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RESEARCH ARTICLE

Ductus arteriosus diameters in fetuses with early- and late-onset fetal growth restriction

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Abstract

Purpose: Fetal growth restriction (FGR) is a common pregnancy complication that can be associated with several adverse perinatal outcomes. One of these negative outcomes is ductus arteriosus, especially in preterm babies. In this study, intrauterine heart function and ductus diameter were evaluated in babies with FGR.

Methods: Thirty-seven fetuses with FGR were compared with 37 normal-weight fetuses at the same gestational week. In our study, ventricular diameters, aorta, pulmonary artery, ductus arteriosus (DA), aortic arch diameter, and flow traces were examined. In addition, the aorta and aortic isthmus diameters were proportioned to the ductus diameter, and the left ventricular myocardial performance index (MPI) [(ICT + IRT)/ET] was evaluated.

Results: There was no difference in DA diameters between the patient and control groups. The intragroup comparison of the cases with early- and late-onset FGR revealed no statistically significant difference between DA diameters. However, the ratios of the aortic annulus diameter/ductus diameter (AOD/DAD) and aortic isthmus diameter/ductus diameter (AID/DAD) were significantly lower in early-onset FGR because the diameter of the DA was greater. In addition, the mod-MPI values were higher in the patient group.

Conclusions: In our study, although the ductal diameters did not change significantly in the patient group, the ductal diameter was greater in the early-onset intrauterine growth restriction (FGR) group compared with other cardiac measurements. The mod-MPI value, a cardiac function indicator, was higher in fetuses with FGR. These findings may be useful for evaluating postnatal cardiac functions in FGR.

KEYWORDS
ductus arteriosus, echocardiography, fetal growth restriction, left ventricle, mitral E/A, mod-MPI

1 | INTRODUCTION

Fetal growth restriction (FGR) is defined as an estimated fetal weight below the 10th percentile according to the week of gestation. An abdominal circumference (AC) <10th percentile for gestational age is another common definition.[1] FGR may occur due to maternal, fetal, and placental reasons,[2] and detection and monitoring of FGR during pregnancy are critical. Findings on Doppler velocimetry of the umbilical artery play a crucial role in managing suspected pregnancies with FGR. The most common Doppler indices used for obstetric applications are

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the peak systolic frequency shift-to-end-diastolic frequency shift ratio (S/D) and the pulsatility index (PI), which represents the difference between the peak systolic and end-diastolic shift divided by the average frequency shift. However, these parameters can sometimes be within normal limits until late pregnancy.

FGR may cause many complications that increase perinatal mortality and morbidity, including premature birth, respiratory distress, and necrotizing enterocolitis.[3] Patent ductus arteriosus (PDA) is a critical condition of prematurity. FGR affects several organ systems, and one of the outcomes of this effect is PDA. The incidence of PDA increases up to 50% after 48–72 h postpartum in preterms with FGR.[4] However, to the best of our knowledge, no study has evaluated FGR and ductal changes during the fetal period. In this study, the diameter of the ductus arteriosus (DA) was evaluated in fetuses with early- and late-onset FGR. Note that FGR is divided into early and late onset based on different pathological mechanisms. Early onset (<32–34 weeks) represents 20%–30% of all intrauterine growth restrictions (FGRs), and late onset represents 70%–80% of FGRs. Early-onset FGR is a more severe condition, wherein perinatal morbidity and mortality rates are significantly higher compared with late-onset FGR. Both early- and late-onset FGR present with cardiovascular remodeling prenatally and postnatally. Further, analyzing fetal heart function can provide important information about cardiovascular adaptation in conditions that lead to perinatal complications, such as FGR. Cardiac diastolic function is often affected in the presence of hypoxia in FGR. Since the right ventricular afterload increases as a result of pulmonary and systemic vasoconstriction in FGR fetuses, diastolic dysfunction may occur due to shifting of the cardiac output to the left ventricle.[5–7] Parameters such as M-mode, atrioventricular (AV) valves' early filling (E) and late filling (A), the E/A ratio, and myocardial performance index (MPI) are used for fetal cardiac evaluation. The MPI provides information about systolic and diastolic cardiac functions.[8,9] It is also an early and consistent marker of heart dysfunction in the early stages of chronic hypoxia or in conditions with cardiac overloads, such as twin-to-twin transfusion syndrome.[10,11] The E/A ratios of AV valves provide information about cardiac diastolic functions. Previous studies have revealed a decrease in E/A ratios in fetuses with FGR.[8,12] In our study, MPI values and AV valves' E/A ratios in fetuses with early- and late-onset FGR were compared with those of normal fetuses.

2 | MATERIALS AND METHODS

2.1 | Study population

The study was approved by the local ethical committee (2019/14-25). This prospective cross-sectional case control study was conducted between January 2019 and January 2021. Consent was obtained from all pregnant women before the study, and all participants provided written consent. The week of gestation was calculated according to the last menstrual period and confirmed by the first-trimester crown-rump length. FGR was defined as an estimated fetal weight below the 10th percentile associated with abnormal Doppler velocimetry.

PI and S/D indices were used for fetal examinations. The S/D ratio is normally less than 3.5 in preterm fetuses and less than 2.5 at term. Worsening blood flow was associated with an increased S/D ratio. Abnormal umbilical artery (UA) was defined as a UA PI greater than the 95th percentile or absent or reversed UA diastolic flow. Those diagnosed with FGR before the 34th gestational week were classified as early FGR, and those after the 34th gestational week were classified as late FGR. Controls were randomly selected from low-risk, normally progressing pregnancies and among the ones appropriate for gestational age. Exclusion criteria were preeclampsia, diabetes, thyroid dysfunction, obesity, or any chronic disease detected before or during pregnancy. The exclusion criteria for the fetus were fetal infections and structural, chromosomal, or cardiac abnormalities.

2.2 | Echocardiography

All ultrasound examinations were performed by experienced operators using real-time scanning Philips Affiniti 50 (Philips Healthcare, Andover, Netherlands) equipped with C5-1 MHz transabdominal curvilinear transducers. Fetal echocardiography was performed according to the American Society of Echocardiography (ASE) guidelines.[13] Left ventricle (LV) and right ventricle (RV) diameters were measured at the end of diastole, and left atrial (LA), right atrial (RA), aorta (AO), aortic isthmus (AI) and descending aorta (DAO), main pulmonary artery (PA), and DA diameters were measured at the end of systole. All diameters were measured thrice. In addition, the ductus diameter was measured in the image of three vessels.[14] These measurements are presented in Figure 1.

The aortic arch was visualized on the sagittal examination. For aortic arch velocity, the cursor was brought parallel to the distal of the left subclavian artery. Intrauterine DA flow was from right to left and characterized by a high Doppler velocity and low diastolic waveform. In our study, the high systolic wave was evaluated for ductus velocity. To minimize the gestational week interaction, the aortic annulus diameter/ductus diameter (AOD/DAD) was proportioned to the aortic isthmus diameter/ductus diameter (AID/DAD).

The fetal diastolic component was assessed using spectral Doppler through the AV valves. The mitral and tricuspid E (early ventricular filling) and A (active atrial filling) waves indicate diastolic dysfunction. The cardiac beat was recorded by placing the PW Doppler at the level of the mitral valve and the tricuspid valve tips. Peak early (E) and late (A) filling speeds were measured, and the E/A ratio was evaluated.

2.3 | Left ventricle MPI (Tei index)

For MPI measurement, the Doppler cursor was placed between the anterior leaf of the mitral valve and the left ventricular outflow tract. The isovolumetric contraction time (ICT) was measured from the beginning of mitral valve closure to aortic valve opening, the isovolumetric relaxation time (IRT) was measured from the time of aortic valve closure to mitral valve opening, and the ejection time (ET) was measured from the time of opening to closing of the aortic valve.

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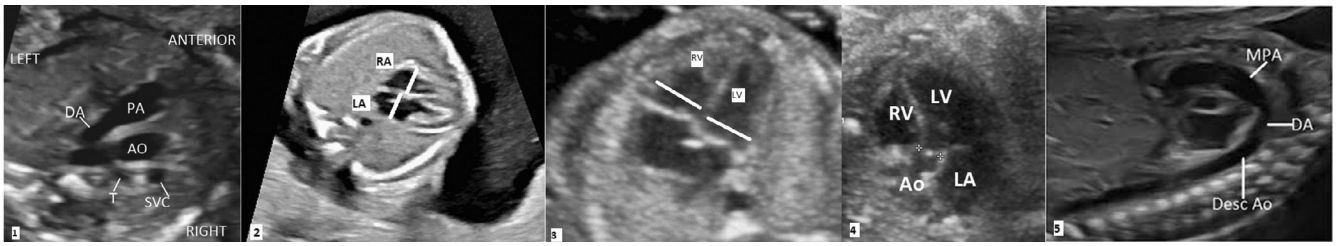


FIGURE 1 All measurements are shown in the figure; (1) Ductus arteriosus diameters in the end systolic phase in three vessel view, (2) left atrium and right atrium diameters in the end systolic phase at the level of the middle atrium in the four chamber view, (3) left ventricle- right ventricle diameters in the end diastolic phase in the four-chamber view, (4) aortic diameter in the end systolic phase in the left ventricular outflow view, (5) aortic isthmus diameter just below the left subclavian artery in the end systolic phase in the aortic arch view. Ao, aorta; DA, ductus arteriosus; LA, left atrium; LV, left ventricle; MPA, main pulmonary artery; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

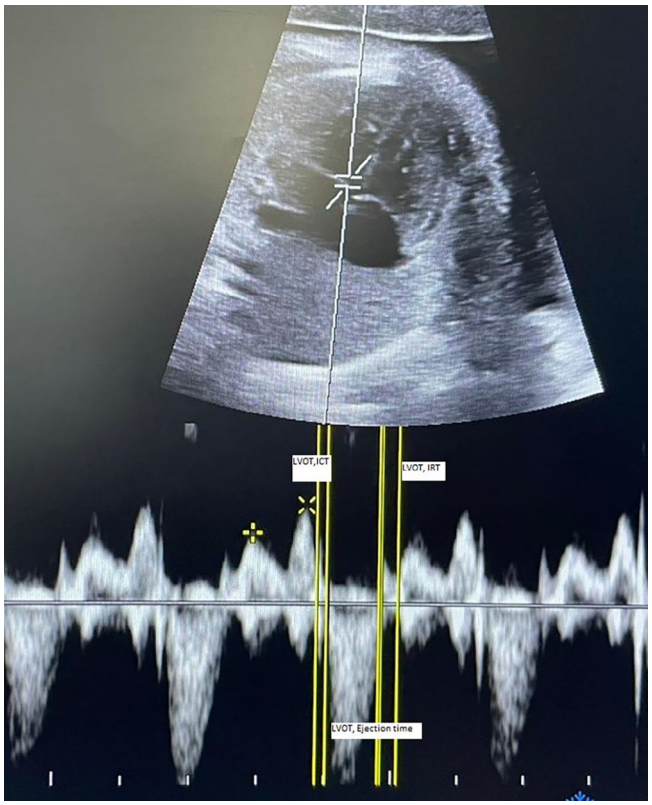


FIGURE 2 Fetal mod-MPI measurement.

Mod-MPI was calculated as (ICT + IRT)/ET (Figure 2). Three consecutive measurements containing these parameters were made and averaged. Both ICT and IRT provide information on the early stages of fetal heart contraction and relaxation processes.

2.4 | Statistical analysis

The data were analyzed using the SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA) statistical program. Descriptive statistics were presented as the number of units (*n*), percentage (%), mean ± standard deviation (*mean* ± *sd*), minimum value (min), maximum value (max), median (median), 25th percentile (Q1), and 75th percentile (Q3) values. The normal distribution of the data belonging to the quantitative variables was evaluated using the Shapiro–Wilk test of normality and Q-Q graphs. The homogeneity of group variances was evaluated using Levene's test. Comparisons between the two groups for continuous variables were made using the independent sample *t*-test or Mann–Whitney *U* test according to the assumption of normal distribution. Comparisons of independent groups with more than two subcategories were evaluated using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test according to the data distribution normality test results. In cases of statistically significant differences with one-way ANOVA, Tukey's multiple comparison test was used for evaluating the homogeneity of variances, and the Tamhane Dunnett's multiple comparison test was used for evaluating heterogeneity. In case of differences in the Kruskal–Wallis analysis, the Bonferroni test was used as a multiple comparison test. A value of $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Cohort characteristics

Thirty-seven women with FGR fetuses were included in the study group, and 37 women with normal-weight fetuses were included in the control group. The clinical characteristics, estimated fetal weight (EFW), EFW percentile, SD, and PI values of the study and control groups are presented in Table 1. There were no statistically significant differences between the study populations regarding maternal age and parity. The gestational weeks of the patient and control groups with FGR were 32.6 ± 4.3 and 30.8 ± 5.19, respectively ($p = 0.01$).

Thirteen patients had early-onset FGR, and 24 patients had late-onset FGR. There was no difference between maternal age and the number of pregnancies in the early-onset FGR, late-onset FGR, and control groups. The week of gestation was 28.69 ± 4.75 in early-onset FGR and 34.71 ± 2.2 in late-onset FGR. When BPD Z scores were compared according to the control-early and late groups, no statistically significant difference was found ($p = 0.163$). No statistically significant correlation was detected between GA and BPD-Z scores

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TABLE 1 The clinical characteristics and perinatal outcomes of the study and control groups.

Variables	Groups	*n*	Mean ± SD M(Q_1-Q_3)	Min–max	*p* value	Pairwise comparisons
Maternal age (*year*)	Control	37	28,70 ± 6.27 28 (24–33)	17–41	0.329[a]	–
	Early-onset	13	28.15 ± 5.47 27 (24–32.5)	19–38		
	Late-onset	24	26.46 ± 4.96 25.50 (23–30.25)	20–37		
Gestational age (week)	Control	37	31.18 ± 4.84 31.3 (27.6–35.55)	22.4–39.6	**<0.001**[a]	C-E: 0.320 C-L: **0.001** E-L: **0.002**
	Early-onset	13	28.69 ± 4.75 28 (25–33)	22–38		
	Late-onset	24	34.71 ± 2.22 35 (33–36)	30–39		
BPD Z scores	Control	18	0.56 ± 0.52	0–1.90	0.163	–
	Early onset	13	0.71 ± 0.44	0.13–1.70		
	Late onset	24	0.98 ± 0.78	0–2.80		
EFW	Control	22	2016.95 ± 868.18 2236.5 (1385.75–2757.5)	285–3077	**<0.001**[b]	C-E: **<0.001** C-L: 0.929 E-L: **<0.001**
	Early-onset	13	1093 ± 598.12 1000 (593–1614)	384–2051		
	Late-onset	24	2063.08 ± 374.31 2088 (1726.75–2333.75)	1298–2773		
EFW percentiles	Control	0	–	–	0.571[c]	–
	Early-onset	7	1.98 ± 1.91 2.00 (0.48–2.20)	0.20–5.89		
	Late-onset	11	2.59 ± 2.29 2.23 (1.17–3.76)	0.08–6.85		
S/D	Control	0	–	–	0.325[c]	–
	Early-onset	9	2.81 ± 0.76 2.64 (2.05–3.54)	2.01–4.1		
	Late-onset	24	2.53 ± 0.70 2.38 (2.02–2.87)	1.56–4.58		
Pulsatility index	Control	0	–	–	0.150[c]	–
	Early-onset	10	1.02 ± 0.28 0.94 (0.81–1.24)	0.70–1.56		
	Late-onset	24	0.89 ± 0.22 0.88 (0.73–1.05)	0.57–1.39		

Note: The bold values indicate statistically significant results ($p < 0.05$).
Abbreviations: EFW, estimated fetal weight; PI, pulsatility index; S/D, peak systolic frequency shift to end-diastolic frequency shift ratio.
[a]One-way ANOVA.
[b]Kruskal Wallis test.
[c]Independent sample *t* test.

(rho = 0.046; $p = 0.739$). Also, When the distributions of BPD Z scores were compared according to groups, negative and positive, no statistically significant difference was detected ($p = 0.166$).

3.2 | Echocardiographic findings

Fetal cardiac measurements, MPI, and other parameters in the patient and control groups are summarized in Table 2. Among these parameters, no statistically significant difference was determined, except in mod-MPI values, which were higher in fetuses with FGR ($p = 0.002$). However, there was no difference in mod-MPI values between patients with early- and late-onset FGR ($p = 0.121$). The cardiac measurements in early- and late-onset FGR are given in Table 3. It was observed that ductal diameters were greater in early-onset FGR, considering the ratios of AO:DA and AI:DA ($p = 0.014+$, $p = 0.001+$).

4 | DISCUSSION

Uteroplacental insufficiency is a major cause of FGR. In addition, FGR is considered a critical risk factor for mortality and morbidity in

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TABLE 2 Cardiac measurements of the control and patient groups.

	Control group ($n = 37$)		Patient group ($n = 37$)		
	Mean ± SD M(Q_1–Q_3)	Min–max	Mean ± SD M(Q_1–Q_3)	Min–max	*p* value
AO diameter (mm)	5.76 ± 1.37 5.6 (4.75–6.5)	3.1–8.8	5.65 ± 1.18 5.5 (4.95–6.65)	3.2–7.9	0.711[a]
AO velocity (mm Hg)	69.51 ± 13.93 70 (60.5–78)	37–97	63.26 ± 16.75 62 (51–77)	32–105	0.085[a]
PA diameter (mm)	6.72 ± 1.6 6.7 (5.65–8.1)	3.7–9.4	6.74 ± 1.43 7 (5.85–7.8)	3.6–8.7	0.833[b]
PA velocity (mm Hg)	63.97 ± 13.57 63 (51–72)	41–94	58.15 ± 12.34 58.8 (51–65)	32–85.4	0.057[a]
LV (mm)	10.64 ± 2.55 10 (8.6–13)	5.5–17	10.31 ± 2.32 10 (8.85–12)	5.6–15	0.553[a]
RV (mm)	11.02 ± 2.65 12 (8.5–13)	5.1–17	10.67 ± 2.81 11 (9.2–12.5)	4–16	0.584[a]
LA (mm)	10.81 ± 2.3 10 (9.45–12)	6–15	10.54 ± 2.37 10.5 (9–12)	6–15	0.613[a]
RA (mm)	11.74 ± 2.7 12 (10–13.5)	6.7–18	11.84 ± 2.72 12 (10.25–13.75)	6.8–18	0.877[a]
Mitral annulus (mm)	9.88 ± 2.16 10 (8.2–11.5)	5.5–15	9.4 ± 2.4 10 (7.7–11)	4.8–13.8	0.368[a]
Mitral E	33.35 ± 5.92 32 (30–38)	23–47	30.25 ± 5.98 30 (24.5–34.75)	21–42	**0.049**[b]
Mitral A	50.76 ± 9.33 50 (44–55)	35–74	48.61 ± 8.26 47.5 (42.25–55.5)	32–65	0.302[a]
Mitral E/A	0.66 ± 0.10 0.68 (0.60–0.73)	0.47–0.86	0.63 ± 0.11 0.61 (0.55–0.70)	0.44–0.97	0.135[a]
Tricuspid annulus (mm)	10.45 ± 2.63 11 (8.35–12)	4.8–16	10.28 ± 3.07 10 (8.2–12.5)	4.9–19	0.792[a]
Tricuspid E	36.03 ± 8.13 37 (29–43)	21–51	36.91 ± 10.72 37 (29–43)	18–69	0.713[a]
Tricuspid A	52.13 ± 8.38 52.5 (47–55.75)	32–71	53.23 ± 10.41 52 (47–58)	32–84	0.636[a]
Tricuspid E/A	0.69 ± 0.10 0.65 (0.62–0.78)	0.51–0.91	0.70 ± 0.13 0.69 (0.63–0.76)	0.48–1.21	0.622[b]
AO-arch diameter (mm)	5.24 ± 1 5.5 (4.7–5.95)	3–7	5.51 ± 1.43 5.65 (4.58–6.7)	2.4–8.9	0.345[a]
AO-arch velocity (mm Hg)	80.49 ± 17.23 78 (69–87.5)	51–120	80.82 ± 19.03 83 (67.2–91)	47.2–134	0.770[b]
DA (mm)	3.55 ± 0.78 3.3 (3–4)	2.3–5.5	3.64 ± 1.18 3.55 (2.63–4.4)	2–6.1	0.990[b]
DA velocity (mm Hg)	73.08 ± 17.64 72.5 (60–87)	40–120	70.77 ± 28.62 67 (57.5–76)	27–200	0.251[b]
MPI	0.51 ± 0.09 0.5 (0.45–0.56)	0.38–0.8	0.58 ± 0.11 0.55 (0.5–0.65)	0.43–0.92	**0.002**[b]
AO/DA	1.67 ± 0.46 1.62 (1.34–1.98)	0.98–2.96	1.72 ± 0.71 1.54 (1.23–2.02)	0.90–3.65	0.745[b]
AI/DA	1.52 ± 0.38 1.50 (1.21–1.74)	1.00–2.59	1.58 ± 0.55 1.41 (1.14–1.93)	0.82–3.00	0.962[b]

Note: The bold values indicate statistically significant results ($p < 0.05$).

Abbreviations: AI, aortic isthmus; AO, aorta; DA, ductus arteriosus; FGR, Fetal growth restriction; LA, left atrium; LV, left ventricle; ModMPI, modified myocardial performance index; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

[a]Independent sample *t* test.

[b]Mann–Whitney *U* test.

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TABLE 3 Cardiac measurements of the early onset FGR and late onset FGR patient groups.

	Early-onset FGR group ($n = 13$)		Late-onset FGR group ($n = 24$)		*p* value
	Mean ± SD M(Q_1–Q_3)	Min–max	Mean ± SD M(Q_1–Q_3)	Min–max	
AO diameter (mm)	4.68 ± 0.93 4.7 (3.9–5.2)	3.2–6.7	6.18 ± 0.95 6.25 (5.33–7.08)	4.8–7.9	**<0.001**[a]
AO velocity (mm Hg)	57 ± 17.63 52 (48–65.5)	32–105	66.65 ± 15.58 65 (54–80)	40–100	0.053[b]
PA diameter (mm)	5.32 ± 1.32 5.4 (4.2–6.2)	3.6–8.3	7.5 ± 0.73 7.5 (7–8.08)	6.2–8.7	**<0.001**[a]
PA velocity (mm Hg)	53.17 ± 12.21 51 (46.8–57)	32.6–80	60.84 ± 11.79 60.5 (53.25–65.75)	32–85.4	0.070[a]
LV (mm)	8.84 ± 2.16 9.3 (7.05–10)	5.6–13	11.1 ± 2.04 11 (9.65–12.88)	7.8–15	**0.003**[a]
RV (mm)	8.28 ± 2.2 8.9 (6.25–10)	4–11	11.97 ± 2.2 12 (10–13.75)	7.6–16	**<0.001**[a]
LA (mm)	8.98 ± 2.38 8.8 (6.75–11)	6–13	11.41 ± 1.89 12 (9.8–13)	8.8–15	**0.002**[a]
RA (mm)	10.09 ± 2.56 10 (7.45–12.5)	6.8–14	12.83 ± 2.32 12 (11–15)	8.5–18	**0.002**[a]
Mitral annulus (mm)	7.98 ± 2.51 7 (5.7–10)	4.8–12	10.17 ± 2 10 (8.5–11)	6–13.8	**0.006**[a]
Mitral E	29.08 ± 5.35 29 (24.5–32.75)	21–40	30.83 ± 6.29 30 (24.5–36)	21–42	0.416[a]
Mitral A	46.33 ± 6.44 44 (42.25–48.25)	40–60	49.75 ± 8.95 50 (42.25–58.25)	32–65	0.188[b]
Mitral E/A	0.63 ± 0.09 0.61 (0.55–0.71)	0.52–0.79	0.63 ± 0.12 0.61 (0.55–0.7)	0.44–0.97	0.969[a]
Tricuspid annulus (mm)	8.05 ± 2.13 8.5 (5.95–10)	4.9–11	11.48 ± 2.83 11 (9.25–13.6)	7–19	**0.001**[a]
Tricuspid E	34.75 ± 9.57 35 (27.5–38)	24–59	38.09 ± 11.33 39.5 (29.75–44.25)	18–69	0.393[a]
Tricuspid A	51.42 ± 9.79 51.5 (43–54.75)	39–70	54.17 ± 10.8 52 (47–61)	32–84	0.465[a]
Tricuspid E/A	0.67 ± 0.1 0.69 (0.62–0.73)	0.49–0.84	0.71 ± 0.15 0.69 (0.63–0.79)	0.48–1.21	0.683[b]
AO-arch diameter (mm)	4.4 ± 1.48 4.05 (3.23–5.68)	2.4–6.9	6.07 ± 1.04 5.95 (5.4–6.78)	4.5–8.9	**<0.001**[a]
AO-arch velocity (mm Hg)	74.23 ± 15.67 71 (60.5–90.5)	50–99	84.38 ± 20.02 85 (70.45–95.1)	47.2–134	0.123[a]
DA diameter (mm)	3.56 ± 1.16 3.25(2.7–4.2)	2.1–6.1	3.69 ± 1.22 3.95 (2.55–4.48)	2–6.1	0.766[a]
DA velocity (mm Hg)	59.89 ± 18.02 62 (45.8–72.5)	27–91	76.67 ± 31.78 70 (60.5–80.25)	40–200	0.116[b]
MPI	0.54 ± 0.07 0.55 (0.48–0.61)	0.44–0.65	0.6 ± 0.12 0.59 (0.5–0.67)	0.43–0.92	0.121[a]
AO/DA	1.39 ± 0.29 1.3 (1.23–1.68)	0.92–1.92	1.92 ± 0.82 1.76 (1.24–2.63)	0.9–3.65	**0.014**[a]
AI/DA	1.24 ± 0.21 1.14 (1.1–1.36)	1–1.64	1.79 ± 0.6 1.65 (1.3–2.31)	0.82–3	**0.001**[a]

Note: The bold values indicate statistically significant results ($p < 0.05$).

Abbreviations: AI, aortic isthmus; AO, aorta; DA, ductus arteriosus; FGR, fetal growth restriction; LA, left atrium; LV, left ventricle; Mod MPI, modified myocardial performance index; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

[a]Independent sample *t* test.

[b]Mann–Whitney *U* test.

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babies.[15,16] Premature birth and PDA are important outcomes of FGR.[17–19] Preterm infants are less likely to have spontaneous closure of the DA as part of the transition to extrauterine life, and this rate is further reduced when FGR is present. Razka et al. evaluated the DA after birth in preterm-FGR and eutrophic preterm infants and observed increased systemic vascular steal and DA diameters in infants with FGR at earlier after birth.[18] Robel-Tillig et al. matched 40 growth-restricted neonates with abnormal prenatal Doppler studies and normal controls and observed a higher frequency of PDA and diminished stroke volumes but a significantly higher heart rate resulting in an increased cardiac output.[17] Studies on this subject mostly focus on newborns with FGR, and, to the best of our knowledge, there are no studies on ductal changes after FGR detection in the prenatal period. In this study, we investigated ductal changes in cases with FGR in fetal life. The FGR patients were compared with a control group with similar characteristics, and no difference was determined between the DA diameter and velocities. Fetuses with FGR were divided into early- and late-onset groups. When these two groups were compared, cardiac diameter measurements were found to be higher in late-onset FGR because this group consisted of pregnancies of 34 weeks and above. To minimize this difference, the aorta annulus and aortic isthmus diameters were proportioned to the ductal diameter. In this rating, it was determined that the ductus was wider in early-onset FGR. Some studies have demonstrated that FGR can be protective against PDA.[20] Moreover, some studies have hypothesized that exposure to chronic intrauterine stress causes premature closure of DA.[21,22] Another hypothesis is that events such as necrosis, bleeding, and intimal thickening in the internal elastic lamina of the DA delay the closure of the PDA.[23] In the lamb model, the sensitivity of the ductus to nitric oxide (NO; a vasodilator) depends on gestational age; the ductus showed a tendency toward more pronounced NO-mediated relaxation during early gestation (corresponding to approximately 29 weeks in humans) compared with late gestation (corresponding to more than 34 weeks in humans).[23,24] In this study, same as ours, early-onset FGR may also explain why the duct is wider. Our study determined greater DA diameters in fetuses with early-onset FGR. Chorioamnionitis is a condition that causes chronic intrauterine stress, such as FGR, and may be associated with PDA. In their systematic review and meta-analysis, Park et al. exposed a relationship between histologically diagnosed maternal chorioamnionitis and PDA.[25] These results indicate that the ductal diameter of a fetus exposed to intrauterine stress, such as early-onset FGR, may be greater from the antenatal period. Villamor-Martinez et al.'s extensive meta-analysis, it was found that the interchangeable use of terms such as small for gestational age (SGA) and FGR posed challenges for analysis. The majority of studies indicate a lower prevalence of patent ductus arteriosus (PDA) in infants with SGA-FGR. However, conflicting studies also exist. It was underscored that discrepancies in findings could stem from inconsistent terminology usage and inadequate subgroup delineation. In our study, while the ductus arteriosus (DA) diameter in fetuses with fetal growth restriction (FGR) resembled that of normal fetuses, there was an observed increase in DA diameter in cases of early-onset FGR. Nonetheless, as demonstrated in their meta-analysis, comprehensive large-scale studies with well-defined subgroups and consideration of all potential factors influencing DA diameter are warranted.[26]

Functional fetal cardiac assessment has long been a crucial issue for many researchers. Cardiac changes that occur in the early postnatal period in FGR remain unclear. Patey et al. performed spectral tissue Doppler and two-dimensional speckle tracking echocardiography a couple of days before and within hours after birth in term FGR and compared the results with normal pregnancies. FGR fetuses and neonates at term exhibited altered cardiac indices indicative of myocardial impairment that reflect adaptation to placental hypoxemia and alterations in hemodynamic load around the time of birth.[27] Both early- and late-onset FGR present cardiovascular remodeling prenatally and postnatally.[28] Mod-MPI is one of the new techniques used to measure heart function. Studies have shown that mod-MPI is a good indicator for monitoring Doppler parameters in FGR.[29–31] One study demonstrated that MPI could be an independent predictor of perinatal death in preterm FGR fetuses, with its accuracy similar to ductus venosus flow.[32] Higher MPI values have been found in growth-restricted fetuses.[33] In our study, mod-MPI values were higher in fetuses with FGR. Notwithstanding, there was no difference in mod-MPI values between patients with early- and late-onset FGR. Some studies did not find any differences between mod-MPI measurements in FGR and normal fetuses.[34] In our study, we concluded that deterioration in cardiac functions of the fetus with FGR was detected early with mod-MPI.

PW Doppler was used to evaluate fetal cardiac function. The E wave is generally smaller than the A wave, and the E/A ratio in fetal life is <1 due to decreased compliance of the fetal ventricular myocardium starting from the 10th week of pregnancy. During pregnancy, the gradual increase in the E wave velocity of both AV valves manifests as an increase in the E/A ratio.[8–35] After birth, the E wave is greater than the A wave. In fetuses with FGR, the E/A ratio is lower than that in normal fetuses at the same gestational week.[8] In our study, a decrease in the mitral E wave was observed in fetuses with FGR. There was no important difference between the mitral and tricuspid valve E/A ratios.

In conclusion, FGR is a significant risk factor that increases mortality and morbidity, especially in preterm infants. Additionally, PDA is one of the main factors causing this condition. Our study revealed that ductal changes in early FGR can begin at very early stages. However, due to the complex nature of the DA tissue, early FGR alone does not fully explain this situation. Postnatal evaluation of fetuses with FGR is important to identify clinically significant PDA. However, it is insufficient on its own, and more extensive research is needed on this subject.

In addition, our study mod-MPI was higher in fetuses with FGR. More research is needed on this subject. Functional cardiac evaluation may be vital for predicting postpartum complications in fetuses with FGR.

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4.1 | Study limitations

Our study has some limitations. First, the patient population in the study was small. The second limitation of the study was that we could not evaluate PDA at the first 24th and 72nd hours after delivery by postnatal echocardiography. The reason for this absence was the COVID-19 pandemic.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study protocol was approved by the research institute's committee on human research (protocol number: 2019/14-25).

INFORMED CONSENT STATEMENT

Informed consent was obtained from all individual participants included in the study.

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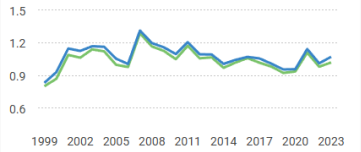
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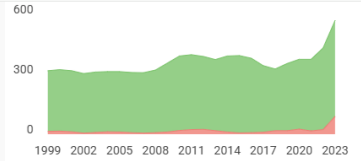
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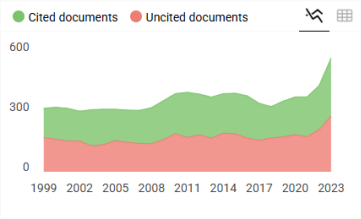
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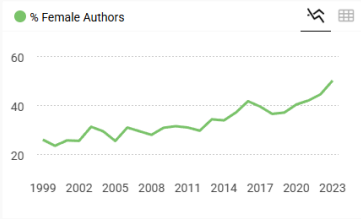


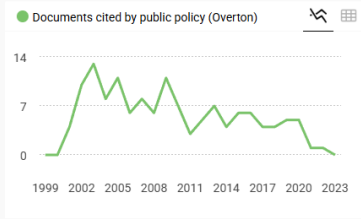


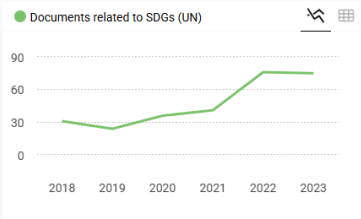














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