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Hemodynamic factors associated with fetal cardiac remodeling in late fetal growth restriction: a prospective study

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Abstract

Background: Altered cardiac geometry affects a proportion of fetuses with growth restriction (FGR). The aim of this study was to explore the hemodynamic factors associated with cardiac remodeling in late FGR.

Methods: This was a prospective study of singleton pregnancies complicated by late-onset FGR undergoing assessment of left (LV) and right (RV) ventricular sphericity-index (SI). The study population was divided in two groups according to the presence of cardiac remodelling, defined as LVSI <5th centile. The following outcomes were explored: gestational age at birth, birthweight, caesarean section (CS) for fetal distress, umbilical artery (UA) pH and neonatal admission to special care unit. The differences between the 2 groups in UA pulsatility index (PI), middle cerebral artery (MCA) PI, uterine artery PI,

cerebroplacental ratio (CPR) and umbilical vein (UV) flow corrected for fetal abdominal circumference (UVBF/AC) were tested.

Results: In total, 212 pregnancies with late FGR were enrolled in the study. An abnormal LV SI was detected in 119 fetuses (56.1%). Late FGR fetuses with cardiac remodeling had a lower birthweight (2390 g vs. 2490; $P=0.04$) and umbilical artery pH (7.21 vs. 7.24; $P=0.04$) and were more likely to have emergency CS (42.8% vs. 26.9%; $P=0.023$) and admission to special care unit (13.4% vs. 4.3%; $P=0.03$) compared to those with normal LVSI. No difference in either UA PI ($p=0.904$), MCA PI ($P=0.575$), CPR ($P=0.607$) and mean uterine artery PI ($P=0.756$) were present between fetuses with or without an abnormal LV SI. Conversely, UVBF/AC z-score was lower (-1.84 vs. -0.99 ; $P\leq 0.001$) in fetuses with cardiac remodeling and correlated with LV ($P\leq 0.01$) and RV SI ($P\leq 0.02$).

Conclusion: Fetal cardiac remodelling occurs in a significant proportion of pregnancies complicated by late FGR and is affected by a high burden of short-term perinatal compromise. The occurrence of LV SI is independent from fetal arterial Dopplers while it is positively associated with umbilical vein blood flow.

Keywords: cardiac remodeling; late fetal growth restriction; sphericity index; umbilical vein flow.

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Introduction

Fetal growth restriction (FGR) is among the main determinants of perinatal mortality and morbidity in singleton pregnancies. The heart plays a pivotal role in the adaptive mechanism occurring during FGR due to placental insufficiency, and cardiovascular dysfunction is a central feature of such condition [1, 2]. In early-onset FGR, defined as that occurring before 32 weeks of gestation [3], severe placental insufficiency leads to redistribution of cardiac output resulting in decreased right to left

cardiac output ratio [4–6]. Conversely, in late FGR, cardiac hemodynamic changes are subtler and mainly characterized by a remodeling of ventricular geometry [1, 7–9]. The sphericity index (SI), calculated as the ratio between the end-diastolic mid-basal-apical and transverse lengths, is among the most reproducible parameters used to quantify cardiac remodeling and has been shown to be reduced in pregnancies complicated by late FGR [10–12].

In early-onset FGR, cardiac hemodynamic changes are thought to be secondary to the high afterload due to the increased impedance to flow occurring in placental circulation [4, 5]. Conversely, the pathophysiology of cardiac remodeling in late FGR has not been completely elucidated yet. Umbilical artery (UA) Doppler is usually normal in these fetuses and the influence of placental resistance in inducing cardiovascular changes seems negligible compared to early-onset disease.

The primary aim of this study was to explore the short-term outcomes of late FGR fetuses presenting with cardiac remodeling, while the secondary aim was to elucidate whether the occurrence of an altered cardiac geometry is affected by fetal Doppler, birth weight and gestational age at diagnosis of FGR.

Materials and methods

Study population and outcomes' measures

This was a prospective study of consecutive singleton pregnancies complicated by late-onset FGR diagnosed between October 2017 and December 2018. The local Institutional Ethical Committee approved the study protocol (IRB 2017/Ob3) and each woman gave her written informed consent to take part in the study.

FGR was defined according to the recently proposed expert consensus statement [3], including: (1) ultrasound estimated fetal weight (EFW) or abdominal circumference (AC) below the 3rd centile using local population charts or, alternatively, EFW or AC <10th centile associated with an UA pulsatility index (PI) >95th centile or a cerebroplacental ratio (CPR) <5th centile [13, 14]. Gestational age was confirmed by crown-rump length in the first trimester. Pregnancies complicated by FGR diagnosed before 32 weeks of gestations, those affected by congenital infections, chromosomal or structural anomalies were excluded from the analysis. EFW was calculated using Hadlock-4 formula [15].

The study population was divided into two groups according to the presence of cardiac remodeling, defined as left ventricle (LV) SI below 1.38 corresponding to the 5th centile of our population of uncomplicated singleton fetuses at 26–40 weeks of gestation.

The following outcomes were explored in fetuses presenting compared to those not presenting abnormal LV SI:

- Gestational age at birth (weeks)
- Birth weight (grams)
- Cesarean section (CS) for fetal distress

- UA pH
- Neonatal admission to special care unit.

Furthermore, we evaluated the differences in the following Doppler parameters between the two study groups:

- UA PI
- Middle cerebral artery (MCA) PI
- CPR
- Uterine artery PI
- Umbilical vein (UV) flow corrected for fetal abdominal circumference (UVBF/AC)

Ultrasound assessment

Doppler recordings were performed using a Samsung W80 (Samsung Medison Co., Ltd, Seoul, South Korea) or Hera W10 ultrasound devices equipped with a 1–8 MHz volumetric probe and color and spectral Doppler functions. Doppler velocity waveforms were obtained from the following vessels: uterine arteries, UA, MCA and UV using previously reported techniques [15, 16]. Briefly, both uterine arteries were recorded at the apparent cross-over with the external iliac artery and the mean PI was calculated as the average between the left and right side. The UA was recorded from a free-floating cord loop and the MCA in an axial section of the fetal head at its origin from the circle of Willis. CPR values were calculated by dividing MCA PI by UA PI. The UV was recorded from the intra-abdominal portion and absolute value of flow corrected for fetal size (UVBF/AC) [17]. All the Doppler parameters explored were measured according to the recommendations provided by the International Society of Ultrasound in Obstetrics and Gynecology [18], with an angle of insonation <30°, in the absence of maternal and fetal movements and using an automated trace of at least three consecutive waveforms or 10 s in the case of UV flow.

LV and right ventricle (RV) SI were calculated by dividing the base-to-apex length by the transverse diameter for each ventricle measured on two-dimensional (2D) images at an apical four-chamber view of the fetal heart at end-diastole. Images were optimized to enhance the borders of ventricular walls and cine clips were stored (Figure 1). Cardiac remodeling was defined as LV SI below 1.38 corresponding to the 5th centile of our population of uncomplicated singleton fetuses at 26–40 weeks of gestation. All Doppler parameters explored were converted into z-scores [14, 15] in order to correct the influence of gestational age on the absolute measurements. Conversely, SI values remained constant through gestation, so normalization was not necessary.

Statistical analysis

Categorical variables were presented as number (n) and proportions (%), while continuous variables as median and interquartile range (IQR). Differences among pregnancies with normal and abnormal outcomes were analyzed using the chi-square test for categorical variables, while differences in continuous variables were analyzed using the Mann-Whitney *U* test. The relationship between variables was tested by the Pearson correlation coefficient. A two-sided P-value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (version 23 IBM Corp., Armonk, NY, USA).

Figure 1: Echocardiographic images of two late FGR fetuses with normal (left panel) and abnormal (right panel) sphericity index (SI) values. For the computation of SI, the end-diastolic mid-basal-apical length (green arrows) is divided by basal transverse length (red arrows). Right ventricle SI was 1.81 and 1.18 and left ventricle SI 1.93 and 1.29, respectively.

Results

Two-hundred and sixty-one pregnancies complicated by late FGR were enrolled in the study and 49 were excluded for incomplete data or missing follow-up leaving 212 pregnancies available for the analysis. An abnormal LV SI was detected in 119 fetuses (56.1%) complicated by late FGR. General characteristics of the study population are reported in Table 1. There was no difference in either maternal age ($P=0.680$), body mass index (BMI)

($P=0.163$), gestational age at diagnosis ($P=0.107$) or delivery ($P=0.08$) between fetuses with a normal compared to those with an abnormal LV SI. Likewise, there was no difference in the incidence of nulliparity ($P=0.874$), hypertensive diseases of pregnancy ($P=0.921$) and assisted conception ($P=0.647$) between the two groups. Late FGR fetuses with an abnormal LV SI had a lower birth weight (2390 g, IQR: 2280–2490 vs. 2490, IQR: 2410–2560; $P=0.04$) and were more likely to have an emergency CS for fetal distress (42.8% vs. 26.9%; $P=0.023$), a lower UA

Table 1: Characteristics of 212 pregnancies with late FGR stratified according to the left ventricle sphericity index.

	Normal (n=93)	Abnormal (n=119)	P-value
Maternal age, years	31.5 (27–34)	31.8 (28–36)	0.680
Body mass index (BMI) at diagnosis, kg/m ²	27.9 (23–31)	28.8 (24–33)	0.163
Nulliparous	70 (75.2%)	88 (73.9%)	0.874
Smoking	7 (7.5%)	10 (8.4%)	0.815
Hypertensive diseases	9 (9.6%)	12 (10.1%)	0.921
Assisted conception	4 (4.3%)	8 (6.7%)	0.647
Gestational age at diagnosis, weeks	36.6 (35.9–37.3)	36.3 (35.8–37.2)	0.107
Gestational age at delivery, weeks	38.2 (37.3–39.2)	38.0 (37.1–38.6)	0.082
Birth weight, g	2490 (2410–2560)	2390 (2280–2490)	0.04
Cesarean section fetal distress	25 (26.9%)	51 (42.8%)	0.023
Umbilical artery pH	7.24 (7.16–7.32)	7.21 (7.12–7.29)	0.04
Neonatal admission to special care unit	4 (4.3%)	16 (13.4%)	0.03

Data are expressed as median (IQR) or n (%). FGR, fetal growth restriction. Bold values indicate significant ($P < 0.05$).

Table 2: Ultrasonographic and Doppler parameters stratified according to left ventricle sphericity index (SI).

	Normal (n=93)	Abnormal (n=119)	P-value
EFW, g	2267 (2060–2368)	2205 (2053–2310)	0.824
EFW <3 rd centile	54 (58.1%)	71 (59.6%)	0.888
Right ventricle SI	1.37 (1.30 to 1.44)	1.32 (1.03 to 1.32)	0.0001
Mean uterine artery PI delta value	1.85 (1.78 to 1.91)	1.89 (1.82 to 1.97)	0.756
UA PI delta value	0.23 (–0.10 to 0.68)	0.24 (–0.09 to 0.78)	0.904
MCA PI delta value	–1.28 (–0.56 to 1.89)	–1.35 (–0.45 to –1.98)	0.575
CPR delta value	–1.38 (–0.47 to –2.04)	–1.46 (–0.55 to –2.11)	0.607
UVBF/AC delta value	–0.99 (–0.66 to –1.16)	–1.84 (–1.40 to –2.25)	0.0001

Data are expressed as median (IQR) and n (%). EFW, estimated fetal weight; UA, umbilical artery; MCA, middle cerebral artery; CPR, cerebroplacental ratio; UVBF/AC, umbilical vein blood flow/abdominal circumference. Bold values indicate significant ($P < 0.05$).

pH (7.21, IQR: 7.12–7.29 vs. 7.24, IQR 7.16–7.32; $P = 0.04$) and admission to neonatal intensive care unit (NICU) (13.4% vs. 4.3%; $P = 0.03$) (Table 1) compared to those with a normal SI (Table 1).

When exploring the different Doppler parameters, there was no difference in either UA PI ($P = 0.904$), MCA PI ($P = 0.575$), CPR ($P = 0.607$) and mean uterine artery PI ($P = 0.756$) between fetuses with compared to those without an abnormal LV SI (Table 2). Conversely, UVBF/AC z-score was lower in the presence of an abnormal LV SI (–1.84 vs. –0.99; $P \leq 0.001$) in fetuses with an abnormal LV SI (Figure 2). Furthermore, UVBF/AC z-score significantly correlated with LV (Pearson correlation coefficient 0.407; $P \leq 0.01$) and RV SI (Pearson correlation coefficient 0.374; $P \leq 0.02$).

Figure 2: Umbilical vein blood flow/abdominal circumference (UVBF/AC) z-values in late FGR fetuses with normal and abnormal SI values.

The median was –0.99 in the former group and –1.84 in the latter group.

Discussion

Main findings

The findings from this study showed that fetal cardiac remodeling occurs in a significant proportion of pregnancies complicated by late-onset FGR and was affected by a high burden of short-term perinatal compromise. The occurrence of LV SI was independent of fetal arterial Dopplers and gestational age at occurrence of FGR. Finally, there was a positive correlation between SI and UVBF/AC in pregnancies complicated by late FGR.

Comparison with other studies

The results of this study are in line with those of Crispi et al. [16], who showed that both LV and RV SI are already decreased in small-for-gestational-age fetuses and even further in those presenting with FGR. The same group reported three different phenotypes of cardiac remodeling occurring in fetuses with late growth restriction namely elongated, hypertrophic and globular [19], the last being associated with a reduced SI in more than half of the cases. More recently, DeVore et al. [10] reported that in FGR the reduction of SI was present only in the RV while the LV SI was normal. The low number of cases included and the different criteria for definition of FGR may partially explain the discrepancies between our findings and this study. The results of the present study are also in line with those of Patey et al. [9] who reported poorest perinatal outcomes in late FGR fetuses presenting with severe myocardial dysfunction. Finally, a positive correlation between venous return and SI was also reported by Channing et al. [20] who found that increased pulmonary

venous return induced by maternal hyperoxygenation alters left ventricular geometry by increasing the SI. This observation validates our finding on the direct relationship between UVBF and cardiac remodeling.

Implications for clinical practice

There is a growing body of evidence that cardiovascular changes occurring in fetal life persist into childhood and adolescence and may be responsible for an increased cardiovascular morbidity in adulthood [21, 22]. Prenatal detection of fetuses at higher risk of cardiac remodeling *in utero* is fundamental as it may allow to undertake different strategies aimed at improving the long-term cardiovascular outcome in these children. Indeed, there is evidence that breastfeeding and consumption of a diet with a high polyunsaturated:saturated fat ratio in early childhood improve cardio remodeling in individuals born with FGR [23, 24]. The findings from this study confirm the previously published research on the role of fetal echocardiography in identifying a subset of small fetuses at higher risk of cardiovascular impairment. Despite this, it has still to be ascertained whether echocardiographic assessment of cardiac morphology may tailor the management and improve the outcome of pregnancies complicated by late FGR. Fetal echocardiography is used mainly in the research setting and requires a peculiar expertise which may be not available outside fetal medicine centers. Furthermore, the inter-observer variability of most of these signs has not been consistently explored in large studies, thus questioning on the clinical applicability of such parameters once exported on a large population. Finally, the large majority of these studies merely report their results as mean differences, thus making it difficult to extrapolate any meaningful cut-off for a given echocardiographic parameter to use in clinical practice.

Further large studies are needed in order to develop multi-parametric predictive models integrating echocardiographic, Doppler and pregnancy characteristics aimed at identifying late growth-restricted fetuses at higher risk of cardiovascular compromise and to elucidate whether systematic echocardiographic assessment of pregnancies complicated by late FGR may improve the long-term outcome in these children. The study of UVBF in late FGR fetuses that is technically more easy and reproducible [17, 25] than the study of cardiac geometry may allow an easier clinical identification of late FGR at risk of cardiac remodeling.

Strengths and limitations

The present study is one of the largest series exploring the association between late FGR and cardiac remodeling. Prospective design, large sample size and inclusion of cases affected exclusively by late-onset FGR represent the main strengths of this study, while its main limitation relies on its cross-sectional design which does not take into account any serial change in Doppler indices and SI through gestation.

Conclusion

A reduced UV blood flow is associated with cardiac remodeling in late FGR independent of fetal size and fetal peripheral arterial Doppler hemodynamics. Identification of such fetuses may improve the identification of FGR fetuses with a higher risk of adverse perinatal outcome and impaired cardiovascular health.

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