Maternal cardiac function in normotensive and pre-eclamptic intrauterine growth restriction

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ABSTRACT

Objectives *To compare maternal cardiac function between pregnancies complicated by normotensive and pre-eclamptic intrauterine growth restriction (IUGR).*

Methods *Two-dimensional Doppler echocardiography and Doppler tissue imaging (DTI) were used to examine 19 pregnant women with IUGR and 17 with pre-eclampsia complicated by IUGR at 20–38 weeks of gestation. Indices were converted into differences in SDs from the expected normal mean for gestation (Z-scores) and compared.*

Results *With respect to normal pregnancy, in the normotensive IUGR compared with the pre-eclamptic IUGR group, there were similar reductions in maternal cardiac output (Z-score, −1.71 vs. −1.37, P = 0.26) and heart rate (Z-score, −3.67 vs. −9.43, P = 0.1) and a similar increase in total vascular resistance (Z-score, 2.91 vs. 3.93, P = 0.05). There was also a greater decrease in stroke volume (Z-score, −1.72 vs. −0.69, P = 0.01), a smaller increase in mean arterial pressure (Z-score, 0.73 vs. 2.94, P < 0.01) and a smaller decrease in DTI systolic velocity at the lateral mitral margin (Z-score, −0.4 vs. −1.42, P = 0.02). In terms of diastolic function, there was a smaller transmitral late diastolic velocity (Z-score, 0.04 vs. 0.93, P = 0.03) and a greater DTI early diastolic velocity at the lateral mitral margin (Z-score, −0.17 vs. −1.6, P < 0.01).*

Conclusions *In normotensive IUGR and pre-eclamptic IUGR there is a similar alteration in maternal left ventricular systolic function, but there is greater impairment in maternal diastolic function in pre-eclamptic IUGR. Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Normal pregnancy is associated with a 50% increase in maternal cardiac output, which is mediated by plasma volume expansion and a decrease in peripheral resistance[1]. Placentation may precipitate these events directly or indirectly and there is some evidence that impaired placentation, with consequent development of pre-eclampsia and intrauterine growth restriction (IUGR), is associated with abnormal maternal hemodynamic changes[2–4].

Current evidence suggests that in pregnancies complicated by IUGR, maternal cardiac output is decreased[3,5]. In contrast, during the preclinical phase of pre-eclampsia, maternal systolic function is increased and peripheral resistance is decreased, but with the onset of clinical symptoms there is a decrease in cardiac output and increase in peripheral resistance[4]. Previous studies have reported on maternal left ventricular (LV) function in heterogeneous groups with IUGR, without distinguishing between normotensive and pre-eclamptic pregnancies[5,6]. Furthermore, there are no reported data on maternal diastolic function in pregnancies with IUGR and pre-eclampsia. Under conditions of increased peripheral resistance, changes in the diastolic function of the LV usually precede changes in systolic function[7]. Consequently, assessment of maternal LV diastolic function may provide an early marker of pre-eclampsia.

The aim of this study was to investigate possible hemodynamic differences, with particular focus on maternal diastolic function, between women with normotensive IUGR and those with pre-eclamptic IUGR.

METHODS

Patient selection

This was a 1-year cross-sectional study of maternal cardiovascular function in women with singleton pregnancies

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referred to a fetal medicine center for further assessment because ultrasound examination in their own hospitals demonstrated that the fetuses had a reduced growth velocity or were small-for-gestational age in the second and third trimesters, with fetal abdominal circumference $< 5^{th}$ centile of the normal range for gestation. Gestational age was calculated from the last menstrual period and was confirmed by ultrasound biometry in the first trimester. 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, UK.

In all cases, evaluation was performed once at the initial visit. Pregnancies with sonographically detectable fetal defects, chromosomal abnormalities, genetic syndromes and infections were excluded. The selection criteria were: healthy women with no previous adverse medical history and taking no medication, with estimated fetal weight $< 3^{rd}$ centile for gestation[8], fetal asymmetry (defined as head circumference/abdominal circumference ratio $> 95^{th}$ centile)[9], cerebral redistribution (defined as umbilical artery/middle cerebral artery pulsatility index (PI) ratio $> 95^{th}$ centile)[10] and oligohydramnios (defined as amniotic fluid index $< 5^{th}$ centile)[11]. The women were either normotensive (IUGR group) or they had pre-eclampsia (pre-eclamptic IUGR group). The definition for pre-eclampsia was according to the guidelines of the International Society for the Study of Hypertension in Pregnancy[12]. Fifteen women developed pregnancy-induced hypertension during the study and were excluded from analysis.

Imaging and Doppler echocardiography were performed using a Toshiba Aplio CV (Toshiba Corporation, Tokyo, Japan) equipped with a 3.5-MHz transducer. Transabdominal ultrasound examination was carried out for measurement of the fetal head circumference, abdominal circumference and femur length. Color Doppler was used to measure the PI in the uterine, umbilical and fetal middle cerebral arteries according to previously described methods[10,13]. The women were studied after a rest period of 15 min in the left lateral decubitus position. Echocardiographic recordings were made when three consecutive measurements of the heart rate from the R-R interval demonstrated a variation below 10%. One examiner (J.B.) performed all measurements and for all parameters three cardiac cycles were averaged.

Echocardiography

Echocardiography was carried out according to the guidelines of the American Society of Echocardiography[14]. LV long-axis M-mode was recorded with the cursor at the lateral and septal sides of the mitral annulus using the apical four-chamber view[15]. Transmitral flow was recorded with the sample volume positioned level with the tips of the mitral leaflets in their fully-open position in diastole. The peak velocity of early (E) and late (A) atrial filling were measured and the E/A ratio calculated[16]. The mitral closing to opening time (a) was measured as the interval from the end to the onset of the mitral inflow velocity pattern.

The LV ejection time (b) was measured from the onset to the end of the Doppler subaortic waveform pattern. The Tei index[17] was calculated as $(a - b)/b$. Stroke volume was calculated as the product of the cross-sectional area of the LV outflow tract and the velocity time integral of the pulsed Doppler subaortic waveform recorded in the five-chamber view. Cardiac output was calculated as the product of heart rate and stroke volume[16]. Total vascular resistance (TVR) was calculated as TVR = mean arterial pressure (MAP) × 80/cardiac output. Tissue Doppler image 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 Echocardiography[18]. The peak velocity of early (E′) and late (A′) diastolic filling and the peak systolic velocity (S′) were measured. The transmitral E to Doppler tissue E′ ratio was derived for the septal and lateral margins of the mitral annulus. Isovolumetric relaxation time (IVRT′) and isovolumetric contraction time (IVCT′) were obtained at each mitral annular margin.

Blood pressure

Blood pressure measurements were performed using a mercury sphygmomanometer (Accoson Dekamet, AC Cossor & Son (Surgical) Ltd, London, UK) according to the recommendations of the British Hypertension Society[19]. MAP (in mmHg) was calculated using the equation: MAP = (systolic pressure + (2 × diastolic pressure))/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.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess normality of the distribution of the data. Differences in the demographic characteristics between the populations were examined by unpaired *t*-tests and the chi-square test for ethnicity and parity. Measurements were transformed to the corresponding Z-scores ((actual measurement − mean measurement for gestational age)/SD for gestational age). Regression equations from our normal reference ranges were used[20]. With multiple regression models, we investigated the independent contribution of maternal race and height. The Z-scores of the cardiac measurements of the two groups were compared using the unpaired *t*-test. Microsoft Excel (Microsoft Corp., Redmond, WA, USA) was used for statistical analysis and, where appropriate, the statistical package SPSS 8.0 (SPSS for Windows, Rel. 8.0.0. 1997, Chicago, IL, USA) was used.

RESULTS

We examined 19 normotensive IUGR and 17 pre-eclamptic IUGR pregnancies. There were no statistically

significant differences in maternal age, parity or height between the two groups, but prepregnancy weight and incidence of Afro-Caribbean ethnicity were higher in the pre-eclamptic IUGR group (Table 1). In the normotensive IUGR group, there were 17 live births at a mean gestational age of 34 (range, 29–38) weeks, one intrauterine death at 29 weeks and one neonatal death. In the pre-eclamptic IUGR group, there were 17 live births at a mean gestational age of 31 (range, 26–37) weeks. The assessment-to-delivery time interval for the normotensive IUGR group was 5 (range, 2–10) weeks, and that for the pre-eclamptic-IUGR group was 3 (range, 2–9) weeks.

The results of the IUGR and pre-eclamptic-IUGR groups are compared in Table 2 and Figure 1. Table 2 shows the Z-scores and actual values. MAP (Table 2) and TVR (Figure 1, Table 2) were higher in the pre-eclamptic IUGR group.

With respect to systole, cardiac output (Table 2, Figure 1), cardiac index, heart rate and long-axis shortening (Table 2) were similar between the groups. In the pre-eclamptic-IUGR group, stroke volume was higher (Table 2, Figure 1) and S′ velocity was lower (Table 2).

With respect to diastole, there were no significant differences in peak transmitral E velocity, and E/A ratio between the two groups (Table 2), but transmitral A velocity was higher in the pre-eclamptic IUGR group. Compared with the IUGR pregnancies, the pre-eclamptic IUGR pregnancies had a lower Doppler tissue imaging (DTI) E′ velocity at the lateral mitral annulus. The E/E′ ratio at the septal margin was significantly higher in the pre-eclamptic IUGR group, while that at the lateral margin was similar between the groups. The lateral E/E′ ratio was > 10 in one patient (5.8%) in the pre-eclamptic IUGR group, compared with none in the IUGR group ($P < 0.01$).

Table 1 Demographic characteristics of the study populations

Characteristic	Normotensive IUGR (n = 19)	Pre-eclamptic IUGR (n = 17)	P
Maternal age (years)	26 ± 6	29 ± 7	0.14
Ethnicity			
Afro-Caribbean	6 (31.6)	10 (58.8)	0.03
Caucasian	6 (31.6)	7 (41.2)	
Other	7 (36.8)	—	
Parity			
0	14 (73.7)	16 (94.1)	0.13
1	4 (21.1)	—	
2	1 (5.3)	1 (5.9)	
Maternal height (m)	1.62 ± 0.07	1.66 ± 0.05	0.11
Prepregnancy weight (kg)	60.4 ± 13.7	70.4 ± 10.2	0.02
Body surface area (m²)	1.64 ± 0.17	1.78 ± 0.14	0.01
GA at entry (weeks)	28 (25–35)	28 (24–33)	0.45
GA at delivery (weeks)	34 (29–38)	31 (26–37)	0.01
Birth weight (g)	1638 ± 579	1258 ± 427	0.03
Birth weight centile	2.88 ± 3.1	3.38 ± 3.2	0.63

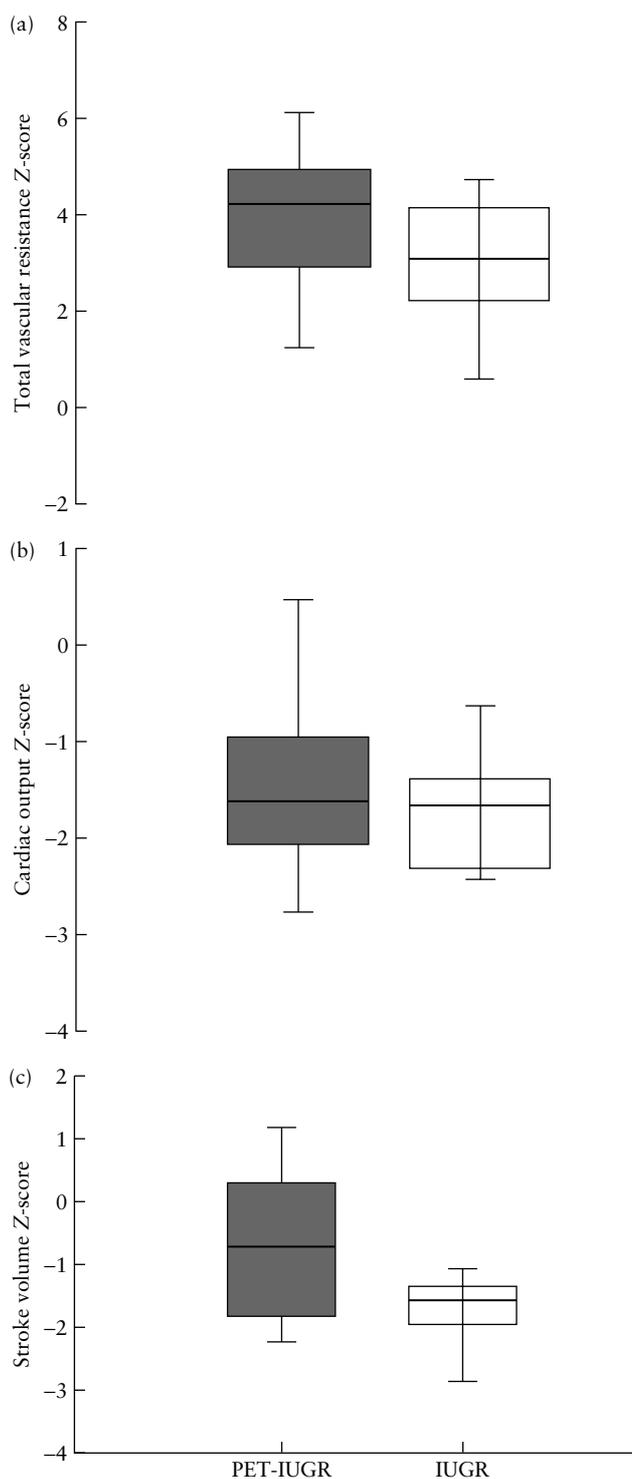Data are given as mean ± SD, *n* (%) or median (range). GA, gestational age.

Figure 1 Box-and-whisker plots comparing Z-scores for total vascular resistance (a), cardiac output (b) and stroke volume (c) in normotensive intrauterine growth-restricted (IUGR) and pre-eclamptic (PET) IUGR pregnancies. Boxes show the median and interquartile range, and the whiskers represent the 5th and 95th percentiles.

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 DTI measurements ranged from 3% to 5% and interobserver variabilities from 3% to 7%.

Table 2 Comparison of normotensive and pre-eclamptic intrauterine growth-restricted (IUGR) pregnancies

Measurement	Z-score (mean (SD))			Mean (SD)		
	Normotensive IUGR (n = 19)	Pre-eclamptic IUGR (n = 17)	P	Normotensive IUGR (n = 19)	Pre-eclamptic IUGR (n = 17)	P
Systolic function						
Cardiac output (L/min)	−1.71 (0.59)	−1.37 (1.12)	0.26	4.79 (0.52)	5.52 (1.21)	0.02
Cardiac index (L/min/m^2)	−1.09 (0.30)	−0.82 (0.57)	0.08	2.94 (0.30)	3.12 (0.71)	0.32
Stroke volume (mL)	−1.72 (0.63)	−0.69 (1.25)	0.01	61.06 (8.80)	75.10 (15.88)	< 0.01
Heart rate (bpm)	−3.67 (10.27)	−9.43 (10.15)	0.10	79.68 (11.97)	74.41 (12.41)	0.20
Long-axis shortening: septal (mm)	0.19 (0.97)	−0.01 (0.94)	0.55	13.58 (1.96)	13.29 (1.93)	0.65
Long-axis shortening: lateral (mm)	−0.28 (1.09)	−0.38 (1.13)	0.78	14.73 (2.52)	14.52 (2.62)	0.81
Mean arterial pressure (mmHg)	0.73 (1.21)	2.94 (1.71)	< 0.01	84.81 (10.94)	105.65 (14.49)	< 0.01
Total vascular resistance (dynes·s/cm^5)	2.91 (1.48)	3.93 (1.55)	0.05	1434.05 (255.93)	1573.51 (268.87)	0.12
Tei index	0.44 (1.3)	0.67 (1.42)	0.61	0.39 (0.15)	0.42 (0.15)	0.62
Diastolic function						
E (cm/s)	0.08 (0.72)	0.45 (1.59)	0.36	75.19 (10.37)	80.87 (22.61)	0.33
A (cm/s)	0.04 (1.03)	0.93 (1.31)	0.03	54.68 (8.26)	63.12 (11.68)	0.02
E/A ratio	−0.14 (0.95)	−0.21 (1.42)	0.86	1.39 (0.23)	1.33 (0.42)	0.54
Doppler tissue imaging systolic indices						
S′ septal (cm/s)	−0.18 (0.81)	−0.63 (0.98)	0.15	10.41 (1.59)	10.25 (1.29)	0.75
IVCT′ septal (s)	0.56 (0.10)	0.84 (0.84)	0.37	0.06 (0.01)	0.07 (0.01)	0.32
S′ lateral (cm/s)	−0.4 (1.15)	−1.42 (1.3)	0.02	12.12 (2.63)	10.41 (1.59)	0.03
IVCT′ lateral (s)	0.45 (1.1)	1.29 (1.85)	0.10	0.06 (0.01)	0.07 (0.02)	0.02
Doppler tissue imaging diastolic indices						
E′ septal (cm/s)	0.17 (0.73)	−0.81 (1.12)	< 0.01	12.50 (2.05)	9.75 (3.21)	< 0.01
A′ septal (cm/s)	−0.06 (0.25)	−0.17 (0.35)	0.27	9.06 (1.60)	9.98 (1.41)	0.17
IVRT′ septal (s)	0.35 (0.82)	1.86 (1.37)	< 0.01	0.07 (0.01)	0.09 (0.02)	< 0.01
E′ lateral (cm/s)	−0.17 (1.2)	−1.6 (1.51)	< 0.01	16.95 (3.49)	13.60 (2.94)	< 0.01
A′ lateral (cm/s)	0.0006 (0.25)	−0.12 (0.35)	0.24	9.04 (2.07)	8.93 (2.06)	0.87
IVRT′ lateral (s)	0.61 (1.4)	1.52 (2.49)	0.18	0.05 (0.01)	0.07 (0.01)	0.02
E/E′ septal	−0.21 (0.62)	1.23 (1.35)	< 0.01	6.13 (1.04)	8.70 (2.31)	< 0.01
E/E′ lateral	0.3 (1.17)	1.64 (2.68)	0.06	4.61 (1.12)	6.27 (2.15)	< 0.01

A, late atrial filling peak velocity; A′, late diastolic filling peak velocity; E, early atrial filling peak velocity; E′, early diastolic filling peak velocity; IVCT′, isovolumetric contraction time; IVRT′, isovolumetric relaxation time; S′, peak systolic velocity.

DISCUSSION

The findings of this study demonstrate that maternal systolic function is reduced to a similar degree in both IUGR and pre-eclamptic IUGR, while there is a greater impairment in diastolic function in pre-eclamptic IUGR.

In both normotensive IUGR and pre-eclamptic IUGR, we found the cardiac index to be substantially lower than that expected in normal pregnancies[15,21]. In normotensive IUGR pregnancies, a lack of intravascular expansion causing a blunted rise in cardiac index has been demonstrated from as early as the first trimester[2,3]. In pre-eclampsia, systolic function is increased in early pregnancy and the cardiac index falls at the end of gestation as the disease progresses[4].

A fall in measures of systolic function can occur as a result of increased systemic vascular resistance or reduced diastolic filling or a fall in intrinsic contractility. In normal pregnancy, long-axis shortening appears most closely related to systemic blood pressure and an increase in arterial pressure leads to a decrease in long-axis shortening[15]. In our study, TVR was increased to a similar degree in both the pre-eclamptic IUGR and the normotensive IUGR groups, but the MAP and stroke volume were lower in the normotensive IUGR group, which is consistent with either a relatively reduced LV contractility, reduced diastolic filling or both. DTI allows the detection of abnormalities of LV longitudinal function which precede abnormalities of transverse systolic function in ischemia[22], cardiomyopathies, essential hypertension and LV hypertrophy[22–24]. Systolic function assessed using the DTI systolic (S′) peak velocity[25] was significantly lower in the pre-eclamptic IUGR group, suggesting relatively reduced LV contractility in this group[26]. Similar observations have been made in non-pregnant people with essential hypertension[27–29].

There are no data in the medical literature comparing diastolic function in IUGR and pre-eclamptic IUGR populations. DTI is useful in assessing diastolic function because the early filling wave (E′ velocity) is relatively independent of loading, while the simultaneous transmitral wave (E velocity) is highly dependent on filling pressure. The ratio of transmitral E to DTI E′ is therefore a good surrogate measure of filling pressure[18]. The DTI E′ was lower and the transmitral to DTI E′ ratio was higher in the pre-eclamptic IUGR group at the lateral margin, which is consistent with higher filling pressures in this group, although the ratio was above normal in only

one patient. The E/E′ ratio might be useful for the early detection of pre-eclampsia.

The results of this study suggest that reduced maternal cardiac function in pregnancies complicated by pre-eclamptic IUGR, compared with normotensive IUGR, is as a result of both reduced intrinsic contractility and reduced diastolic filling. We have shown that DTI can be obtained reliably in pre-eclampsia and IUGR. This technique has the potential to improve the diagnosis of such pathological pregnancies and to monitor the benefit of therapeutic interventions. Further larger studies are required to confirm this.

ACKNOWLEDGMENT

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