OBSTETRICS

Fetal cardiac remodeling and dysfunction is associated with both preeclampsia and fetal growth restriction

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BACKGROUND: Preeclampsia and fetal growth restriction share some pathophysiologic features and are both associated with placental insufficiency. Fetal cardiac remodeling has been described extensively in fetal growth restriction, whereas little is known about preeclampsia with a normally grown fetus.

OBJECTIVE: To describe fetal cardiac structure and function in pregnancies complicated by preeclampsia and/or fetal growth restriction as compared with uncomplicated pregnancies.

STUDY DESIGN: This was a prospective, observational study including pregnancies complicated by normotensive fetal growth restriction (n=36), preeclampsia with a normally grown fetus (n=35), preeclampsia with fetal growth restriction (preeclampsia with a normally grown fetus—fetal growth restriction, n=42), and 111 uncomplicated pregnancies matched by gestational age at ultrasound. Fetal echocardiography was performed at diagnosis for cases and recruitment for uncomplicated pregnancies. Cord blood concentrations of B-type natriuretic peptide and troponin I were measured at delivery. Univariate and multiple regression analysis were conducted.

RESULTS: Pregnancies complicated by preeclampsia and/or fetal growth restriction showed similar patterns of fetal cardiac remodeling with larger hearts (cardiothoracic ratio, median [interquartile range]: uncomplicated pregnancies 0.27 [0.23—0.29], fetal growth restriction 0.31 [0.26—0.34], preeclampsia with a normally grown fetus 0.31 [0.29—0.33), and preeclampsia with fetal growth restriction 0.28 [0.26—0.33]; $P<.001$) and more spherical right ventricles (right ventricular sphericity index: uncomplicated pregnancies 1.42 [1.25—1.72], fetal growth restriction 1.29 [1.22—1.72], preeclampsia with a normally grown fetus 1.30 [1.33—1.51], and preeclampsia with fetal growth restriction 1.35 [1.27—1.46]; $P=.04$) and hypertrophic ventricles (relative wall thickness: uncomplicated pregnancies 0.55 [0.48—0.61], fetal growth restriction 0.67 [0.58—0.8], preeclampsia with a normally grown fetus 0.68 [0.61—0.76], and preeclampsia with fetal growth restriction 0.66 [0.58—0.77]; $P<.001$). Signs of myocardial dysfunction also were observed, with increased myocardial performance index (uncomplicated pregnancies 0.78 z scores [0.32—1.41], fetal growth restriction 1.48 [0.97—2.08], preeclampsia with a normally grown fetus 1.15 [0.75—2.17], and preeclampsia with fetal growth restriction 0.45 [0.54—1.94]; $P<.001$) and greater cord blood B-type natriuretic peptide (uncomplicated pregnancies 14.2 [8.4—30.9] pg/mL, fetal growth restriction 20.8 [13.1—33.5] pg/mL, preeclampsia with a normally grown fetus 31.8 [16.4—45.8] pg/mL and preeclampsia with fetal growth restriction 37.9 [15.7—105.4] pg/mL; $P<.001$) and troponin I as compared with uncomplicated pregnancies.

CONCLUSION: Fetuses of preeclamptic mothers, independently of their growth patterns, presented cardiovascular remodeling and dysfunction in a similar fashion to what has been previously described for fetal growth restriction. Future research is warranted to better elucidate the mechanism(s) underlying fetal cardiac adaptation in these conditions.

Key words: B-type natriuretic peptide, cardiovascular remodeling, fetal echocardiography, fetal programming, intrauterine growth restriction, pregnancy hypertension, troponin I

Preeclampsia (PE) and fetal growth restriction (FGR) represent a major concern in public health, affecting 2—8% and 5—10% of all pregnancies, respectively, and being a leading cause of perinatal morbidity and mortality.[1,2] Both syndromes share some pathophysiologic features, with a variable involvement of placental insufficiency[3,4] and maternal cardiovascular maladaptation.[5,6] Moreover, they occur concurrently in a nonignorable proportion, which could be different according to the population characteristics. In fact, every fifth case of PE also presents with FGR and about 50% of early-onset FGR cases will eventually coexist with PE[1,2]; however, in populations with a high burden of obesity among pregnant women, the prevalence of PE is extremely high, with few cases of FGR.[7]

Besides their association with perinatal morbidity and mortality in the short term, accumulating evidence suggests the existence of long-term cardiovascular consequences on both the mother and the offspring.[8] Concerning the offspring, long-term effects are thought to be explained by fetal adaptations to adverse intrauterine conditions, including metabolic and cardiovascular programming.[9,10] Recent studies consistently have demonstrated structural and functional cardiovascular changes in growth-restricted fetuses[11] that persist into the postnatal life through infancy,[12] childhood,[9] and adolescence,[10] supporting epidemiologic and experimental evidence linking low birthweight and cardiovascular morbidity and mortality later in life.[13,14] In contrast, offspring from preeclamptic pregnancies showed cardiac structural and functional changes and greater blood pressure in

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AJOG at a Glance

Why was this study conducted?

To answer the question: is there any fetal heart affectation in preeclampic pregnancies with normally grown fetuses? And, if there are any signs of fetal cardiac remodeling or dysfunction, are they similar to those described previously in fetal growth restriction?

Key findings

We recruited well-characterized pregnancies complicated by preeclampsia (with or without fetal growth restriction), normotensive fetal growth restriction, and uncomplicated pregnancies. Fetal hearts in complicated pregnancies were larger, more spherical, and thicker, with a similar pattern of fetal cardiac remodeling in preeclampsia and fetal growth restriction. Moreover, cardiac dysfunction was demonstrated by greater myocardial performance index, and cord blood B-type natriuretic peptide and troponin I, both in preeclampsia and fetal growth restriction.

What does this add to what is known?

This is the first study to demonstrate that pregnancies with preeclampsia and a normally grown fetus are associated with cardiac remodeling and dysfunction in a similar fashion to what has previously been described in fetal growth restriction.

childhood and adolescence.[15,16] However, most of these studies did not include pure phenotypes of PE and FGR, ie, studies on FGR included pregnancies complicated by PE and vice versa, which prevents to differentiate the independent effect of each condition on the fetal heart.

Thus, the aim of this study was to evaluate the independent effect of PE and FGR on fetal cardiac structure and function. Well-characterized pregnancies with normotensive FGR, PE associated with FGR, and PE with a normally grown fetus were evaluated by echocardiography and cord blood myocardial biomarkers and compared with uncomplicated pregnancies.

Materials and Methods

Study population

This was a prospective, observational study including singleton pregnancies with a diagnosis of PE and/or FGR who attended the Departments of Maternal-Fetal Medicine at BCNatal (Barcelona, Spain) between July 2016 and December 2017. FGR was defined as estimated fetal weight (EFW) and birthweight below the 10th centile associated with either abnormal cerebroplacental ratio (<5th centile) or abnormal uterine arteries mean pulsatility index (PI) (>95th centile), or birthweight below the 3rd centile.[17] EFW and birthweight centiles were assigned according to local standards.[18] PE was defined as high blood pressure (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg on 2 occasions, at least 4 hours apart), developed after 20 weeks of gestation, with proteinuria (≥300 mg/24 hours or protein/creatinine ratio ≥0.3).[1,19] Uncomplicated pregnancies with normotensive mothers and appropriate growth for gestational age fetuses—defined as EFW and birthweight above the 10th centile—were selected randomly from our general population to be included as controls and frequency paired with cases by gestational age at fetal echocardiography (±2 weeks). In all pregnancies, gestational age was calculated based on the crown–rump length at first trimester ultrasound.[20] Pregnancies with chromosomal/structural anomalies or intrauterine infection were excluded. The study protocol was approved by the local ethics committee (HCB/2016/0253), and patients agreeing to participate provided their written informed consent.

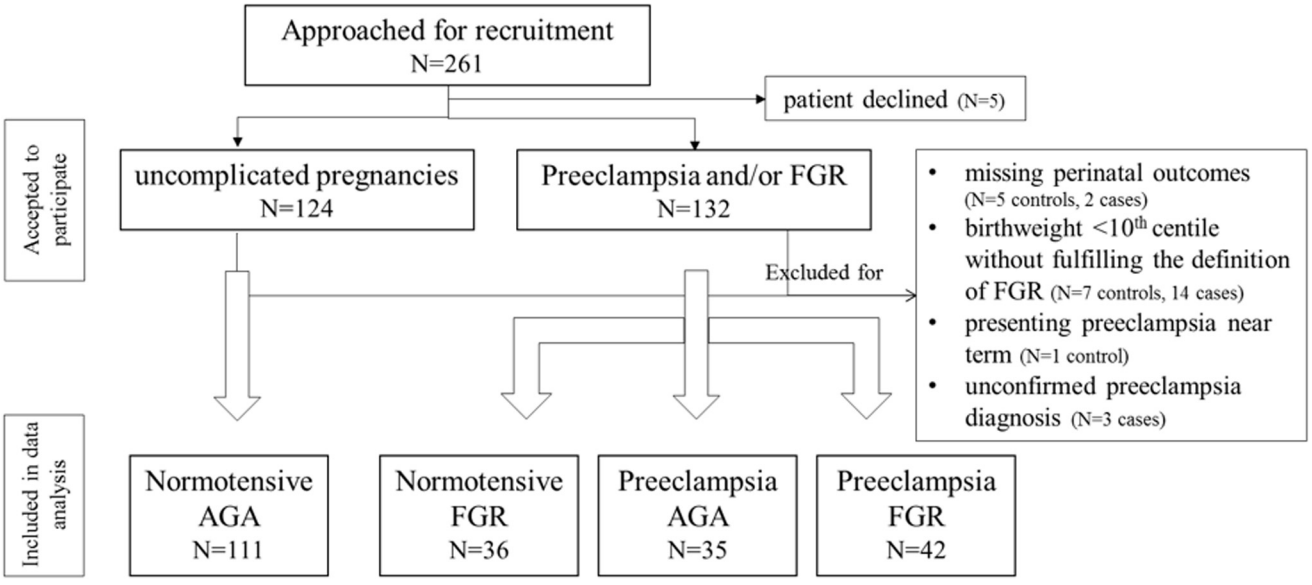
Data collection and study protocol

The following data were recorded on enrollment: maternal age, ethnicity, body mass index, known chronic disease (ie, hypertension, diabetes mellitus), parity, obstetric history, mode of conception, and smoking status. Fetoplacental Doppler, EFW, and fetal echocardiographic parameters were obtained at diagnosis (or at enrollment for controls). Ultrasound studies were performed using a Siemens Sonoline Antares (Siemens Medical Systems, Malvern, PA) or a Voluson 730 Expert (GE Medical Systems, Milwaukee, WI) with 6–4-MHz linear curved-array probes. EFW was calculated using the Hadlock formula[21] and centile based on local reference curves.[18] All estimations were done in the absence of fetal movements and, when required, with the mother in voluntary suspended respiration. An angle of insonation of <30° between the vessel and the Doppler beam was accepted for analysis. The mechanical and thermal indices were maintained below 1, and the wall filter was set to 70 Hz.

Fetoplacental Doppler parameters were obtained from 3 or more successive waveforms in each vessel. Doppler examination included uterine arteries, the umbilical artery (UA), fetal middle cerebral artery (MCA), and aortic isthmus. Uterine artery PI was calculated as the average PI of the right and left arteries.[22] UA-PI was measured from a free loop of the umbilical cord.[23] MCA-PI was measured distal to the junction of the internal carotid artery in a transverse view of the fetal skull at the level of the circle of Willis.[23] The cerebroplacental ratio was calculated as MCA-PI/UA-PI.[24] The aortic isthmus PI was sampled downstream of the left subclavian artery and just upstream of the ductus arteriosus connection in a sagittal view simultaneously visualizing the aortic arch.[25] Fetal echocardiography also was performed in all cases and controls, as described to follow.

At delivery, gestational age, birthweight, birthweight centile, Apgar

FIGURE 1
Recruitment flow chart



Fetal echocardiography data were collected from all the patients who accepted to participate in the study. Some of them were excluded from further analysis according to confirmed birthweight and perinatal outcomes that did not meet the inclusion criteria.

AGA, fetuses with appropriate growth for gestational age; *FGR*, fetal growth restriction.

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scores, umbilical artery pH, admissions to the neonatal intensive care unit, and perinatal mortality were recorded. Those pregnancies with missing perinatal outcomes, unconfirmed diagnosis, or who delivered a small newborn not fulfilling the definition of FGR (ie, birthweight between the 3rd and the 10th centile associated with normal cerebroplacental ratio [≥5th centile] and normal uterine arteries PI [≤95th centile])[17] were excluded from further analysis, as shown in Figure 1. In addition, cord blood from umbilical vein was collected at delivery to measure the concentration of B-type natriuretic peptide (BNP) and troponin I.

Fetal echocardiography

Fetal echocardiography included a comprehensive examination to assess structural heart integrity and rule out cardiac defects following standard protocols.[26] Then, fetal cardiac morphometry and function were evaluated.[27] All the scans were performed by experienced sonographers in fetal echocardiography who were blinded to the study hypothesis. Researchers who performed the offline analysis of the echocardiographic images were blinded to the diagnosis.

Cardiac and ventricular dimensions were measured on 2-dimensional images from an apical or basal 4-chamber view at end-diastole. The cardiothoracic ratio was calculated as heart area divided by thoracic area.[28] Left and right ventricular sphericity indices were calculated as base-to-apex length divided by basal diameter.[29,30] Ventricular end-diastolic septal wall thicknesses were measured from a transverse 4-chamber view. Relative septal wall thickness was calculated as 2 times septal wall thickness divided by the left ventricular diastolic diameter. Ductus venosus PI was measured either in a midsagittal view of the fetal thorax or in a transverse plane through the upper abdomen prior to its entrance into the inferior vena cava, positioning the Doppler gate at the ductus venosus isthmic portion.[31] Left myocardial performance index was obtained in a cross-sectional image of the fetal thorax, placing the Doppler sample volume on the medial wall of the ascending aorta and including the leaflets of the aortic and mitral valves.[32,33] The clicks of the valves registered in the Doppler trace were used as landmarks to calculate the following time periods: isovolumetric contraction time from the closure of the mitral valve to the opening of the aortic valve, ejection time from the opening to the closure of the aortic valve, and isovolumetric relaxation time from the closure of the aortic valve to the opening of the mitral valve. Finally, the myocardial performance index was calculated as (isovolumetric contraction time + isovolumetric relaxation time) / ejection time, and normalized into z scores.[34]

Placental evaluation

Placentas were fixed in 10% buffered formalin. Trimmed placentas were weighted, and samples were taken for routine processing adhering to a standard laboratory protocol.[35] Diagnostics from pathology reports were classified according to Redline's classification[36] following 2014 Amsterdam Placental Workshop Group Consensus Statement.[35]

TABLE 1
Maternal, fetoplacental ultrasound, perinatal characteristics, and placental histopathologic findings of the study population

	Normotensive AGA n=111	Normotensive FGR n=36	Preeclampsia AGA n=35	Preeclampsia FGR n=42
Maternal characteristics				
Age, y	33.7 (30.7–36.7)	33.2 (30–37)	35.4 (32.4–38.1)	35.1 (32.3–37.6)
Caucasian ethnicity	55 (49.6)	24 (66.7)	20 (57.1)	21 (50)
Pregestational BMI, kg/m^2	22.5 (20.6–25.5)	22.3 (19.6–26.2)	23.1 (22.4–28)[a]	24.7 (21.3–27)[a]
Chronic hypertension	0 (0)	2 (5.6)[a]	6 (17.1)[a]	6 (14.3)[a]
Pregestational diabetes	0 (0)	2 (5.6)[a]	9 (25.7)[a]	3 (7.1)[a]
Nulliparity	64 (57.7)	16 (44.4)	21 (60)	26 (61.9)
Assisted reproductive technologies	3 (2.8)	0 (0)	5 (14.3)[a]	5 (11.9)[a]
Smoking during pregnancy	7 (6.3)	7 (20)[a]	3 (8.6)	5 (11.9)
Fetoplacental ultrasound				
Gestational age at assessment, wk	33.4 (29.3–37.6)	33.1 (30.1–35.7)	34.1 (31.3–36.6)	32.5 (30.3–34.9)
Estimated fetal weight, g	2053 (1385–3086)	1152 (834–825)[a]	2077 (1674–2977)	1298 (699–1718)[a]
Estimated fetal weight centile	58 (36–78)	2 (0–5)[a]	30 (10–89)	2 (0–6)[a]
Uterine arteries mean PI (z score)	−0.05 (−1.04 to 0.47)	1.8 (0.21 to 2.9)[a]	0.14 (−1.2 to 1.26)	2.98 (1.96 to 3.53)[a]
Umbilical artery PI (z score)	−0.22 (−0.57 to 0.12)	0.44 (−0.92 to 1.23)[a]	−0.05 (−0.59 to 0.49)	0.47 (−0.04 to 1.65)[a]
Middle cerebral artery PI (z score)	−0.04 (−0.65 to 0.48)	−0.77 (−1.67 to 0.15)[a]	−0.14 (−0.57 to 0.33)	−0.83 (−1.71 to −0.4)[a]
Cerebroplacental ratio (z score)	−0.27 (−0.8 to 0.49)	−1.17 (−2.24 to 0.33)[a]	−0.46 (−1.15 to 0.13)	−1.3 (−1.94 to −0.67)[a]
Aortic isthmus PI (z score)	−0.31 (−1.04 to 0.46)	0.01 (−0.32 to 0.64)	−0.75 (−1.41 to −0.07)	0.12 (−0.91 to 1.44)
Perinatal outcomes				
Gestational age at delivery, wk	40.1 (39.1–40.9)	37.2 (34.9–37.6)[a]	37.1 (34.7–37.7)[a]	34.2 (32–35.9)[a]
Cesarean delivery	23 (18.7)	18 (50)[a]	26 (74.3)[a]	34 (72.3)[a]
Emergency cesarean delivery for fetal distress	2 (1.8)	5 (13.9)[a]	5 (14.3)[a]	6 (14.3)[a]
Male sex	45 (40.5)	19 (52.8)	13 (37.1)	24 (57.1)
Birthweight, g	3354 (3092–3650)	1994 (1665–2254)[a]	3010 (2470–3270)	1548 (1160–1830)[a]
Birth weight centile	49 (26–75)	1 (0–1.5)[a]	57 (21–85)	0 (0–1)[a]
Apgar score, 5 min, <7	0 (0)	0 (0)	0 (0)	6 (14.3)[a]
Umbilical artery pH	7.21 (7.15–7.26)	7.2 (7.13–7.25)	7.19 (7.14–7.23)	7.21 (7.11–7.23)
Admission to neonatal intensive care unit	4 (3.6)	17 (47.2)[a]	13 (38.2)[a]	35 (83.3)[a]
Perinatal mortality	0 (0)	0 (0)	0 (0)	4 (9.5)[a]
Placental weight and vascular histopathologic findings				
Placental weight, g	465 (405–530)	293 (250–340)[a]	503 (365–590)	260 (205–325)[a]

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TABLE 1
Maternal, fetoplacental ultrasound, perinatal characteristics, and placental histopathologic findings of the study population *(continued)*

	Normotensive AGA n=111	Normotensive FGR n=36	Preeclampsia AGA n=35	Preeclampsia FGR n=42
Maternal side lesions				
Maldevelopment, n (%)	0 (0)	3 (9.1)[a]	2 (6.5)	1 (2.4)
Malperfusion, n (%)	14 (15.6)	7 (21.2)	8 (25.8)	26 (61.9)[a]
Loss of integrity, n (%)	2 (2.2)	4 (12.1)	2 (6.5)	0 (0)
Fetal side lesions				
Maldevelopment, n (%)	0 (0)	0 (0)	1 (3.2)	0 (0)
Malperfusion, n (%)	4 (4.4)	2 (6.1)	0 (0)	5 (11.9)
Loss of integrity, n (%)	10 (11.1)	2 (6.1)	6 (19.4)	4 (9.5)

Data are presented as median (interquartile range) or n (%) as appropriate. Perinatal mortality was defined as stillbirth or neonatal mortality within 28 days of delivery. Fetal distress was considered when presenting nonreassuring cardiotocography during labor.

AGA, fetuses with appropriate growth for gestational age; *BMI*, body mass index; *FGR*, fetal growth restriction; *PI*, pulsatility index.

[a] $P<.05$ by Student t or Pearson χ^2 tests as appropriate, compared with normotensive AGA (unadjusted).

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Cord blood sampling and biomarkers assessment

Umbilical cord ethylenediaminetetraacetic acid–treated blood was obtained from the umbilical vein after cord clamp at delivery. Plasma was separated by centrifugation at 1500 g for 10 minutes at 4°C, and samples were immediately stored at −80°C until assayed. Concentrations of BNP and troponin I were measured using Siemens ADVIA Centaur BNP and Centaur CP troponin I assays, respectively.[37] This analysis was performed in 50 cord samples from uncomplicated pregnancies and 30 samples from each group of the cases.

Statistical analysis

Data were analyzed with the statistical software STATA 14.2 (StataCorp LLC, College Station, TX). The study outcome was fetal cardiovascular assessment. The independent variable of interest was the presence of PE and/or FGR, and the covariates were the presence of chronic hypertension, diabetes, the mode of conception (via assisted reproductive technologies vs natural), and smoking during pregnancy. A sample size of 23 patients in each group of the cases and 69 controls was calculated by expecting 1 z-score differences in the myocardial performance index between cases and controls,[38] for a given 5% α error and 80% power and 1:3 sampling ratio.

Results were expressed as median (interquartile range) or percentage as appropriate. Statistical analysis included the use of Student t or Mann–Whitney U tests and Pearson χ^2 test for continuous and categorical variables, respectively, to compare each group of the cases vs the controls. To evaluate the influence of covariates, comparisons of the cardiovascular parameters were adjusted for the presence of chronic hypertension, diabetes, assisted reproductive technologies, smoking, and fetal sex by multiple regression analyses. In addition to these covariates, BNP and troponin I levels also were adjusted for gestational age at sampling and the rate of cesarean deliveries for fetal distress. All reported P values are 2 sided. Differences were considered significant when $P<.05$.

Results

Baseline and perinatal characteristics of the study population

A total of 224 pregnancies were included in data analysis. Baseline characteristics and perinatal outcomes are shown in Table 1. The study groups were similar in terms of maternal baseline characteristics, except for significantly greater prevalence of chronic hypertension and pregestational diabetes among cases, greater proportion of conception by assisted reproductive technologies and maternal pregestational body mass index in preeclamptic mothers, and more smoking women in normotensive FGR as compared with controls. As expected, EFW, birthweight, and weight centiles were lower together with worse fetoplacental Doppler in FGR groups as compared with controls. In addition, gestational age at delivery was earlier in PE and/or FGR, with greater rates of cesarean deliveries and admissions to neonatal intensive care unit. FGR groups presented lower placental weight, with increased malperfusion lesions in the maternal side in PE with FGR group.

Fetal cardiovascular results

Fetal cardiovascular results are shown in Table 2 and Figure 2. Cases complicated by PE and/or FGR showed signs of fetal cardiac remodeling in the form of larger, hypertrophic, and more globular hearts as well as cardiac dysfunction manifested by increased myocardial performance index and cord blood BNP and troponin I concentrations. Most cardiac parameters remained significantly different in complicated pregnancies even after statistical adjustment for potential

TABLE 2
Fetal echocardiographic results in the study populations

	Normotensive AGA n=111	Normotensive FGR n=36	Preeclampsia AGA n=35	Preeclampsia FGR n=42
Gestational age at assessment, wk	33.4 (29.3–37.6)	33.1 (30.1–35.7)	34.1 (31.3–36.6)	32.5 (30.3–34.9)
Fetal cardiac morphometry				
Cardiothoracic ratio	0.27 (0.23–0.29)	0.31 (0.26–0.34)[a,b]	0.31 (0.29–0.33)[a,b]	0.28 (0.26–0.33)[a,b]
Left ventricular sphericity index	1.76 (1.58–1.94)	1.52 (1.47–1.62)[a,b]	1.69 (1.44–1.88)	1.61 (1.49–1.87)
Right ventricular sphericity index	1.42 (1.25–1.72)	1.29 (1.22–1.39)[a,b]	1.30 (1.33–1.51)[a,b]	1.35 (1.27–1.46)[a]
Relative wall thickness	0.55 (0.48–0.61)	0.67 (0.58–0.8)[a,b]	0.68 (0.61–0.76)[a,b]	0.66 (0.58–0.77)[a,b]
Fetal cardiac function				
Ductus venosus PI (z score)	−0.44 (−0.87 to 0.29)	−0.11 (−1.05 to 0.99)	0.16 (−0.85 to 1.01)	−0.46 (−0.93 to 0.65)
Isovolumetric contraction time (z score)	0.66 (0.03–1.14)	0.92 (0.19–1.48)	1.15 (0.5–1.94)[a,b]	0.76 (0.06–1.39)
Ejection time (z score)	0.07 (−0.9 to 0.56)	−0.64 (−1.69 to 0.13)[a,b]	−0.08 (−1.2 to 0.76)	−1.06 (−1.76 to 0.09)[a,b]
Isovolumetric relaxation time (z score)	0.47 (−0.09 to 1.02)	1.38 (0.68–1.61)[a,b]	0.75 (0.12–1.55)	0.81 (0.31–1.34)
Myocardial performance index (z score)	0.78 (−0.32 to 1.41)	1.48 (0.97–2.08)[a,b]	1.15 (0.75–2.17)[a]	1.45 (0.54–1.94)[a,b]

Data are presented as median (interquartile range). Sphericity index was calculated as ventricular longitudinal diameter divided by ventricular basal diameter. Relative septal wall thickness was calculated as 2 times septal wall thickness divided by the left ventricular diastolic diameter.

AGA, fetuses with appropriate growth for gestational age; *FGR*, fetal growth restriction; *PI*, pulsatility index.

[a] $P<.05$ by Student *t* test compared with normotensive AGA (unadjusted); [b] $P<.05$ by multiple regression adjusted for chronic hypertension, pregestational diabetes, assisted reproductive technologies, smoking, and fetal sex, compared with normotensive AGA.

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confounders such as chronic hypertension, pregestational diabetes, assisted reproductive technologies, and smoking.

Comment

Principal findings of the study

This study provides evidence that PE and/or FGR are associated with a similar pattern of cardiac remodeling and dysfunction, as measured by means of echocardiographic and biochemical parameters, whether they present isolated or in association. To our knowledge, this is the first study to demonstrate cardiac remodeling and dysfunction in PE with a normally grown fetus.

Our findings show an altered fetal cardiac structure and function in FGR with or without PE. We further demonstrate similar changes in PE without FGR. In the present assessment, we included a unique group of normally grown fetuses with normal fetoplacental Doppler from preeclamptic mothers. These fetuses presented larger and hypertrophic hearts with more spherical right ventricles. We determined also significant changes at the functional level. Of note, myocardial performance index was greater in all study groups, but with a different pattern of the time periods involved in the calculation of this index. FGR fetuses showed a decreased ejection time and prolonged isovolumetric relaxation time indicating both systolic and diastolic dysfunction while prolonged isovolumetric contraction time was the main feature in PE without FGR reflecting mainly systolic dysfunction. Prolonged isovolumetric contraction time has been described in circumstances of increased afterload—such as hypertension—where myocardial contraction takes longer to generate enough pressure within the heart to open the aortic valve.[39]

Regarding the cord blood biomarkers, all PE and/or FGR groups exhibited increased cord blood BNP and troponin I concentrations supporting the presence of myocardial dysfunction in these fetuses. Cases of FGR with PE exhibited the greatest concentrations of cord blood BNP; however, they didn't show the most severe morphometric changes in fetal hearts, indicating a role of the chronicity of placental insufficiency in fetal cardiac remodeling. Interestingly, all the groups considered in this study presented similar umbilical artery blood pH. This finding could be due to 2 factors: first, most of the included cases were late-onset cases and second, all FGR cases were followed up by a strict protocol,[40] so the majority of them went through an indicated delivery to reduce adverse perinatal outcomes.

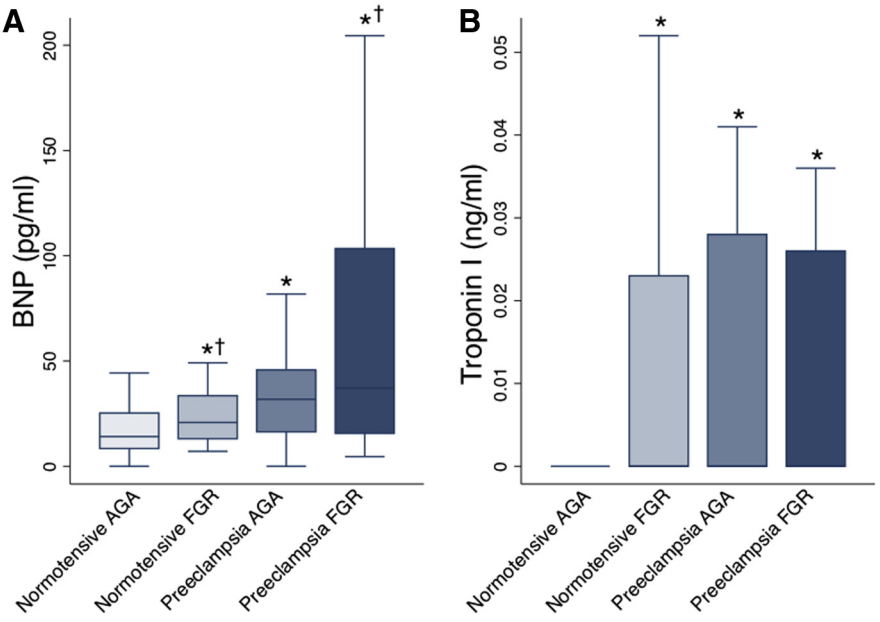
Results of the study in the context of other observations

Our data confirm previous studies reporting remodeled fetal cardiac structure in FGR—with or without PE—including larger and more spherical hearts together with signs of myocardial hypertrophy.[11] We also confirm signs of fetal myocardial dysfunction and injury in FGR both by echocardiography—increased myocardial performance index—and cord blood biomarkers—greater BNP and troponin I concentrations.[11,41] Of interest, we report a similar

degree of cardiac dysfunction in FGR with and without PE, which is consistent with previous data.[38] Former studies also suggested the persistence of these prenatal cardiac structural and functional changes into childhood[9] and preadolescence,[10] underlying an increased cardiovascular risk later in life for FGR offspring.[13] Moreover, experimental data of FGR lamb model had demonstrated high blood pressure and high vascular resistance in affected fetuses.[42]

In contrast, some previous studies have evaluated fetal cardiac structure and function in PE—with and without FGR—reporting elevated myocardial performance index[43,44] and cord blood NT-proBNP and homocysteine.[45] However, the comparison among these studies is difficult, as they mostly included both FGR and non FGR cases, and a high proportion of fetuses presenting altered fetoplacental Doppler.[43–46] In contrast, we selected a unique group of PE cases with normal fetal growth using strict criteria based on fetal biometrics, confirmed birthweight, and fetoplacental Doppler. Our results are concordant with postnatal observations.[16,47] A recent study demonstrated altered myocardial performance index in normally grown newborns of mildly preeclamptic pregnant women within postnatal 24–48 hours.[47] In addition, several cohort studies reported increased cardiovascular risk and blood pressure in young offspring of pregnancies complicated by PE.[15,48,49] Moreover, Timpka et al[16] showed elevated myocardial wall thickness and left ventricular mass with reduced end-diastolic volume approaching concentric remodeling in PE offspring adolescents. Although some studies suggested the influence of genetic and environmental factors in the childhood to the increased cardiovascular risk,[50,51] others demonstrated that PE was independently associated with changes in the systemic and the pulmonary circulation of the offspring.[16,52] Again, a limitation of most postnatal studies is the inclusion of PE with and without FGR. Likewise, the potential influence of gestational age at delivery and of preterm birth needs to be clarified, as discussed later in this section.

FIGURE 2
Cord blood concentrations of myocardial biomarkers



(**A**) BNP and (**B**) troponin I. *Boxes* show median and interquartile range; *whiskers* represent 1.5× interquartile range or the extremes of the distribution. *$P<.05$ by Mann—Whitney *U* test compared with normotensive AGA (unadjusted). †$P<.05$ by multiple regression adjusted for chronic hypertension, pregestational diabetes, assisted reproductive technologies, smoking, fetal sex, gestational age at sampling, and the rate of cesarean deliveries for fetal distress compared with normotensive AGA.

AGA, fetuses with appropriate growth for gestational age; *BNP*, B-type natriuretic peptide; *FGR*, fetal growth restriction.

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Pathophysiologic explanation

The pathophysiologic explanation for the findings observed here requires further research. In FGR, many clinical[11,12,53] and experimental[14,42] studies suggested that cardiac remodeling and dysfunction are attributed to the fetal adaptation to undernutrition and hypoxia, in the presence of pressure/volume overload due to increased placental resistance.[54] The observation of cardiovascular changes in normally grown fetuses from mothers with PE challenges these notions. One potential explanation is the existence of relative placental insufficiency, which can occur even in fetuses with normal fetoplacental Doppler,[4,55] or the occurrence of decidual inflammation and associated acute atherosis late in pregnancy.[56] Alternatively, or in combination with the previous, cardiotoxic compounds—such as antiangiogenic factors[57] or reactive oxygen species originated from oxidative stress[1]—circulating in maternal blood of preeclamptic women could directly disturb the structure and function of fetal hearts. Thus, future investigation is needed to clarify the mechanisms underlying fetal cardiac adaptation in PE and/or FGR.

Strengths and limitations

This study has some strengths and limitations that merit a comment. Cases recruited were recorded prospectively, comprehensively characterized, and matched with controls by gestational age at ultrasound. Moreover, we used EFW, confirmed birthweight, and Doppler parameters to determine the presence of FGR in the study groups.[17] In addition, we excluded uncertain cases, such as small for gestational age fetuses, to include only well-defined phenotypes of FGR.[17] In contrast, we acknowledge that matching for gestational age at cord blood sampling and the timing of cord

clamping was not possible due to the greater rate of elective delivery in PE and/or FGR. However, we believe that the difference in gestational age at delivery is unlikely to explain the differences in cord blood BNP and troponin I, since their concentrations have been reported to remain constant throughout pregnancy and are not affected by preterm delivery.[11,38,58] Moreover, through the statistical analysis we adjusted our results for potential confounders, including the gestational age at cord blood sampling. We also acknowledge the relatively limited sample size that hampered further subanalysis in the study populations. This is relevant for assessing the potential influence of fetal sex, gestational age, and preterm labor. Likewise, early- and late-onset forms of PE and FGR have consistently been reported to display different features in several domains, including severity, associated complications, fetoplacental Doppler patterns, and maternal and fetal angiogenic factors. The present study was largely composed of late-onset forms, which represent the most prevalent for both diseases.

Conclusion, Clinical Implications, and Future Research Directions

In conclusion, independently of their growth pattern, fetuses of preeclamptic mothers and growth restricted fetuses without maternal PE seem to show signs of cardiovascular remodeling and dysfunction. These findings are in line with previous postnatal studies and provide further evidence to support a greater cardiovascular risk in the offspring of these conditions.[1,2] Future studies are warranted to confirm these associations in larger cohort studies and clarify the similarities and dissimilarities in early and late-onset forms of PE and FGR, in addition to investigating in effective measures to prevent or reduce long-term consequences on cardiovascular health in the affected subjects.[59,60] ■

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