left ventricular hypertrophy and reduced compliance^{1,22,23}. One problem with the assessment of diastolic function solely by means of the transmitral flow velocities is that it is both preload- and afterload-dependent. An increase in preload can increase the E-wave; however, an increase in afterload may also increase the A-wave²⁴. In addition, mitral inflow patterns can be affected by heart rate, phase of respiration and maternal age^{13,25}. Therefore, relying on transmitral flow is not sufficient to assess LV diastolic function. Annular velocities by DTI is considered to be less preload-dependent²⁶. In our study, neither method of assessment of LV diastolic function showed any difference between the IUGR and non-IUGR groups. Further studies with larger number of patients may further improve our understanding of diastolic function in such pregnancies.

In the clinical management of pregnancies with SGA fetuses, it is essential to distinguish between those with evidence of fetal hypoxemia (IUGR) and those with apparently normal oxygenation (non-IUGR) because IUGR is associated with poorer long-term neonatal mortality and morbidity^{27,28}. Our findings suggest that assessment of maternal cardiac function at presentation is superior to fetal assessment in the distinction between the two groups. Similarly, Vasapollo *et al.*⁸, who examined SGA fetuses with normal umbilical artery PI at 27–30 weeks, reported impaired maternal cardiac function in those who subsequently developed abnormal Doppler results and fetal heart rate decelerations necessitating delivery by Cesarean section. The extent to which maternal cardiac function assessment will be incorporated into the routine clinical care of pregnancies complicated by SGA will ultimately depend on confirmation of such results by further longitudinal studies. Another potentially important finding is the indirect evidence of impaired plasma volume in those pregnancies that subsequently develop evidence of fetal hypoxemia. Similarly, confirmation of this finding may ultimately help identify those pregnancies that may benefit

from such therapeutic interventions as plasma volume expansion.

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