MANUSCRIPT TITLE PAGE:

TITLE: CARDIAC MORPHOLOGY IN NEONATES WITH FETAL GROWTH RESTRICTION

List of authors:

Lisa Bjarkø [a, b]

Drude Fugelseth [a, b]

Nina Harsem [c]

Torvid Kiserud [d, e]

Guttorm Haugen [a, f]

Eirik Nestaas [a, g]

Author Institutional Affiliations:

[a] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway,

[b] Department of Neonatal Intensive Care, Division of Pediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

[c] Department of Obstetrics, Division of Obstetrics and Gynecology, Oslo University Hospital, Oslo, Norway

[d] Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway

[e] Department of Clinical Science, University of Bergen, Bergen, Norway

[f] Department of Fetal Medicine, Division of Obstetrics and Gynecology, Oslo University Hospital, Oslo, Norway

[g] Clinic of Pediatrics and Adolescence, Akershus University Hospital, Loerenskog, Norway

Corresponding author:

Eirik Nestaas [a, g], eirik.nestaas@medisin.uio.no

Declaration of competing interest: None declared

Category of study: Clinical

ABSTRACT

Objective: Assess effects of fetal growth restriction (FGR) on cardiac modelling in premature and term neonates.

Study design: Prospective echocardiographic study of a cohort of FGR neonates (n=21) and controls (n=41) with normal prenatal growth and circulation.

Results: Unadjusted for gestational age, birth weight, sex and twin/singleton, Late-FGR neonates had smaller hearts than controls, with globular left ventricles and symmetrical right ventricles. Adjusted estimates showed smaller left ventricles and similarly sized right ventricles, with symmetrical left and right ventricles. Early-FGR (compared with Late-FGR) had smaller hearts and globular left ventricles in unadjusted estimates, but after adjustment, sizes and shapes were similar.

Conclusion: FGR had significant impact on cardiac modelling, seen in both statistical models unadjusted and adjusted for gestational age, birth weight, sex and twin/singleton. The adjustments, however, refined the results and revealed more specific effects of FGR, thus underscoring the importance of statistical adjustments in such studies.

Key words: perinatal circulation, cardiac modelling, cardiac remodeling, neonate, heart, echocardiography

INTRODUCTION

Fetal growth restriction (FGR) is one of the major challenges in perinatal care commonly leading to premature birth, neonatal morbidity and mortality. Evidence also suggests that neonates with reduced intrauterine growth carry higher risks for metabolic and cardiovascular diseases in later life than their peers [1].

An expert consensus group has defined FGR using solitary and contributory measurements including circulatory variables and has set the transition between early and late FGR at 32 weeks of gestation [2].

FGR due to placental compromise affects up to ten percent of all pregnancies, depending on population, geographical location and the standards of fetal growth used in those studies [3]. In these cases, the fraction of combined fetal cardiac output that circulates the placenta is reduced and conditions for impaired growth of the fetus [4, 5]. According to the severity of the restricted umbilical circulation, the fetus responds by redistributing its cardiac output to prioritize oxygen and nutrient supply to the heart, brain, and adrenals, the so-called centralization of the circulation. This could lead to a substantial downregulation of supply to other organs, which takes the brunt of the fetal growth impairment.

It is plausible that such developmental challenges can permanently alter the body's structure, function and metabolism, and increase the risk of disease in later life [6], collectively referred to as Developmental Origins of Health and Disease [7-10]. Structural and functional cardiovascular changes in FGR fetuses have been traced into infancy, childhood, and adolescence [11-16]. Such findings could explain why low birth weight (BW) is a risk factor of cardiovascular diseases in adulthood. However, there is a knowledge gap as to what extent gestational age (GA), BW and sex influence such modifications of cardiac morphology in FGR.

Based on the hypothesis that FGR affects early postnatal cardiac morphology, this study aimed at assessing the association between FGR and cardiac morphology in premature and term neonates the first three days of life, and how GA, BW, sex and twin/singleton modify this association.

METHODS

Study population and inclusion criteria

This was a prospective, observational cohort study at Oslo University Hospital, Norway between April 2017 and October 2018. We included pregnant women and their FGR neonates (GA 30-42 weeks) according to locally modified contemporary published guidelines [2] (Figure 1), and a corresponding control group within the same range of GA but with fetal ultrasound documented normal intrauterine growth and circulation. We included singletons and dichorionic diamniotic twin pregnancies. Exclusion criteria were pregnancies with chromosomal aberrations, severe congenital anomalies, or evidence of prenatal infections.

Early-FGR (GA < 32 weeks) was defined as 1) abdominal circumference less than the third centile [17], 2) absent or reversed end diastolic flow in the umbilical artery, or 3) abdominal circumference less than the tenth centile and pulsatility index in the umbilical or uterine arteries above the 95th centile [18].

We defined Late-FGR (GA > 32 weeks) when two of the three following criteria were present; abdominal circumference less than the tenth centile, impaired growth rate by abdominal circumference or estimated fetal weight crossing two of the following centiles on National Fetal Growth Reference: 2.5, 5, 10, 25, 50, 75, 90, 95 and 97.5 [17, 19] with more than two weeks interval, or cerebro-placental ratio less than the fifth centile [20]. Cerebro-placental ratio was defined as the pulsatility index of the middle cerebral artery divided by the pulsatility index of the umbilical artery. Additionally, fetuses with GA > 32 weeks and abdominal circumference less than the third centile were defined as FGR.

Ethics

The Hospital's Data Protection Officer and The Regional Ethics Committee of Research, South East, Norway approved the study (2016/923D). The parents gave written informed consent. The study was conducted in accordance with the Declaration of Helsinki [21].

Maternal and fetal baseline characteristics

The baseline maternal characteristics recorded were: age, height, pre-pregnancy weight and body mass index (BMI), nicotine-use, alcohol consumption, medication and pre-existing and medical conditions during pregnancy. We obtained maternal blood pressure measurements early and late in pregnancy, and noted any documented medication for high blood pressure during pregnancy. We also documented mode of delivery, and noted preeclampsia when present [22]. Higher maternal education was defined as more than fifteen years, or attending a college or university.

Estimated fetal size was based on intrauterine ultrasound measurements of head circumference, abdominal circumference and femur length, and the corresponding percentile derived from growth charts by Johnsen et al. [17, 19] through the CSAM Partus eHealth maternity information system. Fetal circulation was assessed by determining the pulsatility index in the umbilical artery [18], the middle cerebral artery [20], ductus venosus [23] and the uterine artery [24] on both sides.

We determined GA using head circumference or femur length according to Johnsen et al. [25, 26] at the routine ultrasound examination offered nationally at gestational week 18. In the FGR group, the recordings from the last ultrasound examination prior to birth were used as basis for inclusion. The Non-FGR group had one ultrasound examination as part of the prenatal visits to the outpatient clinic as close to term as feasible.

Neonatal baseline characteristics

For baseline neonatal characteristics, we recorded GA, BW, head circumference, sex, twin/singleton and Apgar score at five minutes.

Postnatal echocardiographic assessment and off-line analyses

One neonatologist (LB) performed all the postnatal ultrasound examinations during daytime on day one, two and three as part of a more comprehensive study of the cardiovascular transitional circulation. Vivid S6 (GE Healthcare, Horten, Norway) ultrasound machine equipped with a S6-D transducer frequency 2.4-8.0 MHz was used for all examinations. A complete sequential two-dimensional, M-mode and Doppler echocardiography was performed (from subcostal, apical, parasternal long- and short axis and suprasternal views) to exclude congenital cardiac malformations. Five to ten cardiac cycles from each view were stored for later off-line analyses. Neonates with s.mall insignificant muscular ventricular septum defects were not excluded from analyses. We preferred to examine the neonates when they were relaxed or asleep, usually recently been fed. The neonates were placed in a left semi-lateral supine position during the echocardiographic examination.

The same physician who performed the neonatal scans (LB), did the off-line analyses using EchoPac PC analysis software system version 202 (GE, Vingmed, Horten, Norway). The mean value of the three best images or cycles were analyzed for each measurement and the average value was used in the statistical analysis.

We assessed two-dimensional images of the left atrium, left ventricle, right ventricle and right atrium from the apical four-chamber view. The pulmonary valve was assessed from the parasternal view. We used two-dimensional and M-mode images to assess the diastolic diameters of the interventricular septum, the left ventricular cavity and the left ventricular posterior wall. The aortic root, aortic valve and the left atrium were also assessed using the parasternal axis recordings in M-mode [27]. We assessed the left atrium and aortic diameters to calculate the left atrium/aortic root ratio [27, 28].

Using the apical four chamber view, we measured the end-diastolic diameters of the atrioventricular valve orifices, the mid-cavity right ventricular linear diameter [27], and the area of the right ventricle. The maximal area of the left and right atrium was measured at end-systole. Left and right ventricular septum length were considered as the distance from the apical endocardial border to the hinge point of the septal hinge of the mitral valve [29] and tricuspid valve at end-diastole. To compare the morphology between hearts of various sizes, we used the length of the left ventricle septum at end-diastolic period as the surrogate measure for heart size [29]. We normalized other measurements of heart size by dividing by the length of the left ventricle at end-diastole, and denoted normalized heart size as the indices of heart size.

Statistical analysis

FGR neonates were divided into Early-FGR and Late-FGR according to the inclusion criteria. During the study period, we did not have any Non-FGR-neonates below 34 weeks of gestation requiring an adjusted comparison with the Early-FGR. The analyses were therefore restricted to compare only the Late-FGR group with the Non-FGR group. In a separate analysis, the Early- and Late-FGR groups were compared.

Ten percent relative difference in echocardiographic variables was considered as clinically relevant. Based on previous studies [29, 30], power calculations showed that a sample size of 25-30 would provide 80 percent statistical power for detecting such differences with two-sided five percent p-values.

We used t-test, chi square test and independent-Samples Mann-Whitney U for analyses of independent variables, and two separate mixed-effects linear regression models for analyses of repeated continuous variables. The first mixed-effect model assessed the unadjusted effect of FGR. The second model assessed the adjusted effects of FGR controlling for GA, BW, sex and twin/singleton as covariates. Both models included intercepts and FGR as an independent categorical fixed effect. The second model additionally included sex and twin/singleton as independent categorical fixed effects, and GA and BW as independent continuous fixed effects. Hence, our model allowed for detailed adjustment of the confounding effects of GA and BW. Mixed model statistical analyses take into account the consecutive examinations for each patient. As the GA and BW correlated at a higher level (0.91) than our pre-selected threshold for collinearity (0.75), we were unable to assess the separate effects of BW and GA on the measurements. We present variable estimates as “estimated marginal means”. For estimated marginal means in the second model, the software used the average values for each of the continuous covariates. The software used GA 38 weeks and BW 2.8 kg for the comparisons of estimated marginal means between Late-FGR and Non-FGR, and correspondingly 35 weeks and 1.9 kg in the comparisons between Early-FGR and Late-FGR. Estimated marginal means were hence the estimates of the averaged value for the repeated measurement. We used two-sided tests, 95 percent confidence intervals and five percent p-values for all tests, and IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, N.Y., USA) for all analyses.

RESULTS

Clinical and baseline characteristics data

Sixty-two women gave birth to 69 neonates; 28 FGR (7 Early-FGR and 21 Late-FGR) and 41 Non-FGR. Seventeen of the FGR (30%) and 39 Non-FGR (70%) had gestational age ≥ 34 weeks.

The median number of days from the last prenatal ultrasound examination to delivery was 6 days (interquartile range 2-21); 2 days (1-4) for the FGR group (Early-FGR median 3 days (0-4), Late-FGR median 2 days (1-4)), and 18 days (7-29) for the Non-FGR group.

Figure 1 shows the distribution within the different FGR inclusion criteria where Late-FGR was dominating. Nearly 50% of the study group had intrauterine signs of circulatory compromise, five in the Early- (71%) and eight in the Late-FGR (38%) group. Signs of circulatory compromise were based on elevated pulsatility index in the umbilical or uterine artery, or absent or reversed diastolic flow (ARDF) in Early-FGR, and low cerebroplacental ratio in the Late-FGR group.

We included seven pairs of dichorionic, diamniotic twins. In two pairs, both twins were FGR. Three pairs consisted of one FGR and one Non-FGR. In the remaining two pairs, both were Non-FGR. All twins were premature except for one pair of Non-FGR twins. For analyses of baseline characteristics, we assigned a mother of twins to the FGR group if at least one twin was FGR. Thus, we classified 26 mothers in the FGR group and 36 in the Non-FGR group.

Concerning baseline characteristics (Table 1), the fraction of mothers with higher education was substantial in both groups. Eight mothers were diagnosed with preeclampsia according to Norwegian guidelines based on the ICD-10 criteria [22]. All of them were in the FGR group. None of the mothers had anemia or clinically relevant bacterial or viral infections. Fifty-seven of 62 mothers never smoked; of the 5 who were smokers, none smoked daily during pregnancy.

The mean interval from birth to the first echocardiography was 25 hours (SD 8). The mean interval from birth to the second echocardiography was 47 hours (SD 7), and to the third 71 hours (SD 8).

The FGR neonates had significantly lower GA, BW, and head circumference than the Non-FGR neonates (Table 1). Neonatal sex and the distribution of Apgar score at 5 minutes were not different between the groups. Four neonates (14%) in the term Non-FGR group (n = 29) and seven (58%) in the premature Non-FGR group (n = 12) were delivered by caesarean section. Of the 13 delivered by caesarean section in the Late-FGR group, nine (69%) were premature. The frequency of caesarean section was higher in both the FGR groups than in the Non-FGR group. Only neonates who were either premature or suffered from FGR needed admission to the neonatal intensive care unit. All neonates admitted to the neonatal intensive care unit survived to discharge and none of them were critically ill.

Cardiac morphology

We conducted 189 postnatal ultrasound examinations on days one, two and three. Eighteen examinations were not performed due to logistical reasons.

All reported echocardiographic measurements were performed at end-diastole except the maximal area of the left and right atrium that were measured at end-systole.

Neonates exposed to Late-FGR had generally smaller hearts as all unadjusted left and right sided measurements including the interventricular septum diameter were lower than in their Non-FGR peers (Table 2).

After adjustment, the left ventricular septum length, diameter of the left atrium, aortic valve and the left ventricle internal diameter remained smaller in Late-FGR (Table 2). On the right side of the heart, the pulmonary valve diameter and the right ventricular diameter remained smaller (Figure 2).

The left columns of Table 3 show the same measurements normalized for heart size by dividing the measurement by the left ventricular septum length, unadjusted and adjusted for GA, BW, sex and twin/singleton. The unadjusted indices of the left side of the heart were similar between groups except for larger mitral valve in the Late-FGR group compared with Non-FGR. For the unadjusted right sided indices, the groups were similar except for the right atrial and ventricular area, which was smaller in Late-FGR than in Non-FGR.

The adjusted left and right sided indices for Late-FGR were similar to those in Non-FGR.

Ratios between the corresponding right and left sided measurements were similar for the unadjusted indices except for a lower right ventricular mid-wall to left ventricular internal diameter ratio in the late FGR group compared with Non-FGR. The adjusted indices were also similar, except for a lower ratio of tricuspid to mitral valve diameters in the adjusted Late-FGR group compared with Non-FGR.

When comparing the Early-FGR with the Late-FGR group (columns to the right in Table 2), all the unadjusted measurements were smaller in the Early-FGR group except for the left atrial to aortic diameter ratio. When adjusting for GA, BW and sex, twin/singleton, there were no differences between the groups.

When normalizing for heart size, the left and right atrial areas and right ventricular area indices were smaller for unadjusted measurements in Early-FGR compared with Late-FGR, whereas the intraventricular septum and left ventricular diameter indices were larger in Early-FGR. After adjustment, the left atrial area index remained smaller and the intraventricular septum remained thicker. There were no differences when comparing corresponding left and right sided measurement for unadjusted or adjusted measurements.

Neonatal sex and being born twins or singleton had no effect on any of the measurements or indices (Table 2 and 3).

The effect of adjusting for relevant factors was notable as illustrated in Figure 2. Nine significant differences in unadjusted measurements became non-significant in the models that included adjustments (Table 2). Similarly, among the 14 ratios of intracardiac proportions (Table 3), in the adjusted models four significant findings became not significant, and one not significant ratio became significant.

DISCUSSION

Our main findings were that Late-FGR neonates had smaller hearts with a globular shape compared with Non-FGR neonates during the first three postnatal days. By adjusting for BW, GA, sex and for being twins or singletons, we identified the true effects of Late-FGR as shown in Figure 2, i.e., the left ventricle was small and symmetrical while the right ventricle was symmetrical with a similar length to that of normally grown neonates.

Similarly, we found generally smaller hearts with a globular left ventricle, thicker intraventricular septum and smaller atrial areas for the Early-FGR group compared with the Late-FGR group. We also found significantly smaller left atrial area and thicker intraventricular septum, which remained significantly different after adjusting for BW, GA, sex and twins or singleton.

Several of the differences persisted when adjusting for GA, BW, sex and twins/singleton when comparing Late-FGR with Non-FGR. Hence, our study showed that Late-FGR *per se* was an important determinant for heart morphology. It also showed that adjusting for GA and BW modified the impact of FGR. There was strong collinearity between GA and BW (correlation coefficient > 0.9), preventing us from distinguishing the separate effects of GA and BW.

We found shorter length of the left ventricle both in Early-FGR compared to Non-FGR and Early-FGR compared with Late-FGR, which is in accordance with other studies [14, 31]. Several studies support our findings that both term and premature FGR neonates had smaller diameter of the left ventricle [14, 31-33]. Most studies have examined mainly the left ventricle, while Patey et al. [14] also studied the right ventricle in their term FGR group. Their findings were similar to our findings, demonstrating a significantly lower right ventricle diameter in Late-FGR.

Several studies have demonstrated a globular cardiac morphology following FGR [13, 31, 34, 35], which confirms our findings that prenatal alterations in ventricular shape are also found postnatally following FGR. While none of the other studies adjusted for GA, BW, sex and twins/singleton, we found that adjusted ventricle dimensions were symmetrical and exhibited a symmetrical shape. However, the lower adjusted tricuspid-mitral diameter ratio, the lower diameter but similar length of the right ventricle, and the strong trend of a smaller right ventricle at mid-wall ($p = 0.053$), indicate a tendency towards a slim right ventricle in the Late-FGR neonates. This is plausible as the prenatal function during FGR loads the right ventricle with a disproportionately larger output than the left [4]. After birth, the right ventricular output was reduced to match that of the left side; the transverse diameter is correspondingly reduced whereas the length of the right ventricle is maintained. Crispi et al. [6] and Rodriguez-Lopez et al. [36] have suggested elongated, globular and hypertrophic fetal cardiac phenotypes depending on the level of severity of FGR as a consequence of adaptive cardiovascular modelling. Hearts develop a spherical shape to maintain stroke volume in presence of pressure overload. In the elongated phenotype, one ventricle develops a spherical shape and the other consequently becomes elongated, and in the globular phenotype both ventricles develop a spherical shape. Our findings suggest an elongated phenotype and that our Late-FGR group was at a mild-to-moderate stage of morphological compensation. The increased tricuspid valve/mitral valve ratio when adjusting for GA, BW, sex and twin/singleton was also shown in the study by Patey et al. [14]. However, unlike their study, we found a lower ratio of unadjusted right-to-left ventricle diameters in the Late-FGR group compared with the Non-FGR group. Our groups consisted of premature and term neonates whereas in the study by Patey el al, all were born at term.

As we found lower diameter of the interventricular septum in the Late-FGR group in unadjusted estimates and similar diameter in adjusted estimates, difference in interventricular septum diameter was probably due to differences in these covariates between groups. Cohen et al. [35] found no difference in left ventricle wall thickness on day one when adjusting for body surface area, and Ciccone et al. [37] found the same when normalized for body surface area in both term and premature Non-FGR neonates; the differences in the interventricular septum diameter and left ventricular posterior wall disappeared. Some studies report thinner ventricle septum in FGR [32, 33], whereas others report opposite findings [13, 31]. Differences in study design and inclusion criteria might explain these differences. Crispi et al. [6] regarded hypertrophy as a late sign of cardiovascular modeling in symmetric FGR, following hypoxic incidents occurring early in the pregnancy. As the majority of our FGR neonates were late, asymmetric FGR, interventricular septum and left ventricle posterior wall hypertrophy may not yet have evolved. Another significant factor may be the variation in the definitions of FGR used in other studies. We based our definition of FGR on contemporary criteria by the use of fetal assessments [2]. As others studies have used definitions based solely on estimated fetal centiles [31] or confirmed BW [13], the neonates we studied may not be directly comparable with those of other such studies. We also speculate that different clinical practices concerning timing of delivery might have affected the postnatal cardiac morphology following FGR [38].

The Early-FGR group had smaller hearts than the Late-FGR group and a globular shape of the left ventricle in the unadjusted estimates, whereas adjusted estimates revealed few differences in size and shape between the groups.

FGR is associated with a risk of a differently modelled cardiovascular system in the years following birth [11, 13, 31, 34, 35]. However, less is known to what extent these changes are linked to disease development later in life, something that awaits results of correspondingly designed long-term observational studies.

A strength of our study was the prenatal inclusion criteria. We defined FGR based on contemporary published guidelines [2], and the control group had verified normal prenatal growth and circulation. Several definitions of FGR and small for GA exists [39, 40]. Sometimes the terms are used interchangeably [41], probably contributing to the heterogeneity of findings in this field. Due to the criteria of fetal growth less than a certain centile, both constitutionally small neonates and neonates with true FGR may be included. Only three of our fetuses were included based on the criteria of AC diameter less than the third centile alone. Other fetuses we studied had reduced growth and/or centralized circulation. We recruited pregnant women and their fetuses unselected from our routine outpatient clinic, and our inclusion criteria were based on contemporary published guidelines [2], but were modified based on local standards. The same neonatologist did all the postnatal ultrasound examinations and all off-line analyses eliminating inter-rater variability.

We included the pregnant women in the term Non-FGR group from a unit of only low risk deliveries. They represented a healthy group of pregnant women, possibly reducing the external validity of our study. However, the mothers of the FGR group combined and the Non-FGR group were similar regarding educational level and presence of non-pregnancy risk factors.

We had too few neonates with low gestational age in the Non-FGR group to perform comparative analyses. While this can be seen as limitations of our study, the uneventful course of the neonates in our study-was reassuring that these participants functioned appropriately as control group.

We chose to include dichorionic, diamniotic twin pregnancies because they have separate placentas and could act as each other's controls. One could argue that their circulation is not completely independent. However, twin pregnancies are an important part of the FGR-population. By including them, we improved external validity. Besides, we adjusted for twins/singleton in the statistical analysis.

Adjusting for repeated measurements, GA and BW is usually a relevant refinement, but concerns may be raised when the compared groups in the statistical model differ substantially in these characteristics. In our case, the Non-FGR group had no inclusion below 34 weeks that could match the Early-FGR group (Figure 1 b). We therefore focused on the Late-FGR group to compare with the Non-FGR group, and conducted a separate comparison between Early- and Late-FGR, without control group. Due to low numbers, this latter comparison had a restricted power to detect but clear differences. We acknowledge the fact that Early-FGR conventionally represents a more sinister disease profile that rarely permits the pregnancy to reach term in contrast to Late-FGR. One might therefore expect more pronounced cardiac alterations in Early- than Late-FGR and a potential skewed adjustment when included in the same group.

CONCLUSION

This study showed that FGR significantly affects neonatal cardiac morphology. Late-FGR neonates had smaller hearts, a globular shaped basis most prominent on the left side, and symmetrical right ventricle. When adjusted for GA, BW, sex and twin/singleton, we found smaller left ventricles and similarly sized right ventricles, with symmetrical shapes. Interventricular septum diameters were similar. Unadjusted estimates showed smaller hearts, thicker intraventricular septum and globular left ventricles in Early-FGR compared with Late-FGR, whereas adjusted estimates of sizes and shapes were similar. This underscores the importance of adjusting for relevant factors when assessing the genuine effects of FGR.

ACKNOWLEDGEMENTS:

We thank the parents and their neonates that participated in this study, and to the hospital staff for facilitating the study. We acknowledge the assistance received from Dr. Henrik Husby and Dr. Tom Hartgill for participation in patient recruitment and prenatal data acquisition and valuable advice in the planning of the study. Thanks to Polona Rajar for help with the cardiac illustration.

AUTHOR CONTRIBUTION:

LB was responsible for investigation, writing – original draft, formal analysis, writing, visualization, review & editing. DF was responsible for conceptualization of the study, methodology, writing – original draft, formal analysis, writing, review & editing and supervision. NH was responsible for investigation, writing, and review & editing. TK was responsible for conceptualization of the study, methodology, writing, and review & editing. GH was responsible for conceptualization of the study, methodology, writing, review & editing and supervision. EN was responsible for conceptualization of the study, methodology, writing – original draft, formal analysis, writing, review & editing and supervision.

FUNDING

The research did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors. This study is part of a PhD project funded by the University of Oslo.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Eirik Nestaas.

REFERENCES:

1. Barker DJ, Hales CN, Fall CH, Osmond C, Phipps K, Clark PM. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia. 1993;36(1):62-7. doi: 10.1007/bf00399095.

2. Gordijn SJ, Beune IM, Thilaganathan B, Papageorghiou A, Baschat AA, Baker PN, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48(3):333-9. doi: 10.1002/uog.15884.

3. Demicheva E, Crispi F. Long-term follow-up of intrauterine growth restriction: cardiovascular disorders. Fetal Diagn Ther. 2014;36(2):143-53. doi: 10.1159/000353633.

4. Kiserud T, Ebbing C, Kessler J, Rasmussen S. Fetal cardiac output, distribution to the placenta and impact of placental compromise. Ultrasound Obstet Gynecol. 2006;28(2):126-36. doi: 10.1002/uog.2832.

5. Figueras F, Gratacos E. Stage-based approach to the management of fetal growth restriction. Prenat Diagn. 2014;34(7):655-9. doi: 10.1002/pd.4412.

6. Crispi F, Miranda J, Gratacos E. Long-term cardiovascular consequences of fetal growth restriction: biology, clinical implications, and opportunities for prevention of adult disease. Am J Obstet Gynecol. 2018;218(2S):S869-S79. doi: 10.1016/j.ajog.2017.12.012.

7. Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ. 1989;298(6673):564-7. doi: 10.1136/bmj.298.6673.564.

8. Gillman MW. Developmental origins of health and disease. N Engl J Med. 2005;353(17):1848-50. doi: 10.1056/NEJMe058187.

9. Barker DJ, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of growth among children who have coronary events as adults. N Engl J Med. 2005;353(17):1802-9. doi: 10.1056/NEJMoa044160.

10. Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol Rev. 2014;94(4):1027-76. doi: 10.1152/physrev.00029.2013.

11. Sarvari SI, Rodriguez-Lopez M, Nunez-Garcia M, Sitges M, Sepulveda-Martinez A, Camara O, et al. Persistence of Cardiac Remodeling in Preadolescents With Fetal Growth Restriction. Circ Cardiovasc Imaging. 2017;10(1). doi: 10.1161/CIRCIMAGING.116.005270.

12. Crispi F, Hernandez-Andrade E, Pelsers MM, Plasencia W, Benavides-Serralde JA, Eixarch E, et al. Cardiac dysfunction and cell damage across clinical stages of severity in growth-restricted fetuses. Am J Obstet Gynecol. 2008;199(3):254 e1-8. doi: 10.1016/j.ajog.2008.06.056.

13. Cruz-Lemini M, Crispi F, Valenzuela-Alcaraz B, Figueras F, Sitges M, Bijnens B, et al. Fetal cardiovascular remodeling persists at 6 months in infants with intrauterine growth restriction. Ultrasound Obstet Gynecol. 2016;48(3):349-56. doi: 10.1002/uog.15767.

14. Patey O, Carvalho JS, Thilaganathan B. Perinatal changes in cardiac geometry and function in growth-restricted fetuses at term. Ultrasound Obstet Gynecol. 2019;53(5):655-62. doi: 10.1002/uog.19193.

15. Sehgal A, Murthi P, Dahlstrom JE. Vascular changes in fetal growth restriction: clinical relevance and future therapeutics. J Perinatol. 2019;39(3):366-74. doi: 10.1038/s41372-018-0287-4.

16. Sehgal A, Gwini SM, Menahem S, Allison BJ, Miller SL, Polglase GR. Preterm growth restriction and bronchopulmonary dysplasia: the vascular hypothesis and related physiology. J Physiol. 2019;597(4):1209-20. doi: 10.1113/jp276040.

17. Johnsen SL, Wilsgaard T, Rasmussen S, Sollien R, Kiserud T. Longitudinal reference charts for growth of the fetal head, abdomen and femur. Eur J Obstet Gynecol Reprod Biol. 2006;127(2):172-85. doi: 10.1016/j.ejogrb.2005.10.004.

18. Acharya G, Wilsgaard T, Berntsen GK, Maltau JM, Kiserud T. Reference ranges for serial measurements of umbilical artery Doppler indices in the second half of pregnancy. Am J Obstet Gynecol. 2005;192(3):937-44. doi: 10.1016/j.ajog.2004.09.019.

19. Johnsen SL, Rasmussen S, Wilsgaard T, Sollien R, Kiserud T. Longitudinal reference ranges for estimated fetal weight. Acta Obstet Gynecol Scand. 2006;85(3):286-97. doi: 10.1080/00016340600569133.

20. Ebbing C, Rasmussen S, Kiserud T. Middle cerebral artery blood flow velocities and pulsatility index and the cerebroplacental pulsatility ratio: longitudinal reference ranges and terms for serial measurements. Ultrasound Obstet Gynecol. 2007;30(3):287-96. doi: 10.1002/uog.4088.

21. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4. doi: 10.1001/jama.2013.281053.

22. Staff A: Hypertensive svangerskapskomplikasjoner og eklampsi. (2020). Accessed 03.09 2021.

23. Kessler J, Rasmussen S, Hanson M, Kiserud T. Longitudinal reference ranges for ductus venosus flow velocities and waveform indices. Ultrasound Obstet Gynecol. 2006;28(7):890-8. doi: 10.1002/uog.3857.

24. Gómez O, Figueras F, Fernández S, Bennasar M, Martínez JM, Puerto B, et al. Reference ranges for uterine artery mean pulsatility index at 11-41 weeks of gestation. Ultrasound Obstet Gynecol. 2008;32(2):128-32. doi: 10.1002/uog.5315.

25. Johnsen SL, Rasmussen S, Sollien R, Kiserud T. Fetal age assessment based on femur length at 10-25 weeks of gestation, and reference ranges for femur length to head circumference ratios. Acta Obstet Gynecol Scand. 2005;84(8):725-33. doi: 10.1111/j.0001-6349.2005.00691.x.

26. Johnsen SL, Rasmussen S, Sollien R, Kiserud T. Fetal age assessment based on ultrasound head biometry and the effect of maternal and fetal factors. Acta Obstet Gynecol Scand. 2004;83(8):716-23. doi: 10.1111/j.0001-6349.2004.00485.x.

27. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70. doi: 10.1093/ehjci/jev014.

28. Lopez L, Colan SD, Frommelt PC, Ensing GJ, Kendall K, Younoszai AK, et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr. 2010;23(5):465-95; . doi: 10.1016/j.echo.2010.03.019.

29. Eriksen BH, Nestaas E, Hole T, Liestol K, Stoylen A, Fugelseth D. Myocardial function in term and preterm infants. Influence of heart size, gestational age and postnatal maturation. Early Hum Dev. 2014;90(7):359-64. doi: 10.1016/j.earlhumdev.2014.04.010.

30. Walther FJ, Siassi B, King J, Wu PY. Echocardiographic measurements in normal preterm and term neonates. Acta Paediatr Scand. 1986;75(4):563-8. doi: 10.1111/j.1651-2227.1986.tb10251.x.

31. Sehgal A, Allison BJ, Gwini SM, Miller SL, Polglase GR. Cardiac Morphology and Function in Preterm Growth Restricted Infants: Relevance for Clinical Sequelae. J Pediatr. 2017;188:128-34.e2. doi: 10.1016/j.jpeds.2017.05.076.

32. Zaharie GC, Hasmasanu M, Blaga L, Matyas M, Muresan D, Bolboaca SD. Cardiac left heart morphology and function in newborns with intrauterine growth restriction: relevance for long-term assessment. Med Ultrason. 2019;21(1):62-8. doi: 10.11152/mu-1667.

33. Fouzas S, Karatza AA, Davlouros PA, Chrysis D, Alexopoulos D, Mantagos S, et al. Neonatal cardiac dysfunction in intrauterine growth restriction. Pediatr Res. 2014;75(5):651-7. doi: 10.1038/pr.2014.22.

34. Crispi F, Bijnens B, Figueras F, Bartrons J, Eixarch E, Le Noble F, et al. Fetal growth restriction results in remodeled and less efficient hearts in children. Circulation. 2010;121(22):2427-36. doi: 10.1161/circulationaha.110.937995.

35. Cohen E, Whatley C, Wong FY, Wallace EM, Mockler JC, Odoi A, et al. Effects of foetal growth restriction and preterm birth on cardiac morphology and function during infancy. Acta Paediatr. 2018;107(3):450-5. doi: 10.1111/apa.14144.

36. Rodriguez-Lopez M, Cruz-Lemini M, Valenzuela-Alcaraz B, Garcia-Otero L, Sitges M, Bijnens B, et al. Descriptive analysis of different phenotypes of cardiac remodeling in fetal growth restriction. Ultrasound Obstet Gynecol. 2017;50(2):207-14. doi: 10.1002/uog.17365.

37. Ciccone MM, Scicchitano P, Zito A, Gesualdo M, Sassara M, Calderoni G, et al. Different functional cardiac characteristics observed in term/preterm neonates by echocardiography and tissue doppler imaging. Early Hum Dev. 2011;87(8):555-8. doi: 10.1016/j.earlhumdev.2011.04.012.

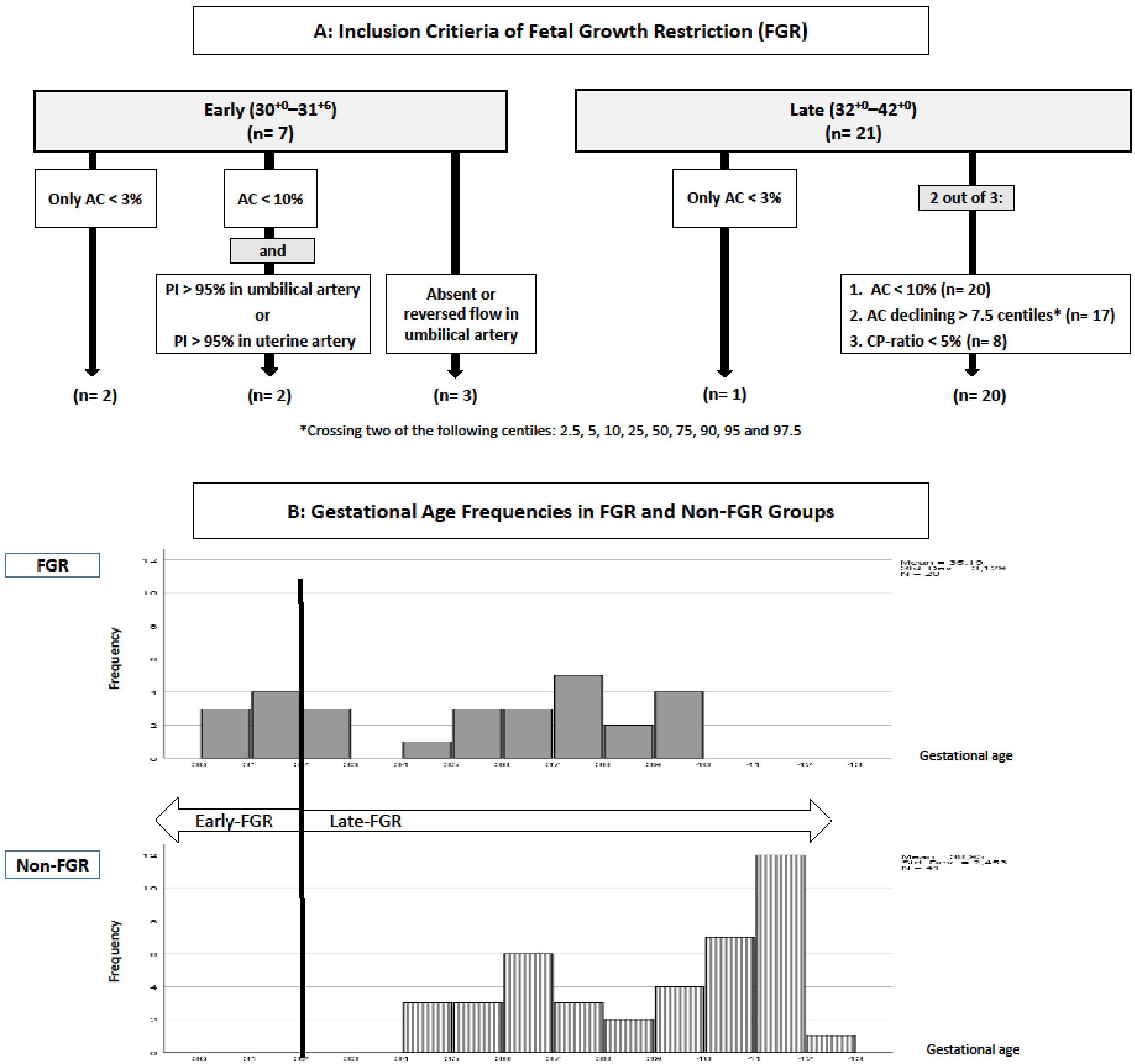
38. Walker DM, Marlow N, Upstone L, Gross H, Hornbuckle J, Vail A, et al. The Growth Restriction Intervention Trial: long-term outcomes in a randomized trial of timing of delivery in fetal growth restriction. Am J Obstet Gynecol. 2011;204(1):34 e1-9. doi: 10.1016/j.ajog.2010.09.019.

39. Shrivastava D, Master A. Fetal Growth Restriction. J Obstet Gynaecol India. 2020;70(2):103-10. doi: 10.1007/s13224-019-01278-4.

40. Gordijn SJ, Beune IM, Ganzevoort W. Building consensus and standards in fetal growth restriction studies. Best Pract Res Clin Obstet Gynaecol. 2018;49:117-26. doi: 10.1016/j.bpobgyn.2018.02.002.

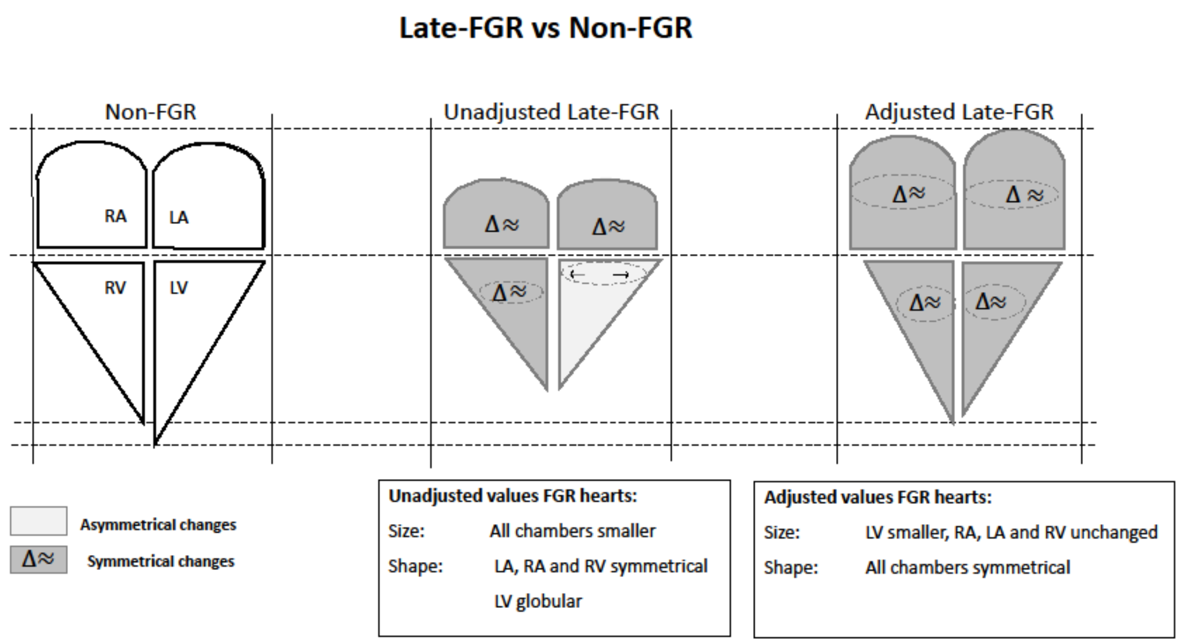
41. Easter SR, Eckert LO, Boghossian N, Spencer R, Oteng-Ntim E, Ioannou C, et al. Fetal growth restriction: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2017;35(48 Pt A):6546-54. doi: 10.1016/j.vaccine.2017.01.042.

Figure 1: Inclusion criteria (A) and gestational age frequencies (B) of early and late fetal growth restriction



FGR – Fetal Growth Restriction, AC - abdominal circumference, PI - pulsatility index

Figure 2: Schematic illustration of the heart shape and size of the late fetal growth restriction group compared with normal hearts based on results unadjusted or adjusted for birth weight, gestational age, sex and twins/singleton.



(RA - right atrium, LA - left atrium, RV - right ventricle and LV - left ventricle, Δ≈ means symmetrical changes, i.e. similar proportion of changes between lengths and widths)

Table 1 Clinical and baseline characteristics

Maternal characteristics n= 62	Early-FGR, n = 7	Late-FGR n= 19	Non-FGR n= 36
Age, years	36 (6)	35 (5)	34 (5)
Height, cm	163 (4)	166 (7)	166 (6)
Pre-pregnancy weight, kg	67 (12)	63 (15)	63 (9)
Pre-pregnancy BMI, kg/m^2	23 (4)	22 (4)	22 (3)
Higher education	6/7 (86%)	12/18 (67%)	28/35 (80%)
Non-smoking during pregnancy	6/7 (86%)	18/19 (95%)	35/36 (97%)
No alcohol during pregnancy	6/7 (86%)	15/19 (79%)	30/36 (83%)
Pre-pregnancy and pregnancy related medical condition	4/7 (57%)	8/19 (42%)	16/36 (46%)
Preeclampsia	4/7 (57%)	4/19 (21%)	0/36 (0%)
Antihypertensive medication	4/6 (66%)	2/17 (12%)	2/34 (6%)
Maternal blood pressure (BP)			
Early systolic BP, mmHg	126 (15)	108 (9)	111 (9)
Early diastolic BP, mmHg	79 (15)	69 (9)	70 (9)
Late systolic BP, mmHg	136 (21)	121 (23)	112 (12)
Late diastolic BP, mmHg	82 (7)	77 (13)	73 (9)
Neonatal characteristics n= 69	**Early-FGR n = 7**	**Late-FGR n= 21**	**Non-FGR n= 41**
Gestational age, weeks	31.0 (0.7)	36.7 (2.2)	39.0 (2.5)
Prematurity, 30 - 37 weeks	7/7 (100%)	12/21 (57%)	12/41 (29%)
Birth weight, kg	1.1 (0.2)	2.2 (0.5)	3.2 (0.7)
Head circumference, cm	27.3 (1.3)	30.3 (2.4)	31.3 (1.7)
Sex, girls	5/7 (71%)	11/21 (52%)	21/41 (51%)
Caesarean section	7/7 (100%)	13/21 (62%)	11/41 (27%)
Apgar, 5 minutes	8 (2)	9 (2)	10 (1)
Ponderal Index	23 (1)	24 (3)	27 (3)
Admission to NICU	7/7 (100%)	7/21 (33%)	6/41 (15%)

Data are presented as mean (+/- SE) or fractions (%). FGR – fetal growth restriction. The number of maternal and neonatal characters differs because of 7 included twin pregnancies Early-FGR defined as gestational age 30^{+0} – 31^{+6}. Late-FGR defined as ≥ 32 weeks. Non-FGR were all ≥ 32 weeks. BP - Blood pressure. BMI - Body mass index. Higher education was defined as > 15 years. Pre-pregnancy and pregnancy related medical conditions for all groups combined were: allergy (28/62), asthma (6/62), hypertension (8/62), gestational diabetes (3/62), gynecological (6/62), or other pre-existing medical conditions (19/62). Ponderal Index – kg/m^3. NICU - Neonatal Intensive Care Unit.

Table 2: Echocardiographic morphological measurements, unadjusted and adjusted for gestational age, birth weight, sex and twin/singleton. Left part of the table shows comparisons between Late-FGR and Non-FGR. Right part of the table shows comparisons between Early-FGR and Late-FGR. Adjusted values are estimated marginal means by use of GA 38 weeks and BW 2.8 kg for Late FGR compared to Non-FGR and by use of GA 35 weeks and BW 1.9 kg for Early-FGR compared to Late-FGR.

	Late-FGR vs. Non-FGR						Early-FGR vs. Late-FGR					
Measurements	**Unadjusted**			**Adjusted**			**Unadjusted**			**Adjusted**		
Gestational Age, weeks	**Late-FGR, n = 21**	**Non-FGR, n = 41**	**p**	**Late-FGR, n = 21**	**Non-FGR, n = 41**	**p**	**Early-FGR, n = 7**	**Late-FGR, n = 21**	**p**	**Early-FGR, n = 7**	**Late-FGR, n = 21**	**p**
Left sided measurements												
Left atrial diam	9.1 (0.3)	11.0 (0.2)	**<0.001**	9.8 (0.46)	11.1 (0.2)	**0.004**	7.6 (0.4)	9.3 (0.2)	**<0.001**	8.1 (0.7)	9.2 (0.46)	0.249
Left atrial area*	137 (7)	170 (5)	**<0.001**	158 (8)	16 (5)	0.715	81 (8)	142 (5)	**<0.001**	94 (14)	134 (8)	0.052
Mitral valve diam	8.5 (0.2)	9.5 (0.1)	**<0.001**	9.3 (0.2)	9.4 (0.1)	0.797	6.7 (0.2)	8.7 (0.2)	**<0.001**	7.7 (0.4)	8.3 (0.2)	0.250
IVS diam	2.1 (0.1)	2.7 (0.1)	**0.002**	2.4 (0.2)	2.6 (0.1)	0.450	1.9 (0.1)	2.1 (0.1)	0.118	2.4 (0.2)	1.9 (0.1)	0.095
Septum length	26.7 (0.6)	31.5 (0.4)	**<0.001**	29.0 (0.6)	30.8 (0.4)	**0.026**	20.7 (0.7)	27.3 (0.5)	**<0.001**	24.2 (1.1)	26.0 (0.6)	0.227
LV internal diam	15.7 (0.3)	17.9 (0.2)	**<0.001**	16.6 (0.4)	17.8 (0.3)	**0.022**	13.4 (0.4)	16.0 (0.3)	**<0.001**	14.5 (0.7)	15.6 (0.4)	0.843
LV post wall diam	2.3 (0.1)	2.7 (0.1)	**<0.001**	2.4 (0.1)	2.6 (0.1)	0.253	1.7 (0.1)	2.3 (0.1)	**<0.001**	2.0 (0.2)	2.2 (0.1)	0.306
Aortic valve diam	5.7 (0.1)	6.7 (0.1)	**<0.001**	6.0 (0.2)	6.6 (0.1)	**0.001**	4.9 (0.1)	5.7 (0.1)	**<0.001**	5.2 (0.3)	5.7 (0.1)	0.192
LA/Ao	1.31 (0.04)	1.38 (0.03)	0.209	1.31 (0.06)	1.41 (0.04)	0.125	1.35 (0.07)	1.31 (0.05)	0.624	1.19 (0.13)	1.39 (0.17)	0.234
Right sided measurements												
Right atrial area*	153 (9)	198 (6)	**<0.001**	177 (10)	191 (7)	0.315	94 (10)	158 (7)	**<0.001**	137 (18)	139 (9)	0.927
Tricuspid valve diam	9.8 (0.2)	11.2 (0.2)	**<0.001**	10.4 (0.3)	11.0 (0.2)	0.061	7.8 (0.3)	10.0 (0.2)	**<0.001**	8.9 (0.4)	9.5 (0.2)	0.292
RV mid-wall diam	7.8 (0.5)	10.3 (0.4)	**<0.001**	8.4 (0.6)	10.4 (0.4)	**0.012**	5.69 (0.4)	8.0 (0.3)	**<0.001**	7.4 (0.6)	7.4 (0.3)	0.976
RV area*	240 (14)	319 (10)	**<0.001**	299 (13)	309 (9)	0.538	14 (15)	253 (10)	**<0.001**	210 (23)	223 (12)	0.672
RV cavity length	22.5 (0.6)	26.1 (0.5)	**<0.001**	25.0 (0.8)	25.4 (0.5)	0.675	18.1 (0.7)	23.1 (0.5)	**<0.001**	19.9 (1.1)	22.3 (0.6)	0.134
Pulmonary valve diam	6.7 (0.2)	8.0 (0.2)	**<0.001**	7.4 (0.2)	8.0 (0.1)	**0.019**	5.3 (0.2)	6.8 (0.2)	**<0.001**	6.0 (0.4)	6.73 (0.2)	0.144

Data are presented as mean (+/-SE). All measurements are in mm except areas* that are measured in mm^2. FGR – fetal growth restriction. Early FGR was defined as gestational age $30^{+0} – 31^{+6}$. Late FGR was defined as gestational age ≥ 32 weeks. All Non-FGR had gestational age ≥ 32 weeks. Diam - diameter, IVSd - interventricular septum at end diastole, LV - left ventricle, LV post wall diameter - left ventricle posterior wall diameter at end diastole, RA - right atrium, RV - right ventricle, Septum length - left ventricular septum length at end diastole.

Table 3. Echocardiographic morphological indices, unadjusted and adjusted for gestational age, birth weight, sex and twin/singleton. Left part of the table shows comparisons between Late-FGR and Non-FGR. Right part of the table shows comparisons between Early-FGR and Late-FGR. Adjusted values are estimated marginal means by use of GA 38 weeks and BW 2.8 kg for Late FGR compared to Non-FGR and by use of GA 35 weeks and BW 1.9 kg for Early FGR compared to Late-FGR.

	Late-FGR vs. Non-FGR						Early-FGR vs. Late-FGR					
Measurements indices	Unadjusted			Adjusted			Unadjusted			Adjusted		
Gestational Age, weeks	Late-FGR, n = 21	Non-FGR, n = 41	p	Late-FGR, n = 21	Non-FGR n = 41	p	Early-FGR n = 7	Late-FGR n = 21	p	Early-FGR n = 7	Late-FGR n = 21	p
Left sided indices – all measurements are divided by septum length												
Aortic valve	0.27 (0.01)	0.27 (0.01)	0.274	0.26 (0.01)	0.26 (0.01)	0.644	0.28 (0.01)	0.27 (0.018)	0.328	0.29 (0.03)	0.27 (0.01)	0.299
Left atrial diam	0.35 (0.01)	0.35 (0.01)	0.669	0.34 (0.01)	0.36 (0.02)	0.098	0.37 (0.01)	0.34 (0.01)	0.068	0.34 (0.03)	0.36 (0.01)	0.645
Left atrial area (mm)	5.1 (0.2)	5.4 (0.1)	0.119	5.4 (0.3)	5.2 (0.2)	0.615	3.9 (0.2)	5.2 (0.2)	**<0.001**	3.7 (0.5)	5.2 (0.3)	**0.030**
Mitral valve diam	0.320 (0.006)	0.305 (0.004)	**0.034**	0.323 (0.008)	0.305 (0.006)	0.092	0.328 (0.008)	0.320 (0.006)	0.430	0.322 (0.017)	0.321 (0.009)	0.986
IVSd diam	0.080 (0.040)	0.084 (0.030)	0.339	0.081 (0.006)	0.083 (0.004)	0.796	0.092 (0.004)	0.078 (0.003)	**0.011**	0.100 (0.008)	0.074 (0.004)	**0.013**
LV internal diam	0.60 (0.01)	0.57 (0.01)	0.133	0.58 (0.02)	0.58 (0.01)	0.829	0.66 (0.02)	0.56 (0.01)	**0.009**	0.62 (0.04)	0.60 (0.04)	0.766
Right sided indices – all measurements are divided by septum length												
Right atrial area (mm)	5.7 (0.2)	6.3 (0.2)	**0.040**	6.1 (0.3)	6.2 (0.2)	0.798	4.6 (0.3)	5.8 (0.2)	**0.007**	5.6 (0.6)	5.3 (0.3)	0.772
Tricuspid valve diam	0.37 (0.01)	0.36 (0.01)	0.165	0.36 (0.01)	0.36 (0.01)	0.921	0.38 (0.01)	0.37 (0.01)	0.428	0.37 (0.02)	0.37 (0.01)	0.933
RV mid-wall diam	0.29 (0.01)	0.33 (0.01)	0.058	0.29 (0.02)	0.34 (0.01)	0.053	0.30 (0.01)	0.30 (0.01)	0.358	0.31 (0.03)	0.28 (0.01)	0.562
RV area (mm)	8.9 (0.4)	10.1 (0.2)	**0.008**	10.2 (0.4)	10.1 (0.3)	0.763	6.5 (0.5)	9.3 (0.3)	**<0.001**	8.4 (0.8)	8.5 (0.4)	0.923
Ratios between corresponding right sided and left sided measurements												
Tricuspid valve diam / Mitral valve diam	1.16 (0.02)	1.18 (0.01)	0.429	1.12 (0.02)	1.18 (0.02)	**0.049**	1.16 (0.02)	1.16 (0.02)	0.888	1.16 (0.05)	1.15 (0.03)	0.943
Right atrial area / Left atrial area	1.15 (0.05)	1.19 (0.04)	0.477	1.15 (0.07)	1.21 (0.05)	0.465	1.20 (0.07)	1.13 (0.05)	0.432	1.37 (0.14)	1.05 (0.17)	0.100
RV cavity length / Septum length	0.85 (0.02)	0.83 (0.01)	0.440	0.87 (0.03)	0.83 (0.02)	0.237	0.88 (0.03)	0.85 (0.02)	0.336	0.83 (0.05)	0.86 (0.03)	0.623
RV midwall diam / LV internal diam	0.50 (0.03)	0.57 (0.02)	**0.040**	0.52 (0.04)	0.58 (0.02)	0.153	0.44 (0.03)	0.51 (0.02)	0.066	0.53 (0.05)	0.48 (0.03)	0.547

Data are presented as mean (+/-SEM). FGR – fetal growth restriction. Early-FGR was defined as gestational age $30^{+0} – 31^{+6}$. Late-FGR was defined as gestational age ≥ 32 weeks. All Non-FGR had gestational age ≥ 32 weeks. Diam - diameter, LV internal diam - left ventricle internal diameter at end diastole, RV - right ventricle, Septum length - left ventricle septum length in diastole.