Fetal cardiovascular remodelling persists at 6 months of life in infants with intrauterine growth restriction

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ABSTRACT

Objectives: Intrauterine growth restriction (IUGR) is associated with increased cardiovascular risk later in life but the link between fetal disease and postnatal risk is poorly documented. We evaluated longitudinally the association between cardiovascular remodelling in fetal life and at 6 months of age in IUGR.

Methods: A cohort of 80 IUGR (estimated fetal and birth weight<10th centile, delivery >34 weeks' gestation) was compared with 80 normally grown control fetuses, and followed at 6 months of corrected age. Cardiovascular evaluation included a comprehensive echocardiographic assessment (fetuses and infants), and blood pressure and aortic intima-media thickness (aIMT) in infants. Parameters were adjusted by gender, gestational age at delivery, prenatal glucocorticoid exposure, cesarean section, neonatal intensive care and body surface area by linear regression analysis.

Results: When compared to controls, IUGR showed more globular cardiac shape both pre- and postnatally (infant left sphericity index: control 1.92 vs. IUGR 1.67, p-<0.001), as well as signs of systolic longitudinal dysfunction (infant mitral lateral annular S' peak velocity: control 7.9 vs. IUGR 6.4 cm/s, p-<0.001; tricuspid annular plane systolic excursion: control 16.0 vs. IUGR 14.2 mm, p-<0.001) and diastolic dysfunction (isovolumetric relaxation time: control 50 vs. IUGR 57 ms, p-<0.001). In addition, IUGR infants had increased mean blood pressure (mean: control 61 vs. IUGR 70 mmHg, p-<0.001) and maximum aIMT (control 0.57 vs. IUGR 0.66 mm, p-<0.001).

Conclusions: Primary cardiovascular changes in IUGR are already present *in utero* and persist at 6 months of age. The data supports prenatal cardiovascular remodelling as a mechanistic pathway of increased risk in IUGR.

Keywords: Cardiovascular risk, Cardiovascular remodelling, Fetal echocardiography, Fetal programming.

MANUSCRIPT

INTRODUCTION

Cardiovascular disease remains the main cause of mortality in developed countries, with research demonstrating a long subclinical phase that may include decades before the presence of clinical symptoms[1, 2]. Large epidemiological studies associating low birth weight with myocardial infarction and cardiovascular related events in adulthood were first reported almost 3 decades ago, introducing the concept of fetal programming of cardiovascular disease[3]. Recently, fetal cardiovascular adaptation to intrauterine growth restriction (IUGR) has been demonstrated to lead to primary cardiac changes, in the form of subclinical cardiovascular dysfunction and remodelling[4-7].

The heart is a key organ in the fetal adaptation to hypoxia and undernutrition due to placental insufficiency in IUGR. Recent studies on fetal cardiac function have demonstrated that IUGR results in subclinical cardiovascular dysfunction *in utero* that can be demonstrated by various echocardiographic parameters, such as pulsed/tissue Doppler imaging or M-mode[4, 5, 8-10]. In addition, placental insufficiency has been associated to aortic restriction, higher resting heart rate, hypertension, increased vascular wall thickness and cardiac remodelling in IUGR newborns, infants, children and young adults[6, 11-14]. However, the transition from fetal to postnatal cardiovascular remodelling has not been evaluated longitudinally. Consequently, the extent to which postnatal changes are a consequence of fetal cardiovascular remodelling or are influenced by other neonatal or early life events remains uncertain.

METHODS

Study population. The study design was a prospective cohort study including cases with IUGR and controls identified in fetal life and followed into infancy. The source population comprised all pregnancies beyond 34 weeks' gestation from April 2010 to September 2012

from Hospital Clínic in Barcelona, Spain. Pregnancies with structural/chromosomal anomalies, twins, evidence of fetal infection or conception by assisted reproduction technologies were excluded from the study. IUGR was defined as an estimated fetal weight (EFW) and confirmed birth weight below the 10th centile according to local reference curves[15]. The reference cohort of fetuses with normal EFW and birth weight were randomly sampled from pregnancies at our institution and paired with IUGR cases by gestational age at fetal scan. The study protocol was approved by the Hospital Clínic Ethics Committee, and written parental consent was obtained for all study participants.

Baseline characteristics and pregnancy outcome. Upon fetal examination maternal characteristics such as age, height, weight, body mass index, smoking during pregnancy and parity were recorded. Gestational age at fetal scan was calculated based on the crown-rump length obtained at first trimester screening[16]. All women underwent ultrasonographic examination using a Siemens Sonoline Antares machine (Siemens Medical Systems, Malvern, PA, USA) which included EFW and standard obstetric Doppler evaluation comprising measurement of uterine arteries' (UtA) mean pulsatility index (PI), umbilical artery PI, middle cerebral artery PI and ductus venosus PI and cerebroplacental ratio (CPR) according to previously published methodology[17-20]. Doppler parameters were normalized into z-scores according to previously published reference values[17-20]. EFW was calculated according to the method of Hadlock et al[21] and EFW centile was calculated using local reference curves[15].

Upon delivery, presence of pregnancy complications, prenatal glucocorticoid exposure, gestational age at birth, mode of delivery, birth weight, birth weight centile, Apgar scores, and days in the neonatal intensive care unit were recorded. Birth weight centile was calculated using local reference curves[15].

Echocardiographic assessment. *Fetal echocardiography* was performed initially to assess structural heart integrity using a Siemens Sonoline Antares machine (Siemens Medical Systems, Malvern, PA, USA). Cardiovascular evaluation was performed using a curved-array 2-6 MHz transducer, with the exception of tissue Doppler measurements that required a phased-array 2-10 MHz transducer. *Infant echocardiography* was performed using Vivid Q (General Electric Healthcare, Horten, Norway). We calculated the estimated date of delivery based on 1st trimester crown-rump length (i.e. 40 weeks gestation) and scheduled follow-up at 6 months from this date (6 months of corrected age). A complete two-dimensional M-mode and Doppler echocardiographic examination, with a 10S-RS phased-array 4.5-11.5 MHz transducer, was performed to verify structural heart integrity, with morphometric and functional data also recorded. A complete description of the prenatal and postnatal evaluation may be found in the Supplementary Methods section; the following measurements were performed at both points in time:

Cardiac morphometry included left atrial area, ventricular sphericity index and interventricular septum thickness.

Systolic function evaluation included heart rate, ejection fraction (EF), stroke volumes (SV), cardiac outputs (CO), mitral/tricuspid annular-plane systolic excursion (MAPSE/TAPSE) and systolic annular peak velocities (S').

Diastolic function was evaluated by left isovolumetric relaxation time (IRT), peak early/late transvalvular filling velocities (E/A) ratio, E deceleration time, A duration time and early diastolic (E') and late diastolic (A') annular peak velocities.

Infant vascular evaluation. *Vascular assessment* included blood pressure measurement and aortic intima-media thickness (aIMT) measurement by ultrasound using Vivid Q (General Electric Healthcare, Horten, Norway) and a 12L-RS linear-array 6.0-13.0 MHz transducer. A controlled environment contributed to the achievement of all infant measurements.

Systolic and diastolic blood pressure was obtained from the brachial artery using a validated ambulatory automated Omron 5 Series device. An appropriate cuff size covering 40% of the arm circumference was used to ensure accurate measurements[22]. Each infant's blood pressure was evaluated twice during quiescence and the average was determined. *Measurement of aIMT* in the upper abdomen involved obtaining longitudinal clips of the far wall of the proximal abdominal aorta in the upper abdomen with a 12L-RS linear-array 6.0-13.0 MHz transducer[23, 24]. aIMT measurements were performed offline according to a standardized protocol based on a trace method with the assistance of a computerized program (GE EchoPAC PC 108.1.x, General Electric Healthcare)[25, 26].

Statistical analysis. Data was analyzed using the IBM SPSS Statistics 21 statistical package. Comparisons between the study and control groups were done with Student's t test, and are presented as mean ± standard deviation (SD) or percentage (%) where appropriate. P-values below 0.05 were considered statistically significant. Fetal parameters were adjusted with linear regression for gender, gestational age at delivery and preeclampsia. Infant parameters were adjusted by gender, gestational age at delivery, prenatal glucocorticoid exposure, cesarean section, neonatal intensive care unit hospitalization and body surface area by linear regression analysis.

RESULTS

In total, 95 late-IUGR fetuses were included for the study in prenatal life; 3 cases were excluded prenatally upon diagnosis of chromosomal and other structural abnormalities. From the remaining 92 patients, 10 were lost on follow-up after delivery and 2 were excluded because of postnatal diagnosis of pulmonary stenosis, leaving us with 80 IUGR cases, paired with 80 controls also recruited in prenatal life.

Baseline and perinatal characteristics of the study groups. Baseline, perinatal and infant anthropometric characteristics of the study groups are shown in Table 1. Maternal characteristics were similar between groups. Gestational age at fetal scan showed no difference, but as expected, prenatal Doppler parameters and pregnancy outcomes were significantly worse in the IUGR group. 21.4% of the IUGR had abnormal UtA and 10.4% abnormal umbilical artery Doppler. 9.1% showed brain vasodilation with abnormal middle cerebral artery PI and 28.6% had abnormal CPR. Anthropometric data for the 6 month-old infants showed IUGR infants with significantly lower height, weight, body mass index and body surface area as compared to controls, with no significant difference in age at assessment or gender.

Fetal and postnatal echocardiography. Results of both fetal and infant echocardiography in the study groups are shown in Table 2 and Figure 1. Cardiac morphometric findings were concordant between the fetal and infant evaluation, showing larger atrial areas in the IUGR group as compared to controls, decreased left sphericity index and thicker septal wall. Global systolic function parameters such as heart rate, EF, SV and CO showed little or no differences between groups at both points in time. Longitudinal motion parameters MAPSE, TAPSE and S' peak velocities were all significantly decreased in the IUGR group with respect to controls both pre- and postnatally. For diastolic function parameters, the IRT was increased in the IUGR group, while tissue Doppler velocities E' and A' were significantly decreased in fetuses and infants alike. E/A ratios showed a significant increase in the IUGR fetus, but this did not persist into infancy. On the contrary, both E deceleration and A duration times showed a non-significant trend towards higher values in the IUGR fetus, that became significant in the IUGR infants when compared to controls.

Prenatal classification of IUGR severity and cardiac function. We performed a comparison of echocardiographic parameters between different stages of severity within the

IUGR group, in accordance to the classification published recently[27]. We subdivided the group into small-for-gestational-age (SGA), defined by EFW between the 3rd and 9th centile together with normal CPR and UtA Doppler; and IUGR defined by EFW <3rd centile or EFW <10th centile together with CPR <5th centile and/or mean UtA PI >95th centile. Fetal echocardiographic results are displayed in Table 3. Both SGA and IUGR presented changes in cardiac shape, with larger and more globular hearts, and signs of cardiac dysfunction, however there were no significant differences in cardiac function between these groups.

Infant vascular assessment. Vascular data (Table 4) showed systolic, diastolic and mean blood pressures significantly higher in the IUGR group. Both mean and maximum aIMT measurements were significantly increased in IUGR infants when compared to controls, and these differences were maintained when adjusted by linear regression to perinatal confounding factors.

DISCUSSION

This study confirms the presence of cardiovascular remodelling and dysfunction in IUGR and demonstrates that a pattern of change is already present in fetal life and remains essentially the same at 6 months of age. Our findings support the notion that primary cardiovascular remodelling starts in fetal life and is a main determinant of postnatal cardiac and vascular changes observed in IUGR children. Likewise, the study supports cardiovascular remodelling can be evidenced by functional echocardiography *in utero* and early infancy.

To our knowledge, this study is the first to perform an extensive functional echocardiography pre- and postnatally in the same IUGR subjects. The data supports previous studies demonstrating cardiac and vascular remodelling in IUGR children, characterized by more globular hearts, maintained EF and CO with subclinical systolic dysfunction and subclinical diastolic dysfunction, along with increased blood pressure and aIMT[6, 7, 23, 24, 28]. Our study

also concurs with previous studies that have reported some of these findings prenatally, such as longitudinal dysfunction in IUGR fetuses[4, 5, 9, 28], or diastolic dysfunction by prolonged IRT[28, 29]. Fetal cardiac output demonstrated a right-sided dominance, with higher values in IUGR fetuses, in line with previous data demonstrating a shift towards higher volume load in the right ventricle, augmented during the last weeks of pregnancy and in presence of IUGR[30]. We also observed changes in CO, from prenatal to postnatal circulation, consistent with previous reports that suggest a change in RV to LV cardiac output ratio[31], demonstrating left ventricle dominance in infancy, as expected. Our data shows that most of the aforementioned parameters present significant differences between groups at both evaluations, supporting the fact that there exists primary fetal cardiovascular programming, which persists into infancy.

In this study we also found cardiac morphometric changes not previously reported in fetuses with IUGR[32, 33]. A more globular shape, dilated atria and thicker myocardial walls have been associated to pressure changes and volume overload to the fetal heart, due to the chronic state of hypoxia and elevated placental resistances[34, 35]. Pressure changes may lead to hypertrophy of the ventricular walls and changes in the local radius of curvature of the heart (creating a more spherical cavity) in order to compensate[36]. Previous studies have also demonstrated that IUGR children, adolescents and adults have higher blood pressures and markers for cardiovascular risk, such as increased carotid and aortic IMT[24] or changes in vessel diameter and heart rate[6, 12, 37]. In our study we confirm a significant difference in blood pressure and aIMT amongst our study groups in infancy, thus demonstrating that these changes can be characterized at an early stage in life. Some studies in animal models have found dilated-like cardiomyopathy in severe early IUGR, with lower ventricular mass and thinner myocardial walls[38, 39], which may be explained that the variability in timing of onset (early or late in gestation) and severity of the placental disease among the studies and different animal models. The majority of our population was comprised of near term (late) IUGR, which may

not be comparable to the described changes in very preterm (early) IUGR, subjected to extreme hypoxia early in gestation. Furthermore, our data agrees with other studies that evidence the presence of subtle cardiac dysfunction in late-onset IUGR, regardless of the presence of Doppler abnormalities that are predictors of poorer perinatal outcome[40]. This reinforces the idea that these parameters do not discriminate fetal cardiovascular programming, and all IUGR infants are, potentially, at risk for cardiovascular disease and may benefit from postnatal surveillance.

Strengths and limitations. Among the strengths of our study is the longitudinal workup from fetal life to infancy, which allowed a prospective evaluation of structural and functional echocardiographic parameters. Results were adjusted by all parameters considered relevant or potential perinatal confounders. Examination at 6 months of age was chosen as a reasonable point in time to avoid effects of neonatal cardiovascular transition to postnatal life, although we recognize that blood pressure measurement at 6 months of age is challenging and presents high variability, in spite of strict protocols[22]. We also acknowledge there might be differences in measurements when using different equipments pre- and postnatally[41]. Likewise, we admit that cardiac output is a very variable parameter with limitations for its acquisition in fetal and postnatal life, although low coefficients of variation and good intra-class correlations have been reported in spite of the lack of concurrent electrical timing of events in the fetus[30, 42]. This data provides strong evidence to support that, regardless of the logical existence of postnatal environmental modulators, primary cardiovascular remodelling occurring *in utero* is a main determinant of cardiovascular dysfunction in children with IUGR. We also acknowledge that although this study provides evidence of cardiac remodelling at 6 months of age, a direct association with cardiovascular outcomes or persistence of these findings in the long-term remains to be seen and further follow-up of this cohort is required.

Overall, our study provides more evidence supporting the notion that fetal primary cardiovascular remodelling exists in IUGR and that this group should be considered at risk for cardiovascular disease later in life. The diagnosis of IUGR is established in about 5-10% of pregnancies thus, the findings of this study would affect thousands of children per year. Hypertension in the child has been associated with substantial long-term health risks[22], whereas aIMT measurement allows detection of increased cardiovascular risk, as an indicator of arterial remodelling in children[23, 24, 43]. Our study supports earlier screening in this population so that they may benefit of early interventions, such as lack of exposure to other risk factors, surveillance of catch-up growth and promotion of breastfeeding, exercise and physical activity[22]. Recent studies have also demonstrated the benefit of a high intake of dietary long-chain ω-3 fatty acids in reducing blood pressure, preventing progression of subclinical atherosclerosis in children born with low birth weight[43] or the benefit of a Mediterranean diet in reduction of cardiovascular risk[44, 45]. These all are interventions that could be applied to this population to reduce the probability of cardiovascular disease later in life.

CONCLUSIONS

Primary cardiovascular changes in IUGR are present in the fetus and persist at 6 months of age. The data supports the ability to demonstrate changes early in life, which could be used to monitor early interventions and diminish cardiovascular risk in this population.

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Conflict of interest: none declared.

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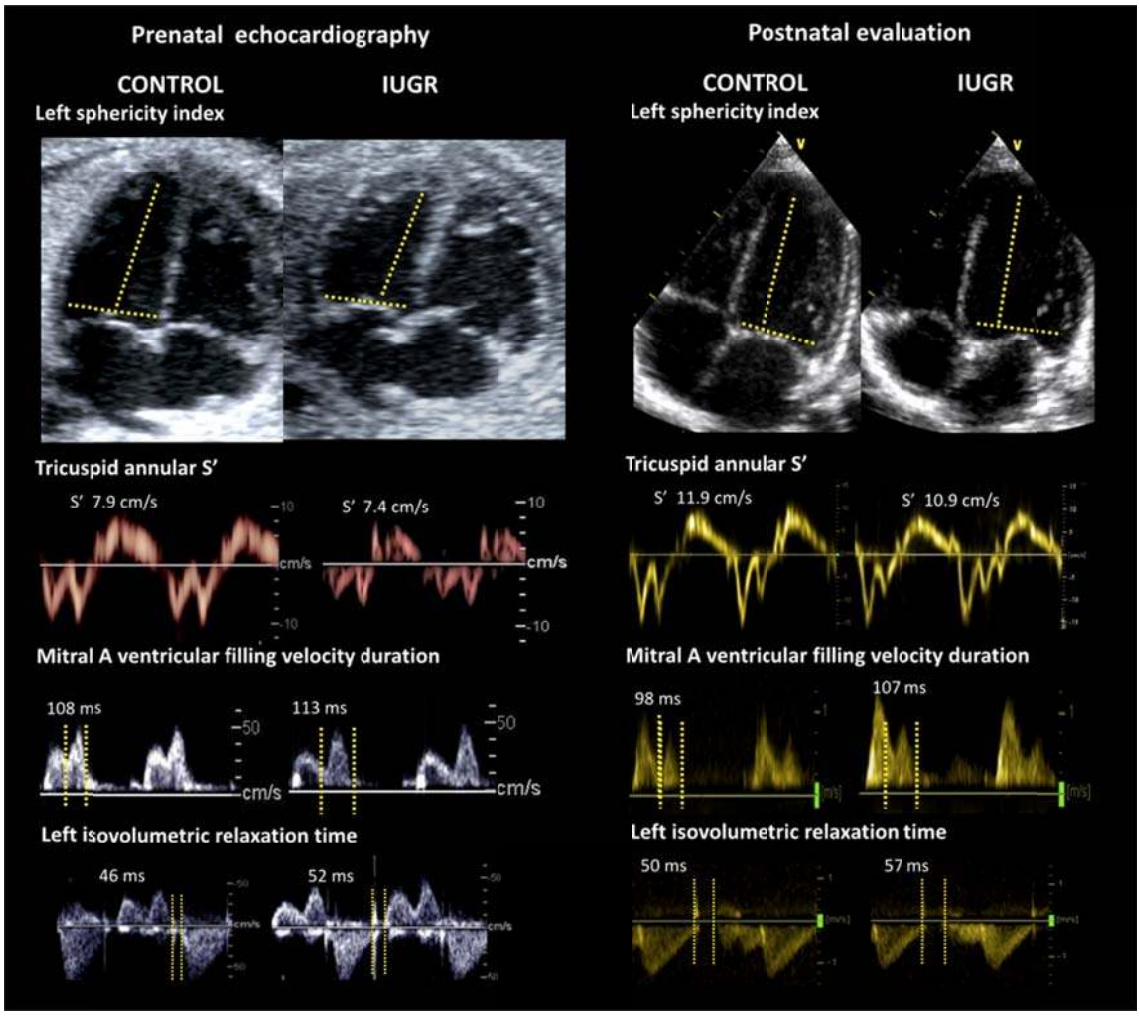
Figure 1. Echocardiographic images of pre- and postnatal echocardiography in a control and IUGR patient.



From top to bottom: a) two-dimensional apical 4-chamber views at end-diastole illustrating left ventricule sphericity index measurement, b) tricuspid systolic (S') annular myocardial peak velocity, c) mitral A transvalvular filling velocity duration and d) left isovolumetric relaxation time.

Table 1. Baseline characteristics of the study groups.

	Controls (n=80)	IUGR (n=80)	p-value
Maternal characteristics			
Age (years)	33 ± 5	33 ± 6	0.289
Height (cm)	164 ± 7	161 ± 6	0.388
Weight (Kg)	60.6 ± 11.3	58.8 ± 13.1	0.353
Body mass index (Kg/m^2)	22.4 ± 3.8	22.6 ± 4.6	0.692
Smoking (%)	21	23	0.685
Nulliparity (%)	57	68	0.073
Fetoplacental ultrasound			
Gestational age at scan (weeks)	37.9 ± 3.44	37.1 ± 2.33	0.078
Estimated fetal weight (grams)	2149 ± 456	1919 ± 812	0.028
Estimated fetal weight centile	52 ± 24	3 ± 3	<0.001
Mean uterine artery PI	0.68 ± 0.18	0.75 ± 0.26	0.022
Umbilical artery PI	1.04 ± 0.20	1.11 ± 0.34	0.004
Middle cerebral artery PI	1.99 ± 0.34	1.51 ± 0.42	<0.001
Cerebroplacental ratio	1.99 ± 0.50	1.52 ± 0.60	<0.001
Ductus venosus PI	0.52 ± 0.16	0.51 ± 0.17	0.089
Pregnancy outcomes			
Prenatal glucocorticoid exposure (%)	0	6	0.020
Preeclampsia (%)	1	4	0.287
Gestational age at delivery (weeks)	40.2 ± 1.1	38.6 ± 1.5	<0.001
Delivery >37 weeks (%)	100	85	0.003
Cesarean section (%)	15	29	0.022
Birth weight (g)	3390 ± 368	2394 ± 400	<0.001
Birth weight centile	50 ± 25	3 ± 4	<0.001
5-minute Apgar score <7 (%)	0	5	0.035
Days in neonatal intensive care unit	0 ± 1	3 ± 8	<0.001
Infant anthropometric data			
Corrected age at evaluation (months)	6.5 ± 0.5	6.4 ± 0.5	0.303
Male gender (%)	44	55	0.086
Height (cm)	67.7 ± 2.7	65.1 ± 2.4	<0.001
Weight (grams)	7713 ± 725	6907 ± 793	<0.001
Body mass index (Kg/m^2)	16.9 ± 1.9	16.3 ± 1.7	0.048
Body surface area (m^2)	0.36 ± 0.02	0.34 ± 0.02	<0.001

Data shown as mean ± SD or percentage. IUGR, intrauterine growth restriction; PI, pulsatility index.

Table 2. Echocardiographic evaluation of the study populations at fetal life and 6 months of age.

	Prenatal echocardiography			Postnatal evaluation		
	Controls (n=80)	**IUGR (n=80)**	**p value***	**Controls (n=80)**	**IUGR (n=80)**	**p value†**
Age at echocardiography	37.9 ± 3.44 weeks' gestation	37.1 ± 2.33 weeks' gestation	0.078	6.5 ± 0.5 months of age	6.4 ± 0.5 months of age	0.303
Cardiac morphometry						
Left atrial area (cm^2)	1.6 ± 0.6	1.9 ± 0.6	0.008	3.6 ± 0.9	3.8 ± 0.7	0.006
Left sphericity index	2.06 ± 0.37	1.87 ± 0.45	0.022	1.92 ± 0.28	1.67 ± 0.22	0.007
Interventricular septum thickness (mm)	2.7 ± 0.6	3.5 ± 0.8	<0.001	3.9 ± 0.7	4.6 ± 0.9	<0.001
Systolic function						
Heart rate (bpm)	140 ± 9	138 ± 12	0.239	134 ± 12	132 ± 12	0.560
Left ejection fraction (%)	70.9 ± 8.7	70.9 ± 9.6	0.692	65.7 ± 8.1	68.9 ± 9.4	0.083
Left stroke volume (mL)	2.7 ± 1.8	3.3 ± 1.5	0.043	18.1 ± 5.1	20.1 ± 6.9	0.062
Right stroke volume (mL)	3.8 ± 1.8	4.7 ± 1.8	<0.001	14.3 ± 3.7	12.9 ± 4.3	0.081
Left cardiac output (L/min)	0.4 ± 0.2	0.5 ± 0.2	0.265	2.4 ± 0.6	2.7 ± 0.8	0.089
Right cardiac output (L/min)	0.5 ± 0.2	0.6 ± 0.2	0.001	1.9 ± 0.5	1.7 ± 0.5	0.021
MAPSE (mm)	5.3 ± 1.2	5.0 ± 1.0	0.913	10.9 ± 1.9	9.8 ± 1.5	0.001
TAPSE (mm)	7.2 ± 1.3	6.8 ± 1.2	0.015	16.0 ± 0.8	14.2 ± 0.8	<0.001
Mitral S' peak velocity (cm/s)	7.2 ± 1.3	6.3 ± 1.1	0.003	7.9 ± 1.7	6.4 ± 1.3	<0.001
Tricuspid S' peak velocity (cm/s)	7.9 ± 1.4	7.4 ± 1.3	0.045	11.9 ± 2.1	10.9 ± 2.2	0.039
Diastolic function						
Left isovolumetric relaxation time (ms)	46 ± 8	52 ± 8	<0.001	50 ± 10	57 ± 10	0.034
Mitral E/A ratio	0.74 ± 0.14	0.80 ± 0.15	0.003	1.37 ± 0.27	1.35 ± 0.28	0.638
Mitral E deceleration time (ms)	87 ± 34	97 ± 28	0.072	89 ± 28	97 ± 25	0.021
Mitral A duration time (ms)	108 ± 21	113 ± 20	0.043	98 ± 21	107 ± 23	0.002
Mitral lateral annular E' peak velocity (cm/s)	7.9 ± 1.7	6.9 ± 1.4	0.005	12.9 ± 2.5	11.1 ± 2.0	0.001
Mitral lateral annular A' peak velocity (cm/s)	9.7 ± 2.2	7.6 ± 1.4	<0.001	8.9 ± 3.0	6.9 ± 1.9	<0.001
Tricuspid E/A ratio	0.75 ± 0.11	0.80 ± 0.18	0.027	1.07 ± 0.32	0.99 ± 0.23	0.029

Tricuspid E deceleration time (ms)	83 ± 29	90 ± 25	0.301	89 ± 31	97 ± 27	0.046
Tricuspid A duration time (ms)	103 ± 26	115 ± 18	0.003	102 ± 25	113 ± 17	0.007
Tricuspid lateral annular E' peak velocity (cm/s)	8.6 ± 1.5	7.9 ± 1.4	0.019	15.9 ± 3.6	14.3 ± 2.9	0.026
Tricuspid lateral annular A' peak velocity (cm/s)	11.5 ± 2.0	10.2 ± 1.5	<0.001	13.2 ± 4.2	11.3 ± 3.7	0.020

Data shown as mean ± SD or percentage. IUGR, intrauterine growth restriction; MAPSE, mitral annular plane systolic excursion; S', systolic annular peak velocity; TAPSE, tricuspid annular plane systolic excursion; E, peak early transvalvular filling velocity; A, peak late transvalvular filling velocity; E', early diastole annular peak velocity; A', late diastole annular peak velocity.

*Fetal p values adjusted with linear regression for gender, gestational age at delivery and preeclampsia. †Infant p values adjusted with linear regression for gender, gestational age at delivery, prenatal glucocorticoid exposure, cesarean section, NICU hospitalization and body surface area.

Table 3. Fetal echocardiographic parameters at different stages of severity.

	SGA (n=29)	IUGR (n=51)	*p value*
Gestational age at scan (weeks)	37.3 ± 2.0	36.7 ± 2.6	0.840
Myocardial performance index	0.55 ± 0.08	0.56 ± 0.10	0.625
Cardiac morphometry			
Left sphericity index	1.55 ± 0.25	1.67 ± 0.35	0.082
Right sphericity index	1.43 ± 0.30	1.42 ± 0.22	0.765
Interventricular septum thickness (mm)	3.4 ± 0.8	3.5 ± 0.9	0.708
Systolic function			
MAPSE (mm)	5.2 ± 1.1	5.2 ± 0.9	0.970
TAPSE (mm)	6.8 ± 1.5	6.8 ± 1.1	0.825
Mitral lateral S' peak velocity (cm/s)	6.0 ± 0.8	6.2 ± 1.2	0.390
Tricuspid S' peak velocity (cm/s)	7.2 ± 1.3	7.5 ± 1.3	0.334
Diastolic function			
Left isovolumetric relaxation time (ms)	52 ± 8	53 ± 8	0.678
Mitral lateral E' peak velocity (cm/s)	6.6 ± 1.2	7.1 ± 1.5	0.079
Mitral lateral A' peak velocity (cm/s)	7.4 ± 1.5	7.7 ± 1.4	0.354
Tricuspid E' peak velocity (cm/s)	7.9 ± 1.4	7.9 ± 1.5	0.978
Tricuspid A' peak velocity (cm/s)	9.9 ± 1.6	10.1 ± 1.7	0.604

Data shown as mean ± SD. SGA, small for gestational age; IUGR, intrauterine growth restriction, in accordance to classification proposed by Figueras F, Gratacós E. *Fetal Diagn Ther* 2014;36:86-98.

Table 4. Vascular evaluation at 6 months of age.

	Controls (n=80)	IUGR (n=80)	p-value
Blood pressure			
Systolic blood pressure (mmHg)	76 ± 10	85 ± 8	<0.001
Diastolic blood pressure (mmHg)	54 ± 8	62 ± 7	<0.001
Mean blood pressure (mmHg)	61 ± 8	70 ± 7	<0.001
aIMT			
Mean aIMT (mm)	0.487 ± 0.066	0.567 ± 0.065	<0.001
Maximum aIMT (mm)	0.566 ± 0.070	0.664 ± 0.068	<0.001

Data shown as mean ± SD or percentage. IUGR, intrauterine growth restriction; aIMT, aortic intima-media thickness. P-values adjusted with linear regression for gender, gestational age at delivery, prenatal glucocorticoid exposure, cesarean section, neonatal intensive care unit hospitalization and body surface area.