

Pregnancy

Maternal Cardiovascular Impairment in Pregnancies Complicated by Severe Fetal Growth Restriction

Karen Melchiorre, George Ross Sutherland, Marco Liberati, Basky Thilaganathan

Abstract—Fetal growth restriction and preeclampsia are both conditions of placental etiology and associated to increased risk for the long-term development of cardiovascular disease in the mother. At presentation, preeclampsia is associated with maternal global diastolic dysfunction, which is determined, at least in part, by increased afterload and myocardial stiffness. The aim of this study is to test the hypothesis that women with normotensive fetal growth-restricted pregnancies also exhibit global diastolic dysfunction. This was a prospective case-control study conducted over a 3-year period involving 29 preterm fetal growth-restricted pregnancies, 25 preeclamptic with fetal growth restriction pregnancies, and 58 matched control pregnancies. Women were assessed by conventional echocardiography and tissue Doppler imaging at diagnosis of the complication and followed-up at 12 weeks postpartum. Fetal growth-restricted pregnancies are characterized by a lower cardiac index and higher total vascular resistance index than expected for gestation. Compared with controls, fetal growth-restricted pregnancy was associated with significantly increased prevalence ($P < 0.001$) of asymptomatic left ventricular diastolic dysfunction (28% versus 4%) and widespread impaired myocardial relaxation (59% versus 21%). Unlike preeclampsia, cardiac geometry and intrinsic myocardial contractility were preserved in fetal growth-restricted pregnancy. Fetal growth-restricted pregnancies are characterized by a low output, high resistance circulatory state, as well as a higher prevalence of asymptomatic global diastolic dysfunction and poor cardiac reserve. These findings may explain the increased long-term cardiovascular risk in these women who have had fetal growth-restricted pregnancies. Further studies are needed to clarify the postnatal natural history of cardiac dysfunction in these women. (*Hypertension*. 2012;60:437-443.) • [Online Data Supplement](#)

Key Words: fetal growth restriction ■ cardiac function ■ echocardiography ■ tissue Doppler ■ strain rate
■ hemodynamics ■ preeclampsia ■ preterm birth

Fetal growth restriction (FGR) and preeclampsia (PE) are both conditions of placental etiology with shared characteristics of maternal vascular endothelial activation, oxidative stress, and upregulation of the inflammatory state.^{1,2} FGR and PE are both also associated with increased risk for the long-term development of metabolic syndrome and cardiovascular disease in the mother.³⁻⁹ Acute PE is associated with cardiac remodeling, impaired myocardial relaxation and global left ventricular (LV) diastolic chamber dysfunction.^{10,11} Furthermore, it is evident that the cardiovascular implications of PE do not cease with the birth of the infant, with a significant proportion of women demonstrating asymptomatic LV diastolic chamber dysfunction and essential hypertension for within 2 years of delivery.^{11,12} Despite these cardiovascular findings in PE, previous studies of maternal cardiac function in FGR pregnancy failed to identify a clear pattern of myocardial impairment or chamber dysfunction.¹³⁻¹⁶ This is possibly due to the

inadequacy of the load-dependent indices used and the interpretation of diastolic measures in isolation, disregarding the interdependency of cardiac events. The aim of this study was to test the hypothesis that women with normotensive FGR pregnancies also exhibit cardiac remodeling and myocardial and ventricular dysfunction, as seen in PE pregnancies using established diagnostic algorithms integrating conventional echocardiographic and tissue Doppler indices.

Methods

This was a prospective case-control study carried out over a 3-year period from February 2008. All of the women with singleton pregnancy and normotensive FGR attributed to placental insufficiency severe enough to require iatrogenic preterm (before 37 weeks) delivery were recruited consecutively as cases, after informed consent and with local institutional review committee approval. Only women without comorbidities, who were nonsmokers, not on medication, or in labor were asked to take part in the study. Normoten-

Received February 28, 2012; first decision March 24, 2012; revision accepted May 29, 2012.

From the Fetal Maternal Medicine Unit, Departments of Obstetrics and Gynecology (K.M., B.T.), and Cardiology and Cardiothoracic Surgery (K.M., G.R.S.), St Georges Hospital, University of London, London, United Kingdom; Department of Obstetrics and Gynecology (K.M., M.L.), University of Chieti, Chieti, Italy.

This study was approved by the Wandsworth Local Research Ethics Committee (ref No. 01.78.5).

The online-only Data Supplement is available with this article at <http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.112.194159/-DC1>.

Correspondence to Basky Thilaganathan, Fetal Maternal Medicine Unit, St George's University of London, Cranmer Terrace, London SW17 0RE, United Kingdom. E-mail basky@pobox.com

© 2012 American Heart Association, Inc.

Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.112.194159

sive FGR because of placental insufficiency was defined as an abdominal circumference <10th centile, umbilical artery pulsatility index above the 95th centile, need of preterm iatrogenic delivery for fetal compromise, absence of known chromosomal/structural fetal abnormality, and no concurrent maternal illness. All of the FGR pregnancies underwent a full assessment of fetal biometry, fetal Doppler, biophysical profile, and computerized cardiotocography at study entry and ≥ 3 times weekly until delivery. Women who developed hypertension or other medical complications during pregnancy or postpartum were subsequently excluded. For each FGR pregnancy, 2 normotensive, healthy, nonsmoking controls matched for maternal age, gestational age, and ethnicity were recruited from the routine antenatal clinic. Women with adverse pregnancy outcome were retrospectively excluded from being controls. Women with preterm PE with FGR recruited to another study during the same period were matched for gestational age and used as a secondary control group.¹¹ Maternal assessment included a medical and family history, measurement of anthropometric indices, blood pressure profile, conventional echocardiography, tissue Doppler and strain rate assessment, and 12-lead ECG. Twelve weeks postpartum, women underwent physical examination and repeat blood pressure profile. Maternal blood pressure was measured manually from the brachial artery using a mercury sphygmomanometer according to the guidelines of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.¹²

Echocardiography

All of the subjects were studied by standard 2D and Doppler transthoracic echocardiography at rest, as described previously.¹⁰ In brief, patients were studied in the left lateral decubitus position and data acquired at end expiration from standard parasternal/apical views using a GE Vivid 9 scanner. For each acquisition, 3 cardiac cycles of noncompressed data were stored in cine-loop format and analyzed without blinding offline by one investigator (K.M.). Tissue Doppler, strain, and strain rate indices are given as absolute values. Diastolic chamber function, chamber filling pressures, and geometry were assessed and graded using standard diagnostic algorithms with the recommended adjustments reflecting the concomitant systolic function, age, and pregnancy.^{10,17} Ejection fraction was evaluated by biplane Simpson method, and left ventricular LV global radial systolic dysfunction was defined as Ejection fraction <55%.¹⁸ Systolic chamber dysfunction was defined as average peak systolic velocity at the level of the left and septal sites of mitral valve annulus (Av S1) index 2 SDs below the expected mean for age. The severity of LV dysfunction and remodeling was graded accordingly to the European Association and American Society of Echocardiography guidelines.^{17,18} Impaired myocardial contractility was diagnosed if the peak systolic strain rate indices were 2 SDs below the expected mean for age. Impaired myocardial relaxation was defined as early:late strain rate ratio ≤ 1 . All of the conventional echocardiographic indices were adjusted for body surface area, and all of the tissue Doppler velocity indices were adjusted for the end-diastolic LV long-axis length. Please also see the extended methodology in the online-only Data Supplement.

Statistical Analysis

Data were analyzed using SPSS 15 software (SPSS Inc, Chicago, IL). Variables were compared using Mann-Whitney *U* or χ^2 tests, as appropriate. Paired-group comparisons were only undertaken if Kruskal-Wallis testing indicated significant differences. Stepwise multiple regression analysis was used to assess the influence of cardiac parameters, demographic variables (ethnicity, maternal age, and body mass index), and pregnancy characteristics on indices of cardiac function and remodeling. A required sample size of 22 in each group was calculated to observe a >20% difference in average E/E1 ratio between cases and controls with 85% power and a 5% type 1 risk.¹⁰ The reproducibility and repeatability of both conventional and tissue Doppler indices were assessed previously and found to be very good.¹⁰

Results

A total of 29 normotensive women with severe preterm FGR, 25 women with preterm PE with FGR, and 58 women with normal pregnancies were included in the study. Cases and controls did not differ significantly for maternal age, ethnicity, and gestational age at assessment, but FGR cases had significantly higher body mass index than controls (Table 1). As expected, PE women presented with abnormal liver and kidney function, whereas abnormal hematology was present in both pregnancy complications (please see Table S1 in the online-only Data Supplement). Both PE and normotensive FGR pregnancies had a high prevalence of adverse fetal and neonatal outcomes (41% and 36%, respectively, versus 0% of controls; Table 1).

Hemodynamic and Remodeling Indices

FGR women had significantly higher total vascular resistance index and mean arterial pressure and lower cardiac index and heart rate compared with controls. There was no difference in stroke volume, heart remodeling indices, wall stress, and cardiac work indices between cases and controls (Table 2 and Figure 1; see Table S2).

Diastolic Function

Women with normotensive FGR had a significantly higher prevalence of severe impaired myocardial relaxation (59%) than controls (21%; $P=0.0001$; Tables 3 and 4; please see Table S3). Eight women with FGR (27.6%; 5 grade I, 2 grade Ia, and 1 grade II) exhibited overt diastolic chamber dysfunction compared with 2 (4%; 2 grade I) in the control group ($P=0.009$; Tables 3 and 4 and Figure 2; please see the grading system of diastolic dysfunction in the online-only Data Supplement).

Systolic Function

Pulsed tissue Doppler peak systolic velocity indices at lateral and septal mitral annulus sites were significantly reduced in FGR cases versus controls irrespective of correction for LV end-diastolic long-axis length (Table 2). Peak systolic strain, strain rate, and LV radial systolic function indices were not significantly different between the 2 study groups (Table 2; see Tables S4 and S5).

Cardiovascular Changes in PE With FGR

Women with PE presented with higher total vascular resistance index and mean arterial pressure and lower cardiac index and stroke volume index than controls. LV geometry was significantly altered in PE with marked concentric hypertrophy with overt systolic and diastolic chamber dysfunction (Tables 2–4 and Figures 1 and 2). Global diastolic dysfunction was seen in 52% of women with PE, and half of them also presented increased left chamber filling pressures (Tables 3 and 4). PE women also exhibited extensive impaired myocardial relaxation and depressed myocardial contractility, as demonstrated by the strain rate indices at multiple cardiac sites (Tables 3 and 4 and Figures 1 and 2).

FGR Versus PE

Women with normotensive FGR demonstrated similar changes in cardiac ventricular function to women with preterm PE with

Table 1. Demographic and Pregnancy Characteristics of Cases With Normotensive Preterm FGR, PE With FGR, and Controls

Parameter	Controls (n=58)	FGR (n=29)	PE With FGR (n=25)	FGR vs Controls	PE With FGR vs Controls	FGR vs PE
Demographic characteristics						
Maternal age, y	31 (27–35)	30 (27–34)	32 (25–35)	0.9*	0.9	0.06
Nulliparous	28 (48)	14 (48)	18 (72)	0.82	0.08	0.2
White	34 (59)	17 (59)	9 (36)	0.82*	0.1	0.2
Afro-Caribbean	6 (10)	3 (10)	7 (28)	0.71*	0.1	0.2
Asian	18 (31)	9 (31)	11 (44)	0.81*	0.4	0.5
Prepregnancy BMI, kg/m ²	22.5 (21.2–25.5)	28.1 (23.2–32.4)	26.3 (21.6–33.1)	0.037	0.8	0.24
Prepregnancy BMI >30, kg/m ²	3 (6)	7 (32)	3 (12)	0.024	0.5	0.4
Prepregnancy BSA, m ²	1.44 (1.32–1.58)	1.42 (1.2–1.9)	1.54 (1.45–1.59)	0.3	0.2	0.34
Maternal height, m	1.65 (1.60–1.70)	1.63 (1.55–1.68)	1.68 (1.60–1.71)	0.2	0.5	0.09
Pregnancy characteristics						
SBP at 12 wk (mm Hg)	110 (100–115)	106 (100–110)	120 (110–130)	0.7	0.001	0.001
DBP at 12 wk (mm Hg)	67 (60–71)	65 (60–72)	60 (60–70)	0.5	0.5	0.5
Second trimester UtA mean PI	0.70 (0.67–1.05)	1.21 (1.52–1.97)	1.28 (1.50–2.1)	0.0001	0.0001	0.6
BMI at assessment (kg/m ²)	26.5 (22.1–30.0)	30.1 (25.8–33.1)	27.2 (24–38.2)	0.028	0.2	0.07
BSA at assessment (m ²)	1.62 (1.54–1.76)	1.57 (1.34–2.35)	1.61 (1.54–1.82)	0.69	0.1	0.7
Gestational age at assessment (wks)	31 (26–35)	30 (26.5–32)	30 (26–33)	0.6*	0.7	0.3
Pregnancy outcome						
Gestational age at delivery (wks)	40.5 (39–41.7)	32 (29.2–34.1)	33 (29.5–34.5)	0.0001†	0.0001	0.9
Birth weight centiles‡ (%)	45.2 (24–57.2)	1.52 (0.34–3.58)	2.5 (2.13–6.7)	0.0001†	0.0001	0.0001
Adverse fetal or neonatal outcomes§	0	12 (41)	9 (36)	0.0001	0.0001	0.6

Values are given as median (interquartile range) or No. of subjects (percentage). FGR indicates fetal growth restriction; BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure; UtA, uterine artery; PE, preeclampsia; PI, pulsatility index.

*Data are not significant as per method.

†Data are significant as per method.

§Adverse fetal or neonatal outcome is defined as the presence of at least one of the following: respiratory distress, broncho-pulmonary dysplasia, need of mechanical ventilation, necrotizing enterocolitis, intracerebral hemorrhage, periventricular leucomalacia, sepsis, or perinatal death.

‡Birth weight centiles were determined using the curve references from Gardosi et al.³⁵

FGR. Changes in indices and impairment of cardiac function were always significantly more frequent and more severe in PE with FGR compared with normotensive FGR alone (Tables 2–4 and Figures 1 and 2). In contrast to PE with FGR, women with normotensive FGR had no evidence of LV altered geometry or impaired myocardial contractility compared with controls (Table 4 and Figure 2).

Interdependency of Indices

Multiple regression analysis showed that diastolic function indices were independently associated with mean arterial pressure and body mass index (please see Table S6). The other demographic and pregnancy characteristics did not independently contribute to the echocardiographic findings.

Discussion

The findings of this study demonstrate that the maternal cardiovascular responses in FGR are similar to those seen in PE, albeit less severe. Two thirds of women with FGR pregnancies showed evidence of poorer diastolic reserve, as demonstrated by impaired myocardial relaxation, and a third had overt diastolic chamber dysfunction despite a normal ejection fraction. These findings are in keeping with the common placental etiology of both FGR and PE pregnancies

and have clinical relevance in view of the high long-term risk of overt heart failure in patients with impaired left ventricle diastolic function. The cardiovascular findings were either more prevalent or more severe in women with PE pregnancies, with features of impaired myocardial contractility and systolic chamber dysfunction. Although previous studies assessed cardiac function in FGR pregnancies, they failed to demonstrate definitive or consistent findings. The most likely reason for this discrepancy is that previous studies invariably evaluated cardiac indices in isolation, where no individual echo index is capable of diagnosing or grading diastolic dysfunction, a distinct entity from systolic dysfunction or failure.^{12,17} Moreover, previous studies did not take into account the strong age-dependency of diastolic indices and used only conventional echocardiography. Although the gold standard for assessing diastolic function remains the invasive acquired pressure-volume relationship, the integration of conventional echo indices with tissue Doppler and strain rate indices applying age-adjusted cutoff allowed us to accurately diagnose and grade diastolic function in these young women. In contrast, the preservation of myocardial contractility and radial systolic function despite impairment of longitudinal systolic function in women with FGR pregnancies were supported by those of previous studies.^{13–15}

Table 2. Hemodynamic and Left Ventricular Geometric and Systolic Functional Parameters of Normotensive Preterm FGR, PE With FGR, and Controls

Parameters	Controls (n=58)	FGR (n=29)	PE With FGR (n=25)	FGR vs Controls	PE With FGR vs Controls	FGR vs PE
Hemodynamic indices						
HR, bpm	77 (75–91)	67 (62–74)	78 (70–90)	0.0001	0.08	0.004
SBP at assessment, mm Hg	110 (93–120)	120 (110–130)	150 (150–160)	0.006	0.0001	0.0001
DBP at assessment, mm Hg	70 (60–80)	78 (70–80)	100 (95–105)	0.037	0.0001	0.0001
MAP, mm Hg	80 (73–88)	94 (87–98)	118 (115–120)	0.0001	0.0001	0.0001
CI, L/min/m ²	3.48 (3.09–3.90)	2.73 (2.55–3.26)	2.58 (2.16–2.70)	0.0001	0.0001	0.013
SVI, mL/m ²	40 (38–46)	42 (35–48)	35 (26–46)	0.6	0.001	0.031
TVRI, (dyne×s ⁻¹ ×cm ⁻⁵)×m ²	1857 (1553–2005)	2456 (2197–2894)	3622 (3205–4391)	0.0001	0.0001	0.0001
Hematocrit, %	33 (31.5–35.0)	36 (35.8–37.3)	0.36 (34.7–37.5)	0.001	0.001	0.9
Hemoglobin, g/dL	10.6 (10.5–11.8)	12.3 (11.5–12.7)	11.9 (11.2–12.6)	0.006	0.008	0.6
Geometric indices						
LVMi, g/m ²	68 (51–79)	69 (61–80)	75 (58–112)	0.3	0.01	0.03
RWT	0.31 (0.29–0.35)	0.35 (0.30–0.37)	0.44 (0.40–0.53)	0.7	0.0001	0.0001
Longitudinal systolic function, mitral annulus sampling						
S ¹ /LAX (1/s) septal side	1.1 (0.95–1.3)	0.89 (0.84–1.1)	0.90 (0.73–1.2)	0.03	0.04	0.09
S ¹ /LAX (1/s) lateral side	1.3 (1.0–1.9)	0.90 (0.81–1.1)	0.93 (0.75–1.2)	0.01	0.01	0.5

Values are given as median (interquartile) or No. (percentage). HR indicates heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; CI, cardiac index; SVI, stroke volume index; TVRI, total vascular resistance index; LVM, left ventricular mass; LVMi, left ventricular mass index normalized for body surface area (BSA); RWT, relative wall thickness; S¹, pulsed wave Doppler peak systolic velocity; LV, left ventricle; LAX, end-diastolic LV long axis length; long-axis shortening, mitral ring displacement normalized for LAX (expressed in mm); S¹/LAX, pulsed wave Doppler peak systolic velocity normalized for LAX (expressed in cm); FGR, fetal growth restriction; PE, preeclampsia.

Diastolic dysfunction is known to occur variably as a consequence of increased LV stiffness, increased afterload, and/or derangements of the myocardial milieu.¹⁶ Multiple regression analysis in our cohort of normotensive FGR pregnancies suggested that global diastolic dysfunction was related to both a higher afterload, as demonstrated by the increased mean arterial pressure and maternal increased body

mass index. Several mechanisms evident in high body mass index individuals could influence maternal cardiac function, including inflammation, endothelial dysfunction, thrombotic tendency, and LV hypertrophy attributed to an increased blood volume.¹⁹ In particular, the metabolic effects of obesity resulting in dyslipidemia and insulin resistance seem to be the most likely mediators of changes in maternal cardiac function

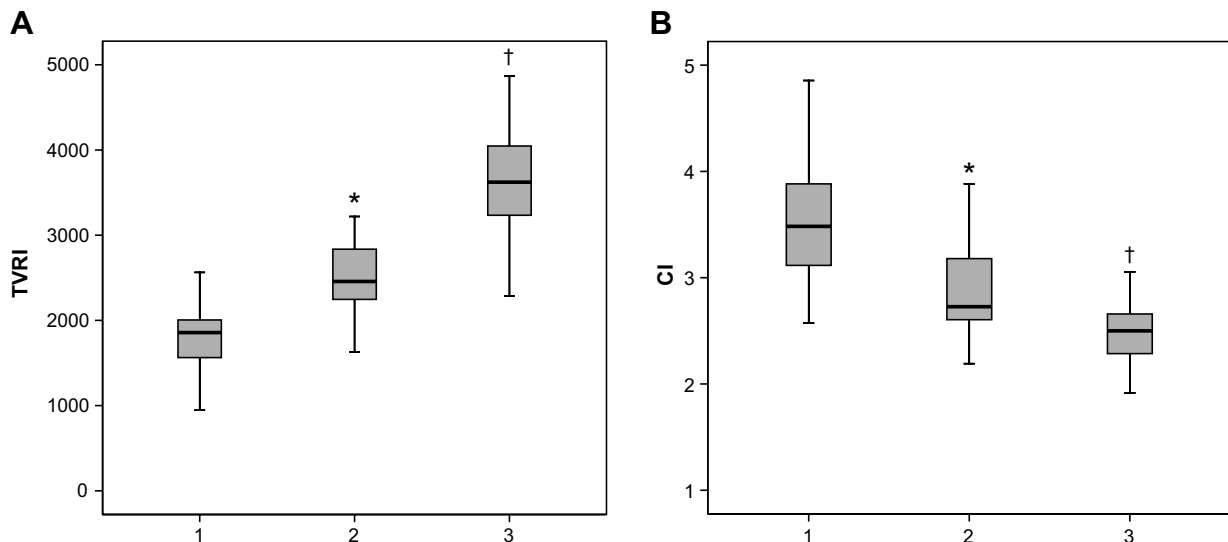


Figure 1. Hemodynamic status in pregnant controls (1), normotensive preterm fetal growth restriction (NT FGR; 2), and preterm preeclampsia (PE) associated with FGR (3). **A**, Total vascular resistance index (TVRI); total vascular resistance index expressed in (dyne×s⁻¹×cm⁻⁵)×m². **B**, CI indicates cardiac index in L×min⁻¹×m⁻². (*P<0.01 vs pregnant control; †P<0.01 vs pregnant control and NT FGR).

Table 3. Diastolic Function Indices in Normotensive Preterm FGR, PE With FGR, and Controls

Parameter	Controls (n=58)	FGR (n=29)	PE With FGR (n=25)	FGR vs Controls	PE With FGR vs Controls	FGR vs PE
Mitral inflow indices						
E/A ratio	1.6 (1.2–1.9)	1.4 (1.2–1.6)	1.1 (0.7–1.5)	0.13	0.022	0.03
DT, ms	159 (135–181)	179 (154–208)	210 (192–242)	0.013	0.0001	0.005
IVRT, ms	75 (71–88)	94 (81–99)	88 (74–107)	0.007	0.0001	0.032
Pulmonary venous flow indices						
S/D ratio	1.1 (0.9–1.3)	0.9 (0.7–1.2)	1.1 (0.9–1.3)	0.040	0.9	0.04
AR >0.35 m/s	3 (6)	7 (27)	9 (36)	0.023	0.0001	0.5
ARdur–Adur >30 ms	1 (2)	3 (12)	10 (40)	0.2	0.0001	0.3
Mitral annular motion indices						
Septal E ¹ , cm/s	10 (9–14)	9 (7–12)	8 (6.2–9)	0.01	0.0001	0.001
Lateral E ¹ , cm/s	17 (13–19)	16 (13–17)	11.5 (6.4–11.5)	0.9	0.0001	0.0001
Left heart filling pressure indices						
Average E/E1 ratio	5.4 (4.8–6.1)	6.2 (6–6.6)	7.7 (7.4–10.7)	0.011	0.0001	0.0001
E/Vp ratio	0.87 (0.85–1.2)	1.3 (1.1–1.5)	1.5 (1.2–1.7)	0.010	0.0001	0.0001
Strain rate study (8 segment model)						
Global early diastole strain rate	2.2 (2.0–2.3)	1.9 (1.3–2.1)	1.6 (0.9–1.8)	0.015	0.0001	0.03
Global early to late diastole strain rate ratio	1.8 (1.5–2.2)	1.6 (1.1–1.8)	1.1 (0.8–1.5)	0.019	0.0001	0.002

Values are given as either median (interquartile) or No. of subjects (percentage). FGR indicates fetal growth restriction; PE, preeclampsia; E, peak early diastole transmitral wave velocity; A, peak late diastole transmitral wave velocity; E/A, early to late diastole peak transmitral velocity ratio; DT, deceleration time of E wave; IVRT, isovolumetric relaxation time; S, peak systolic velocity of pulmonary flow; D, peak antegrade early diastolic velocity of pulmonary flow; S/D, S:D ratio; AR, peak retrograde late diastolic velocity; ARdur, AR duration; (ARdur–Adur), the time difference between pulmonary AR duration and mitral A-wave duration; E1, peak early diastolic velocity at mitral valve annulus; A1, peak late diastolic velocity at the mitral valve annulus; E/E1, E:E1 ratio; Vp, color M-mode propagation flow velocity; E/Vp, E:Vp ratio.

through changes in the composition and material properties of the myocardium.^{19–24} This assertion is indirectly supported by a recent study demonstrating that ≈20% of women who previously had a normotensive FGR pregnancy had features of metabolic syndrome.²⁵ The endothelial dysfunction is another known mechanism of diastolic impairment²⁶ and could also play a role in the diastolic abnormalities seen in normotensive FGR, as well as PE pregnancies. This is indirectly supported by studies demonstrating signs of endo-

thelial dysfunction in normotensive FGR pregnancies, such as abnormal endothelial-dependent microvascular dilatation²⁷ and increased intercellular adhesion molecule and vascular cell adhesion molecule.²⁸

During normal pregnancy, the cardiac output and plasma volume both expand by ≈50%, whereas the increase in red cell mass is ≈30%, resulting in a dilutional “fall” in hemoglobin concentration.^{29,30} This low-resistance, high-volume, hyperdynamic and hemodiluted pregnant state would appear

Table 4. Cardiovascular Changes in Preterm Normotensive FGR, Preterm PE With FGR, and Controls

Parameter	Control (n=58)	FGR (n=29)	PE With FGR (n=25)	FGR vs Controls	PE With FGR vs Controls	FGR vs PE
Hemodynamic						
MAP, mm Hg	80 (73–88)	94 (87–98)	118 (115–120)	0.0001	0.0001	0.0001
TVRI, (dyne×s ⁻¹ ×cm ⁻⁵)×m ²	1857 (1553–2005)	2456 (2197–2894)	3622 (3205–4391)	0.0001	0.0001	0.0001
CI, L/min/m ²	3.48 (3.09–3.90)	2.73 (2.55–3.26)	2.58 (2.16–2.70)	0.0001	0.0001	0.013
HR	78 (74–87)	67 (60–74)	78 (70–90)	0.0001	0.08	0.004
SVI	40 (38–46)	42 (35–48)	35 (26–46)	0.6	0.001	0.031
Altered geometry	8 (14)	8 (28)	20 (80)	0.2	0.0001	0.0001
Myocardial function						
Impaired relaxation	12 (21)	17 (59)	19 (76)	0.0001	0.0001	0.3
Impaired contractility	8 (5)	7 (24)	12 (48)	0.1	0.0001	0.033
Chamber function						
Diastolic dysfunction	2 (4)	8 (28)	13 (52)	0.009	0.0001	0.0001
Radial systolic dysfunction	0	1 (4)	7 (28)	0.06	0.0001	0.03

Values are given as median (interquartile range) when indices are provided or as No. (percentage). FGR indicates fetal growth restriction; PE, preeclampsia; MAP, mean arterial pressure; TVRI, total vascular resistance index; CI, cardiac index; HR, heart rate; SVI, stroke volume index.

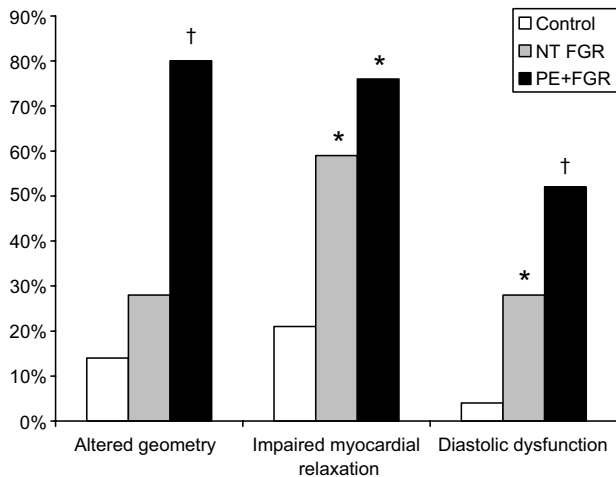


Figure 2. Prevalence of left ventricular cardiac findings in controls, normotensive preterm fetal growth restriction (NT FGR), and preterm preeclampsia associated with FGR (PE+FGR). Only significant *P* values are shown in the graph (**P*<0.01 vs control; †*P*<0.01 vs control and NT FGR). □, control; ▒, NT FGR; ■, PE+FGR.

to be important for appropriate utero-placental perfusion and effective fetomaternal exchange.^{29,30} Our study demonstrates that women with FGR pregnancies fail to achieve these physiological cardiovascular changes and exhibit relatively nonpregnant hemodynamic characteristics (high resistance, low volume, and hypodynamic state) compared with pregnant controls. The lack of physiological adaptation appears to be more severe in women with acute preterm PE. These results on hemodynamics in FGR pregnancies are in agreement with those from previous studies.^{13–15} Given the study design of assessment at disease presentation, it is not possible to ascertain whether these hemodynamic characteristics are a cause or effect of the pregnancy pathologies. However, it would be interesting to hypothesize that, although FGR and PE share common etiologies, the better cardiovascular reserve evident in women with FGR may protect them from the development of PE and result in slightly better long-term cardiovascular outcomes.

Limitations

The sample size was small but adequate to the primary outcome of the study, which was the detection of diastolic dysfunction. The exclusion of smokers from the study limits the ability to evaluate the confounding effect of smoking on cardiovascular changes and the extrapolation of results to FGR cases in smoking pregnancies.

Perspectives

Normotensive FGR pregnancy is associated with a failure to develop a low resistance-high volume circulation, impaired myocardial relaxation, and asymptomatic diastolic dysfunction in keeping with PE pregnancy, which shares a common placental etiology. The finding that women with normotensive FGR pregnancies have preserved systolic function and unaltered cardiac geometry compared with PE introduces the concept that better cardiac function in these FGRs may be important in preventing the development of PE.

The cardiovascular findings seen in FGR pregnancies are the expression of poor cardiac reserve and may partly explain the higher risk of cardiovascular disease in these women. Recent studies of women whose pregnancies were complicated by PE have shown persistence of LV moderate-severe asymptomatic abnormal function and geometry within 1 to 2 years of delivery in a significant proportion of women.^{11,12} These findings predispose the latter women to a much higher risk of hypertension, heart failure, and cardiac death, all of which may be ameliorated by appropriately timed therapeutic interventions.^{31–34} The natural history of asymptomatic diastolic dysfunction in women whose pregnancies were affected by FGR is unknown, and follow-up studies are needed to assess the latter, as well as the role of interventions, in preventing cardiovascular morbidity in these women.

Acknowledgments

We are grateful to the midwives and sonographers of the Fetal Maternal Medicine Unit (St George's Hospital) for their invaluable help with patient recruitment.

Sources of Funding

K.M. was funded for her PhD thesis by the University of Chieti.

Disclosures

None.

References

- Ness RB, Sibai BM. Shared and disparate components of the pathophysiologies of fetal growth restriction and preeclampsia. *Am J Obstet Gynecol.* 2006;195:40–49.
- Yinon Y, Kingdom JC, Odutayo A, Moineddin R, Drewlo S, Lai V, Cherney DZ, Hladunewich MA. Vascular dysfunction in women with a history of preeclampsia and intrauterine growth restriction: insights into future vascular risk. *Circulation.* 2010;122:1846–1853.
- Sattar N. Do pregnancy complications and CVD share common antecedents [review]? *Atheroscler Suppl.* 2004;5:3–7.
- Smith GD, Harding S, Rosato M. Relation between infants' birth weight and mothers' mortality: prospective observational study. *BMJ.* 2000;320:839–840.
- Paradisi G, Mattoli MV, Tomei C, Zuppi C, Lulli P, Quagliozzi L, Caruso A. Cardiovascular risk factors in healthy women with previous small for gestational age infants. *J Obstet Gynaecol Res.* 2011;37:1397–1404.
- Smith GC, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet.* 2001;357:2002–2006.
- Manten GT, Sikkema MJ, Voorbij HA, Visser GH, Bruinse HW, Franx A. Risk factors for cardiovascular disease in women with a history of pregnancy complicated by preeclampsia or intrauterine growth restriction. *Hypertens Pregnancy.* 2007;26:39–50.
- Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension.* 2009;53:944–951.
- Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. *Hypertension.* 2010;56:166–171.
- Melchiorre K, Sutherland GR, Baltabaeva A, Liberati M, Thilaganathan B. Maternal cardiac dysfunction and remodeling in women with preeclampsia at term. *Hypertension.* 2011;57:85–93.
- Melchiorre K, Sutherland GR, Liberati M, Thilaganathan B. Preeclampsia is associated with persistent postpartum cardiovascular impairment. *Hypertension.* 2011;58:709–715.
- Melchiorre K, Thilaganathan B. Maternal cardiac function in preeclampsia [review]. *Curr Opin Obstet Gynecol.* 2011;23:440–447.
- Bamfo JE, Kametas NA, Turan O, Khaw A, Nicolaides KH. Maternal cardiac function in fetal growth restriction. *BJOG.* 2006;113:784–791.
- Vasapollo B, Valensise H, Novelli GP, Larciprete G, Di Piero G, Altomare F, Casalino B, Galante A, Arduini D. Abnormal maternal

- cardiac function and morphology in pregnancies complicated by intrauterine fetal growth restriction. *Ultrasound Obstet Gynecol.* 2002;20:452–457.
15. Bamfo JE, Kametas NA, Chambers JB, Nicolaides KH. Maternal cardiac function in normotensive and pre-eclamptic intrauterine growth restriction. *Ultrasound Obstet Gynecol.* 2008;32:682–686.
 16. Bamfo JE, Kametas NA, Chambers JB, Nicolaides KH. Maternal cardiac function in fetal growth-restricted and non-growth-restricted small-for-gestational age pregnancies. *Ultrasound Obstet Gynecol.* 2007;29:51–57.
 17. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr.* 2009;22:107–133.
 18. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W, for the American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee; American Heart Association; European Association of Echocardiography; European Society of Cardiology. Recommendations for chamber quantification. *Eur J Echocardiogr.* 2006;7:79–108.
 19. Saltzman E, Benotti PN. Effects of obesity on the cardiovascular system. In: Bray GA, Bouchard C, eds. *Handbook of Obesity: Etiology and Pathophysiology.* 2nd ed. New York, NY: Marcel Dekker Ltd;2003:825–843.
 20. Bouchard DR, Langlois MF, Brochu M, Dionne IJ, Baillargeon JP. Metabolically healthy obese women and functional capacity. *Metab Syndr Relat Disord.* 2011;9:225–229.
 21. Utz W, Engeli S, Haufe S, Kast P, Hermsdorf M, Wiesner S, Pofahl M, Traber J, Luft FC, Boschmann M, Schulz-Menger J, Jordan J. Myocardial steatosis, cardiac remodelling and fitness in insulin-sensitive and insulin-resistant obese women. *Heart.* 2011;97:1585–1589.
 22. Zibadi S, Cordova F, Slack EH, Watson RR, Larson DF. Leptin's regulation of obesity-induced cardiac extracellular matrix remodeling. *Cardiovasc Toxicol.* 2011;11:325–333.
 23. Wu CK, Yang CY, Lin JW, Hsieh HJ, Chiu FC, Chen JJ, Lee JK, Huang SW, Li HY, Chiang FT, Tsai CT. The relationship among central obesity, systemic inflammation, and left ventricular diastolic dysfunction as determined by structural equation modeling. *Obesity (Silver Spring).* 2012;20:730–737.
 24. Hwang YC, Jee JH, Kang M, Rhee EJ, Sung J, Lee MK. Metabolic syndrome and insulin resistance are associated with abnormal left ventricular diastolic function and structure independent of blood pressure and fasting plasma glucose level. *Int J Cardiol.* March 9, 2011. DOI: 10.1016/j.ijcard.2011.02.039. <http://www.internationaljournalofcardiology.com/article/S0167-5273%2811%2900200-2/fulltext>. Accessed June 13, 2012.
 25. Zandstra M, Stekinger E, van der Vlugt MJ, van Dijk AP, Lotgering FK, Spaanderman ME. Cardiac diastolic dysfunction and metabolic syndrome in young women after placental syndrome. *Obstet Gynecol.* 2010;115:101–108.
 26. Deswal A. Diastolic dysfunction and diastolic heart failure: mechanisms and epidemiology [review]. *Curr Cardiol Rep.* 2005;7:178–183.
 27. Koopmans CM, Blaauw J, van Pampus MG, Rakhorst G, Aarnoudse JG. Abnormal endothelium-dependent microvascular dilator reactivity in pregnancies complicated by normotensive intrauterine growth restriction. *Am J Obstet Gynecol.* 2009;200:66.e1–66.e6.
 28. Johnson MR, Anim-Nyame N, Johnson P, Sooranna SR, Steer PJ. Does endothelial cell activation occur with intrauterine growth restriction? *BJOG.* 2002;109:836–839.
 29. Poppas A, Shroff SG, Korcarz CE, Hibbard JU, Berger DS, Lindheimer MD, Lang RM. Serial assessment of the cardiovascular system in normal pregnancy. Role of arterial compliance and pulsatile arterial load. *Circulation.* 1997;20:2407–2415.
 30. Carbillon L, Uzan M, Uzan S. Pregnancy, vascular tone, and maternal hemodynamics: a crucial adaptation. *Obstet Gynecol Surv.* 2000;55:574–581.
 31. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults; a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation.* 2009;119:1977–2016.
 32. Ammar KA, Jacobsen SJ, Mahoney DW, Kors JA, Redfield MM, Burnett JC Jr, Rodeheffer RJ. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation.* 2007;115:1563–1570.
 33. Kuznetsova T, Herbots L, Jin Y, Stolarz-Skrzypek K, Staessen JA. Systolic and diastolic left ventricular dysfunction: from risk factors to overt heart failure. *Expert Rev Cardiovasc Ther.* 2010;8:251–258.
 34. Vogel MW, Slusser JP, Hodge DO, Chen HH. The natural history of preclinical diastolic dysfunction: a population based study. *Circ Heart Fail.* 2012;5:144–151.
 35. Gardosi J, Mongelli M, Chang A. An adjustable fetal weight standard. *Ultrasound Obstet Gynecol.* 1995;6:168–174.

Novelty and Significance

What Is New?

- One third of women with pregnancy complicated by FGR are affected by asymptomatic global LV diastolic dysfunction with preserved ejection fraction. Two thirds of them present impaired LV myocardial relaxation.

What Is Relevant?

- The findings of this study have clinical relevance in view of the high long-term risk of overt heart failure in patients with impaired LV diastolic function.

Summary

Normotensive FGR pregnancy is associated with a failure to develop a low resistance-high volume circulation, impaired myocardial relaxation, and asymptomatic global diastolic dysfunction in keeping with PE pregnancy, which shares a common placental etiology and common adverse long-term cardiovascular outcome.