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Investigation of fetal cardiac function using tissue doppler imaging in fetuses compromised by growth restriction

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ABSTRACT

Objectives: The primary aim of this study was to evaluate fetal cardiac systolic and diastolic function using the tissue Doppler technique in pregnancies with complications of fetal growth restriction (FGR) and to examine the relationship between FGR with umbilical artery Doppler parameters and fetal cardiac function in complicated pregnancies.

Material and methods: This study included 30 pregnant women with FGR complications and 46 pregnant women without FGR complications. Both groups were at 24–34 gestational weeks. Fetal cardiac examination was performed using pulsed Doppler and tissue Doppler imaging (TDI) in all pregnancies. In the analysis of myocardial tissue by tissue Doppler, the tracing obtained from the junction of the tricuspid valve annulus with the right ventricle was recorded by measuring the duration of the isovolumetric contraction wave (IVC), ejection time (ET), and isovolumetric relaxation time (IVR). Furthermore, we calculated the myocardial performance index (MPI) and then measured and recorded the early diastolic annular rate.

Results: Based on the TDI studies, the mean IVC and IVR values were significantly longer and the ET values were significantly shorter in the study group than those in the control group. The study group also had significantly longer MPI measurements.

Conclusions: Because TDI is a considerably more sensitive method than cardiac sonographic evaluation using pulsed Doppler, tissue Doppler parameters facilitate the detection of cardiac dysfunction at a relatively early stage. In addition, TDI and myocardial evaluation in fetuses with FGR can be noninvasively performed in clinical practice.

Key words: fetal cardiac function; FGR; myocardial performance index; tissue Doppler imaging

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INTRODUCTION

Fetal growth restriction (FGR) is usually expressed as the statistical deviation of fetal size based on a population-based reference, with a typical threshold at the 10th, 5th, or 3rd centile; such a threshold is designed better to demonstrate a "small-for-gestational-age" (SGA) fetus [1, 2]. In a significant proportion of cases, low birth weight was found to be a cardiovascular risk factor, and the onset of cardiovascular diseases coincided with the prenatal period [3, 4].

Placental insufficiency with increased vascular resistance is a significant cause of FGR-related to hypoxia, premature birth, fetal acidemia, and even fetal death [5, 6]. Hypoxic environment frequently affects cardiac diastolic function, occurring earlier in the spectrum of FGR-related cardiac disorders [7]. Fetal cardiac involvement has been found in the late stages with developmental retardation, as supported by various studies; accordingly, the fetal heart is the main organ involved in adaptation mechanisms to placental insufficiency, and fetal development retardation plays a central role in physiopathology [8–13]. Moreover, echocardiographic and biochemical findings of subclinical cardiac dysfunction are mainly associated with diastolic dysfunction [8, 9, 14]. Tissue Doppler imaging (TDI) allows direct measurement of regional myocardial velocities [15]. Various studies using angiography

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in adults have shown that the systolic myocardial velocity of the mitral valve annulus along the left axis of the LV is closely related to the changes in the LV pressure and the EF [10].

In fetuses with FGR, pulmonary and systemic vasoconstriction causes an increase in right ventricular (RV) afterload, thereby displacing the cardiac output to the left ventricle (LV); these outcomes indicate diastolic dysfunction [7]. The etiology of neonatal mortality and morbidity caused by pathological conditions such as FGR and fetal anemia is fetal cardiac failure. Parameters such as ejection fraction (EF), ventricular ejection force, ratio of early diastole rate (E) to atrial systole rate (A) (E/A), cardiac output, and myocardial performance index (MPI) are generally employed for examining fetal cardiac function [5, 6, 11, 12]. Thus, the ratio of flow rate (E) to annular rate (E') **(**E/E'**)** in early diastole is also closely related to filling pressures. Therefore, regional myocardial rates reflect global cardiac function and can be used to predict systolic and diastolic functions in both ventricles [10].

Considering the importance of detecting fetal cardiac function related to FGR, TDI can be used as an additional method for evaluating ventricular diastolic function because it improves the decision-making process and helps determine neonatal prognosis [13]. This study aimed to investigate fetal cardiac functions by TDI in pregnancies complicated with FGR to compare these with the control group.

MATERIAL AND METHODS

Study design, setting and participants

In this prospective study, we included 30 pregnant women complicated with FGR without known fetal anomaly and additional maternal disease as the study group and 46 pregnant women without FGR complication as the control group. All were at 24–34 gestational weeks and applied to the Perinatology Clinic of Kanuni Sultan Suleyman Training and Research Hospital between May 2016 and May 2017. The exclusion criteria were as follows: multiple pregnancies, diabetes, cholestasis, preeclampsia, chromosomal or structural fetal anomaly, FGR diagnosis below the viability limit, early membrane rupture, oligohydramnios, fetal heart complication, or any maternal medical illness. Before starting the study, all volunteers received an informed consent form. The study was approved by the local ethics committee (date: December 1, 2016; approval number: 2016/2/10).

The small fetus is explained as an estimated fetal weight (EFW) below the 10th percentile. Small fetuses were defined as fetal growth restriction or SGA according to estimated fetal weight (EFW), umbilical artery pulsatility index (PI), cerebroplacental ratio (CPR) and uterine artery PI.

FGR was described as an EFW < 3rd percentile, or EFW < 10th percentile with umbilical artery (UA) PI > 95th percentile and/or cerebroplacental ratio (CPR) < 5th percentile and/or mean UtA-PI > 95th percentile.

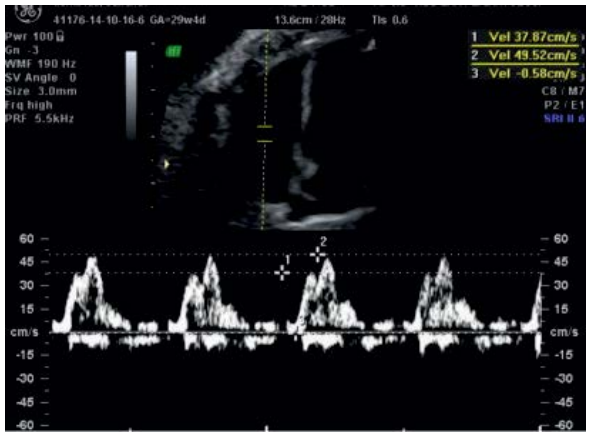


Figure 1. Measurement of E- and A-wave velocity; 1 — E-wave velocity; 2 — A-wave velocity

SGA was characterized as an EFW between 3rd and 9th percentile with normal Doppler indicators.

The obstetric and gynecological anamnesis, maternal age, body mass indexes (BMIs), smoking history, and gestational ages according to CRL of all participating pregnant women were recorded. Umbilical artery Doppler was measured when the fetus was immobile, from the free angle of the umbilical artery to the angle of sound waves less than 20°. PIs were grouped into above and below the 90th percentile according to gestational week. All of them underwent fetal cardiac examination using pulse Doppler and TDI. The fetal heart was evaluated in four apical or basal chamber views. Using pulse Doppler, we measured the early (E) and late (A) transvalvular filling rates (Fig. 1). Atrioventricular flow velocity waveforms were obtained from four apical or basal chamber views. The sample volume was acquired from the tip of the tricuspid valve leaves and measured thrice. In fetal echocardiographic examination, arterial and venous Doppler parameters (umbilical artery, middle cerebral artery, and ductus venous) and RV MPIs were studied in both groups without major anomaly. Measurements were calculated by examining the tricuspid valve annulus for the RV in four apical or basal quadrant images and measuring the peak flow rates. The PVE', PVA', and E'/A' ratio reflected the diastolic function of RV, whereas the PVS' value reflected the systolic function; then, the MPIs were documented. In the analysis of myocardial tissue with tissue Doppler, the tricuspid valve annulus was measured by identifying the duration of the isovolumetric contraction wave (IVC), ejection time (ET), and isovolumetric relaxation time (IVR). The MPI was also calculated. Moreover, the early diastolic annular velocity (E') was measured and recorded. Meanwhile, eight patients with increased umbilical artery PI from fetuses with FGR were compared with 22 patients with normal umbilical artery PI. A further comparison was made with and without a history of FGR.

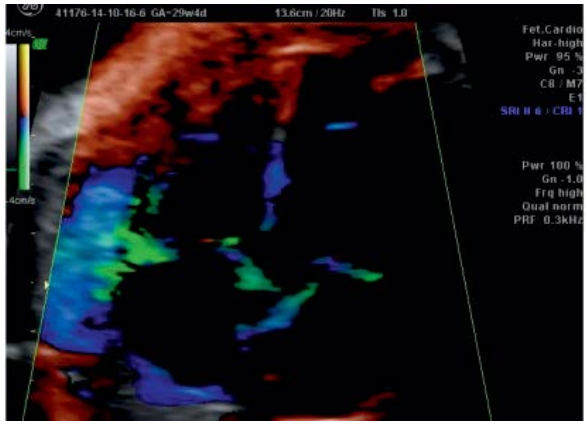


Figure 2. Doppler imaging view

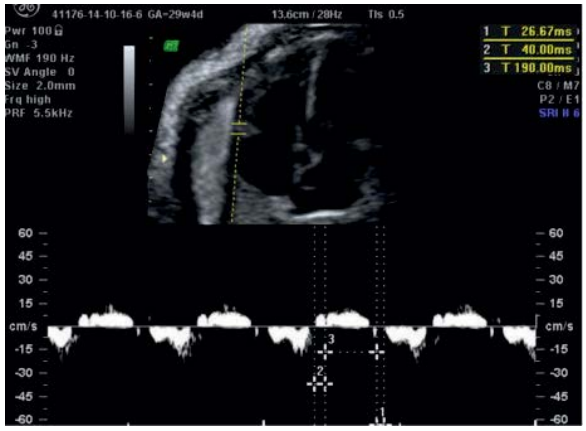


Figure 3. Isovolumetric contraction wave (IVR), isovolumetric relaxation time (IVC) and ET′ measurements; 1 — IVR; 2 — IVC; 3 — ET′ MPI′ is the ratio of the sum of IVR and IVC to ET

TDI was performed in real time using probes with a 2 to 10 MHz frequency. The device settings for pulsed tissue Doppler were as follows: flow rate (sweep speed), 5 cm/s; gain, 10 dB; wall motion filter (WMF), 210 Hz (Fig. 2). At the plane where the tricuspid valve annulus joins the right ventricle in the four apical or basal chamber sections, a sampling interval was maintained between 2 and 4 mm, and myocardial tissue was analyzed using pulse tissue Doppler. The angle between the RV free wall and probe was maintained at < 20°, with no angle correction.

In the trace obtained using pulsed tissue Doppler, the duration of the first positive wave; the IVC, beginning after the late diastolic annular velocity wave (A'); the ET', which is the second positive wave; and the IVR, which is the click between the end of systole and the tricuspid valve, were measured. Each measurement was obtained thrice and then averaged. MPI' was calculated, which indicates the ratio of the sum of the IVC and IVR values to the ET' value (Fig. 3). E' velocity was measured. The ratio of the E value to E' value (E/E') measured using pulse Doppler was calculated (Fig. 4).

Statistical analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences, version 20 (SPSS Inc.). The chi- square and Student's t tests were used for statistical comparisons. $p < 0.05$ was considered statistically significant.

RESULTS

The mean abdominal circumference (AC) percentile measurements of the patients in the study group were significantly lower than those of patients in the control group: 2.47 ± 0.75 and 50.71 ± 22.05, respectively ($p = 0.0001$). Moreover, the EFW percentile measurements were 3.37 ± 0.77 in the study group and 45.82 ± 21.55 in the control group, and the difference was significant ($p = 0.0001$). Furthermore,

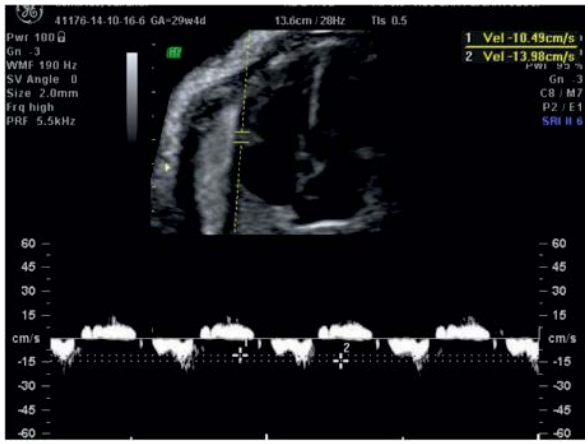


Figure 4. E′ (**1**) and A′ (**2**) wave velocity measurements

E, A, IVC, IVR, ET′, MPI′, E′ and umbilical artery values were statistically significant in the study group (Tab. 1).

The mean gestational period, as determined by the birth week measurement, was significantly lower in patients in the study group (35.8 ± 3.02 weeks) than in the control group (38.61 ± 2.27 weeks; $p = 0.0001$). In addition, the mean birth weight was significantly lower in the study group (2011 ± 701.21 g) than in the control group (3319.07 ± 517.21 g; $p = 0.0001$). The study group showed a higher incidence of NICU hospitalization than the control group [16 (53.33%) vs 3% (6.52%); $p = 0.0001$] (Tab. 2).

The mean gestational period, mean birth weight, mean 1-min Apgar score, and mean 5-min Apgar score of the PI Low group were significantly higher than the PI High group. The duration of NICU stay and the incidence of NICU hospitalization of the PI Low group were significantly lower than the PI High group (Tab. 3).

There was no statistically significant difference between the gestational weeks of the groups ($p > 0.05$). MCA PI and

Table 1. Evaluation of ultrasound variables by group

		Control (n = 46)	Case (n = 30)	p
AC percentiles	Mean ± SD	50.71 ± 22.05	2.47 ± 0.75	[b]0.0001***
	Min–Max (Median)	48.2 (32. 65–69.2)	2 (2–2.925)	
EFW percentiles	Mean ± SD	45.82 ± 21.55	3.37 ± 0.77	[b]0.0001***
	Min–Max (Median)	41 (27.65–58.88)	3 (3–3.35)	
E	Mean ± SD	38.37 ± 6.2	34.08 ± 9.36	[a]0.019
	Min–Max (Median)	38.45 (35. 1–42.9)	36.53 (28.15–40.32)	
A	Mean ± SD	52.51 ± 7.96	45.4 ± 10.94	[a]0.002
	Min–Max (Median)	51.99 (45. 4–57.73)	45.63 (40.14–52.86)	
E/A	Mean ± SD	0.73 ± 0.08	0.74 ± 0.1	[a]0.557
	Min–Max (Median)	0.72 (0. 68–077)	0.73 (0.68–0.83)	
IVC	Mean ± SD	0.037 ± 0.007	0.047 ± 0.012	[b]0.0001***
	Min–Max (Median)	0.037 (0.03–0.04)	0.047 (0.04–0.05)	
IVR	Mean ± SD	0.030 ± 0.007	0.052 ± 0.011	[b]0.0001***
	Min–Max (Median)	0.03 (0.03–0.03)	0.05 (0.04–0.06)	
ET'	Mean ± SD	0.19 ± 0.01	0.16 ± 0.01	[a]0.0001***
	Min–Max (Median)	0.19 (0.18–0.2075)	0.17 (0.16–0.18)	
MPI'	Mean ± SD	0.34 ± 0.07	0.61 ± 0.16	[a]0.0001***
	Min–Max (Median)	0.35 (0.31–0.38)	0.6 (0.5–0.7)	
E'	Mean ± SD	9.52 ± 1.4	8.25 ± 1.19	[a]0.0001**
	Min–Max (Median)	9.44 (8.39–10.49)	8.24 (7.4–9.08)	
E/E'	Mean ± SD	4.12 ± 0.91	4.18 ± 1.18	[a]0.800
	Min–Max (Median)	4.11 (3.38–4.88)	4.24 (3.64–5.14)	
UA PI	Mean ± SD	0.93 ± 0.13	1.3 ± 0.55	[a]0.0001***
	Min–Max (Median)	0.9 (0.84–1.025)	1.07 (0.99–1.475)	
UA PI Percentile	Mean ± SD	35.37 ± 15.13	62.37 ± 25.26	[a]0.0001***
	Min–Max (Median)	32 (24.5–45.75)	57 (45.5–92.25)	

[a]Independent t Test; [b]Mann–Whitney U Test; [c]Fisher's Exact Test; *p < 0.05; **p < 0.01; ***p < 0.0001; SD — standard deviation; AC — abdominal circumference; EFW — estimated fetal weight; E — early diastole rate; A — atrial systole rate; E/A — ratio of early diastole rate (E) to atrial systole rate (A); IVC — isovolumetric contraction wave; IVR — isovolumetric relaxation time; ET' — ejection time; MPI' — myocardial performance index; E' — early diastolic annular velocity; E/E' — the ratio of flow rate (E) to annular rate (E'); PI — pulsatility index; UA — umbilical artery

Table 2. Evaluation of infant variables by group

		Control (n = 46)	Case (n = 30)	p
Sex	Male	25 (54.35)	16 (43.33)	**[c]0.931**
	Female	21 (45.65)	14 (46.67)	
Birth week	Mean ± SD	38.61 ± 2.27	35.8 ± 3.02	**[a]0.0001*** **
	Median (IQR)	39 (38–40)	37 (34–38)	
Birth weight	Mean ± SD	3319.07 ± 517.21	2011 ± 701.21	**[a]0.0001*** **
	Median (IQR)	3400 (2992.5–3585)	2140 (1517.5–2632.5)	
Birth weight percentile	Mean ± SD	54.22 ± 28.49	7.1 ± 7.6	**[b]0.0001*** **
	Median (IQR)	50 (25–75)	3 (3–10)	
Apgar 1st minute	Mean ± SD	8.46 ± 1.03	7.7 ± 1.99	**[a]0.032***
	Median (IQR)	9 (8–9)	8.5 (7.75–9)	
Apgar 5th minute	Mean ± SD	9.76 ± 0.6	9.37 ± 1.07	**[a]0.043***
	Median (IQR)	10 (10–10)	10 (9–10)	

[a]Independent t Test; [b]Mann–Whitney U Test; *p < 0.05; **p < 0.01; ***p < 0.0001; SD — standard deviation; IQR — interquartile range

Table 3. Evaluation of variables according to umbilical artery pulsatility index percentile groups

UA PI > 90th percentile (n = 8)		UA PI percentile		p
		UA PI < 90th percentile (n = 22)		
Birth week	Mean ± SD	32.38 ± 3.07	37.05 ± 1.84	[a]**0.0001**
	Median (IQR)	33 (29.75–34.75)	37 (36–38)	
Birth weight	Mean ± SD	1218.13 ± 415.13	2299.32 ± 543.12	[a]**0.0001**
	Median (IQR)	1227.5 (785–1597.5)	2350 (2027.5–2727.5)	
Apgar 1st minute	Mean ± SD	6.25 ± 2.76	8.23 ± 1.34	[a]**0.013**
	Median (IQR)	8 (3.25–8)	9 (8–9)	
Apgar 5th minute	Mean ± SD	8.5 ± 1.51	9.68 ± 0.65	[a]**0.005**
	Median (IQR)	9 (8.25–9)	10 (9.75–10)	
Duration of NICU Hospitalization	Mean ± SD	52.57 ± 36.51	15.22 ± 11.55	[a]**0.011**
	Median (IQR)	47 (14–72)	13 (7.5–22)	
		n (%)	**n (%)**	
Delivery Method	SVD	7 (87.5)	14 (63.6)	[c]**0.1207**
	C-Section	1 (12.5)	8 (36.4)	
Sex	Male	5 (62.5)	11 (50)	[c]**0.544**
	Female	3 (37.5)	11 (50)	
NICU need	No	1 (12.5)	13 (59.1)	[c]**0.024**
	Yes	7 (87.5)	9 (40.9)	

[a]Independent t Test; [b]Mann–Whitney U Test; [c]Fisher's Exact Test; SD — standard deviation; PI — pulsatility index; UA — umbilical artery; SVD — spontaneous vaginal delivery; C-Section — cesarean section

MCA PI percentile measurements were found to be significantly lower in the study group ($p < 0.01$). CPR and CPR percentile measurements were also found to be statistically significantly lower in the study group ($p < 0.01$). DV PI and DV PI percentile measurements do not show statistically significant difference according to the groups ($p > 0.05$). UT mean PI and UT PI percentile measurements were found to be statistically significantly higher in the study group ($p < 0.01$). UA PI and UA PI percentile measurements were found to be statistically significantly higher in the study group ($p < 0.01$) (Tab. 4).

No statistically significant difference was found between the patients in the study group, Apgar 1 min, Apgar 5 min, Umbilical artery PH and NICU hospitalization periods compared to the CPR percentile groups ($p > 0.05$) (Tab. 5).

No statistically significant difference was found in the study group patients in terms of Apgar 1.min, Apgar 5 min, Umbilical artery PH and NICU hospitalization periods compared to Ut A PI percentile groups ($p > 0.05$) (Tab. 6).

MPI values have been shown to vary slightly during pregnancy and have an average of 0.36 MPI (between 0.28–0.44).

According to this study, the cut off value was calculated as 0.47 and below in the ROC curve. Fetuses whose cut off value was calculated as 0.47 and below were found to be compatible with gestational age at birth. In fetuses with cut off value above 0.47, FGR development sensitivity was 97.83% and specificity was 86.67% (Fig. 5).

DISCUSSION

Fetal cardiac involvement has been found in the late stages with developmental retardation, as supported by various studies; accordingly, the fetal heart is the main organ involved in adaptation mechanisms to placental insufficiency, and fetal development retardation plays a central role in physiopathology [8, 14–21]. The most accepted theory is "fetal metabolic programming," which causes diseases such as obesity, diabetes mellitus, and hypertension associated with cardiovascular diseases and secondarily increases cardiovascular risk [16, 17].

Ductus venosus is the most important indicator of perinatal death, implying the need for birth in preterm FGR [13, 22, 23]. However, MPI, which is a combined indicator of systolic and diastolic function, starts to rise in the early stages of FGR and increases proportionally with weight [14, 24]. Importantly, these parameters are affected by preload and afterload. Tissue Doppler imaging (TDI) reflects myocardial movement better than the conventional echocardiography, because it evaluates cardiac function directly on the myocardium and is also less affected by preload and afterload [25, 26]. Diastolic dysfunction is an earlier sign of cardiac failure. In the evaluation of fetal cardiac function, TDI practices are associated with increased gestational age and myocardial rate changes [27]. In addition, the E/E′ ratio is significantly higher in fetuses with RV heart failure. The TDI technique can measure the relaxation rate of myocardium directly

Table 4. Doppler indices of the groups				
		Control (n = 46)	**Case (n = 30)**	**p**
Gestational Age	Mean ± SD	30.34 ± 1.85	30.8 ± 2.08	[a]0.316
	Min–Max (median)	27–34 (30.4)	26.1–33.9 (31.2)	
MCA PI	Mean ± SD	1.98 ± 0.4	1.39 ± 0.24	[b]**0.001****
	Min–Max (median)	1.3–2.6 (2)	0.9–2 (1.4)	
MCA PI percentile	Mean ± SD	53.7 ± 37.21	7.27 ± 9.46	[b]**0.001****
	Min–Max (median)	1–99 (59)	1–44 (3)	
CPR	Mean ± SD	2.16 ± 0.57	1.16 ± 0.28	[b]**0.001****
	Min–Max (median)	0.9–3.9 (2.1)	0.4–1.5 (1.3)	
CPR percentile	Mean ± SD	63.85 ± 29.48	3.13 ± 2.27	[b]**0.001****
	Min–Max (median)	6–99 (71.5)	1–7 (2)	
	> 5; n (%)	46 (100)	6 (20.0)	[c]**0.001****
	< 5	0	24 (80.0)	
DV PI	Mean ± SD	0.56 ± 0.2	0.57 ± 0.22	[a]0.842
	Min–Max (median)	0.3–1.3 (0.5)	0.3–1.3 (0.5)	
DV PI percentile	Mean ± SD	49.74 ± 33.95	49.77 ± 34.17	[b]0.924
	Min–Max (median)	3–99 (42)	3–99 (41.5)	
Ut A PI	Mean ± SD	0.84 ± 0.11	1.46 ± 0.35	[b]**0.001****
	Min–Max (median)	0.6–1 (0.8)	1–2.4 (1.4)	
Ut A PI percentile	Mean ± SD	62.04 ± 18.57	97.5 ± 2.3	[b]**0.001****
	Min–Max (median)	14–88 (61.5)	91–99 (99)	
	< 95; n (%)	46 (100)	6 (20.0)	[c]**0.001****
	> 95	0	24 (80.0)	
UA PI	Mean ± SD	0.92 ± 0.12	1.3 ± 0.55	[b]**0.001****
	Min–Max (median)	0.7–1.2 (0.9)	0.7–2.9 (1.1)	
UA PI percentile	Mean ± SD	31.43 ± 23.92	62.37 ± 25.26	[b]**0.001****
	Min–Max (median)	1–88 (23)	11–99 (57)	
	< 90; n (%)	46 (100)	22 (73.3)	[c]**0.001****
	> 90	0	8 (26.7)	

[a]Independent t Test; [b]Mann–Whitney U Test; [c]Ki kare test; **p < 0.01; SD — standard deviation; MCA — middle cerebral artery; CPR — cerebroplacental ratio; DV — ductus venosus; Ut A — uterine artery; UA — umbilical artery; PI — pulsatility index

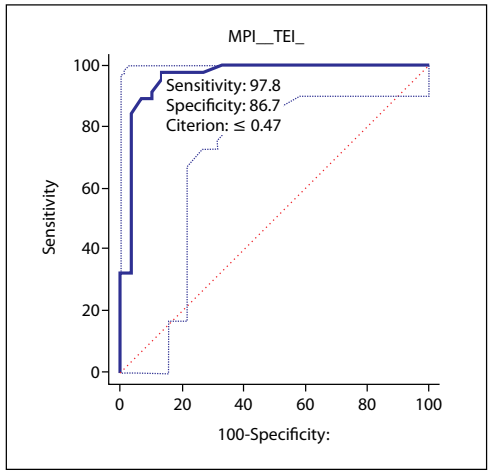
Table 5. Evaluation of neonatal outcomes according to cerebroplacental ratio percentile groups				
		CPR percentile		**p**
		> 5 (n = 6)	**< 5 (n = 24)**	
Apgar 1st minute	Mean ± SD	8.33 ± 1.21	7.54 ± 2.13	**0.432**
	Min–Max (median)	6–9 (9)	2–9 (8)	
Apgar 5th minute	Mean ± SD	9.67 ± 0.82	9.29 ± 1.12	**0.374**
	Min–Max (median)	8–10 (10)	5–10 (10)	
Umbilical Artery pH	Mean ± SD	7.37 ± 0.05	7.37 ± 0.05	**1.000**
	Min–Max (median)	7.3–7.4 (7.4)	7.2–7.5 (7.4)	
Duration of NICU Hospitalization	Mean ± SD	4 ± 9.32	20.04 ± 29.73	**0.230**
	Min–Max (median)	0–23 (0)	0–120 (9.5)	

Mann Whitney U test; SD — standard deviation; CPR — cerebroplacental ratio; NICU — neonatal intensive care unit

Table 6. Evaluation of neonatal outcomes according to uterine artery pulsatility index percentile groups

		Ut A PI percentile		p
		< 95	> 95	
Apgar 1st minute	Mean ± SD	6.5 ± 1.91	7.88 ± 1.97	**0.071**
	Min–Max (median)	4–8 (7)	2–9 (9)	
Apgar 5th minute	Mean ± SD	9 ± 0.82	9.42 ± 1.1	**0.200**
	Min–Max (median)	8–10 (9)	5–10 (10)	
Umbilical Artery pH	Mean ± SD	7.38 ± 0.05	7.37 ± 0.05	**0.791**
	Min–Max (median)	7.3–7.4 (7.4)	7.2–7.5 (7.4)	
Duration of NICU Hospitalization	Mean ± SD	18.75 ± 16.64	16.54 ± 29.09	**0.391**
	Min–Max (median)	0–40 (17.5)	0–120 (0.5)	

Mann Whitney U test; PI — pulsatility index; SD — standard deviation; NICU — neonatal intensive care unit



Area under the ROC curve (AUC)	0.964
Standard error[a]	0.0239
95% confidence interval[b]	0.894 to 0.993
z statistic	19.367
Significance level, p (area = 0.5)	< 0.0001

[a]DeLong et al., 1988
[b]Binomial exact

Youden index	
Youden index J	0.8449
Associated criterion	≤ 0.47
Sensitivity	97.83
Specificity	86.67

Figure 5. Area under the ROC curve (AUC)

and unlike conventional pulse Doppler studies, the diastolic function evaluated by TDI is considerably less affected by the loading state. TDI can also measure the myocardial systole and diastole rates without the limitations of transvalvular flow analysis performed with pulse Doppler, which is affected by high heart rate and preload and afterload conditions. Chan et al. [27] claimed that myocardial velocity determined by tissue Doppler varies with gestational age and constituted reference tables for the myocardial tissue Doppler with the result that diastolic function was evaluated more accurately with TDI in intrauterine fetal evaluation than transvalvular flow rates and concluded diastolic dysfunction may be an early marker of fetal hypoxia in FGR.

FGR progressing with fetal hypoxia and acidemia has been associated with long-term cardiovascular outcomes, leading to perinatal morbidity and even mortality. Conventional Doppler and mitral and tricuspid valve flow analyses are affected by heart rate, preload, and afterload. Considering the increased pulmonary and systemic vascular resistance in FGR, the RV afterload increases, and the cardiac flow shifts from the RV to the LV. These changes in cardiac output and afterload reduce the reliability of conventional Doppler analysis in fetuses with FGR. Despite that, myocardial velocities can be measured by the tissue Doppler technique without being affected by these parameters. Tissue Doppler technique allows for a quantitative evaluation of the myocardial activity. Changes in myocardial rates are a marker for mildly affected systolic and diastolic dysfunctions; thus, cardiac dysfunction can be detected early with tissue Doppler.

In our study, the IVC, IVR, and MPI increased in fetuses with FGR whose umbilical artery Doppler findings were either normal or affected, compared with the control group. In cases wherein the umbilical artery Doppler findings are not disrupted, an increase in MPI supports the view that diastolic dysfunction may be an early marker of hypoxia in fetuses with FGR. The prolongation of the isovolumetric contraction period in the fetal heart was associated with systolic dysfunction, whereas IVR prolongation was associated with diastolic dysfunction [14].

Similarly, decreased myocardial rates are early markers of systolic and diastolic dysfunctions. In our study, we detected a decrease in myocardial rates in fetuses with FGR. Ventricular filling rates determined by tissue Doppler technique were significantly lower in the study group than in the control group, supporting the presence of diastolic dysfunction in fetuses with FGR. However, in using the conventional Doppler, the E/A ratio used in detecting diastolic dysfunction was similar in both groups. In some studies, the E/A ratio determined by conventional Doppler can only be detected in severely affected fetuses with FGR having a reverse flow in the umbilical artery [7]. However, in our study, we found diastolic dysfunction in fetuses with FGR having normal umbilical artery Doppler findings by detecting an increase in IVR and a decrease in ventricular filling rates using the tissue Doppler technique.

Considering that TDI is considerably more sensitive than cardiac sonographic evaluation using pulse Doppler, tissue Doppler parameters allow to determine cardiac dysfunctions at a relatively earlier stage. Myocardial evaluation with TDI in fetuses with FGR can be used in clinical practice noninvasively. When we compared the cases with normal and abnormal umbilical artery Doppler findings, we could not find a difference between the groups in terms of parameters predicting cardiac systolic and diastolic functions. This situation can be explained by the view wherein in the early stages of hypoxia, the cardiac function was affected extending throughout various periods of fetal exposure. It can also be explained by the limited number of cases with impaired umbilical artery Doppler parameters. Our current study clearly shows that in fetuses with FGR, systolic and diastolic function changes were detected more sensitively by TDI than by pulse Doppler. Tissue Doppler parameters are important because they allow early monitoring by determining the cardiac dysfunction at an early stage. Another advantage is that through TDI, the findings of systolic and diastolic cardiac dysfunction in fetuses can be determined; such findings cannot be detected by pulse Doppler. Generally, the LV in the fetus is responsible for coronary circulation and cranium, whereas the RV is the main distributor of the lower trunk, lungs, and placenta. Considering this distribution, the afterload is different in both ventricles [10]. In this study, we used tricuspid annulus and tricuspid flow measurements to evaluate the RV, which is dominant in fetal circulation.

In addition, RV function evaluation is more accurate because myocardial velocity is evaluated only on the long axis in which the movement of the longitudinal myocardial fibers can be measured; meanwhile, the LV function depends on the lengthening and shortening of circumferential and longitudinal fibers at the appropriate degree and timing. However, the orientation of myocardial fibers of the RV is different and tends to contract along its long axis compared to the short axis. Therefore, the evaluation of systolic function on the long axis allows the LV function to appear less than expected and the RV function to be better evaluated. The anatomical alignment of myocardial fibers highly influences the systolic myocardial velocities of the RV and LV walls [10]. The most important limitation of the transvalvular flow rate is the indirect evaluation of diastolic function by measuring the flow of blood passing through the AV valves, which are also affected by fetal blood volume and vascular resistance, namely, preload and afterload. Direct measurement of myocardial relaxation rate in TDI is a more sensitive indicator of diastolic function. More importantly, TDI is less dependent on preload and afterload.

The MPI value measured from the tricuspid annulus in the study group was significantly higher than that in the control group. The MPI in FGR was previously evaluated in several studies [10, 28–30], and parallel to our study, it was found to be high in fetuses with FGR. In addition, increased right MPI values were detected in a study evaluating fetuses with heart failure. The E/E' ratio in early diastole is also closely related to filling pressures [10], and it is significantly higher in fetuses with RV heart failure. In our study, when comparing the E/E' ratio, no significant difference was found between the case and the control group, further supporting the view that other TDI parameters are impaired before heart failure develops and that TDI is a sensitive tool in evaluating cardiac function. When TDI measurements (IVC, IVR, ET', MPI, and E') were examined in pregnant women in different gestational weeks, no significant relationship was found between the gestational week and TDI values.

When the umbilical artery Doppler pulsatility index is> 95th percentile, CPR is very valuable in predicting adverse neonatal outcome.

However, in our study there are only 8 patients have seen UA PI > 90^{th} percentile. Hence, FGR was defined as an EFW < 10^{th} percentile, CPR < 5^{th} percentile and mean UtA-PI > 95^{th} percentile.

Abnormal CPR increases the level of abnormal fetal growth rate, significantly increased fetal distress rates at birth, relatively lower umbilical cord pH, and the need for neonatal intensive care unit support for fetuses with FGR [31]. An additional finding of abnormal CPR in such cases adds to adverse neonatal outcomes, umbilical artery end-diastolic flow deficiency, and signs of reversal.

If the end-diastolic flow does not increase during pregnancy and a small uterine artery notch is observed at the end of systole, the development of FGR for the fetus will have high risks. [32]. There may be no diastolic blood flow and reversal with excessive placental dysfunction. In our study, absent end-diastolic flow (AEDF) was observed in only 4 patients in the study group. No reversed end-diastolic flow (REDF) was observed.

With this study, we concluded that it is possible to achieve good perinatal outcomes without REDF.

The study group also had significantly higher umbilical artery PI and umbilical artery PI percentiles than the control group. Furthermore, birth weight percentiles and Apgar 1st- and 5th-minute measurements were statistically significantly lower in the study group. When NICU was compared in terms of duration of stay, no significant difference was found between the two groups, but the need for NICU hospitalization was significantly higher in the study group. Considering the limited access to the fetus, physicians find the evaluation of fetal well-being difficult.

Fetal diastolic dysfunction is an early marker of fetal hypoxia. Therefore, evaluation of diastolic function using TDI in any abnormal pregnancy should be the modality in determining fetal well-being. TDI is useful in early fetal delivery, determining the time of intrauterine interventions and/or close follow-up for such cases [27–30].

CONCLUSIONS

The fetal heart is the main organ involved in placental hypoperfusion, and hypoxia adaptation mechanisms, which play an important role in FGR pathogenesis, and early placental changes are not likely to affect the fetus. In our study, we detected the presence of cardiac systolic and diastolic dysfunctions in all fetuses who suffered from FGR with and without umbilical artery Doppler findings by using the tissue Doppler technique. Assessment of cardiac function using the tissue Doppler is applicable during the intrauterine period, repeatable, and useful in various fetal conditions. This technique is an indicator of early fetal adaptation to the fetal pathophysiological process and is more sensitive in predicting pregnancy outcomes and long-term cardiovascular outcomes in fetuses with FGR than the conventional Doppler. The ability to detect preclinical cardiac dysfunction is the superior aspect of the technique. However, in terms of its limitations, only clinicians experienced in fetal echocardiography can perform it, and its application can be challenging. TDI is a more sensitive tool than pulse Doppler in cardiac evaluation; thus, tissue Doppler parameters can determine cardiac dysfunction at an early stage, allowing for early monitoring. Myocardial evaluation using TDI should be used as a noninvasive method in fetuses with FGR.

Ethical approval

The study was approved by the local ethics committee (date: December 1, 2016; approval number: 2016/2/10).

Research involving human participants and/or animal

This article does not contain any studies with animals performed by any of the authors.

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Conflict of interest

The authors report no conflict of interest.

Informed Consent

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

REFERENCES

1. Lausman A, Kingdom J, Gagnon R, et al. Intrauterine Growth Restriction: Screening, Diagnosis, and Management. J Obstet Gynaecol Can. 2013; 35(8): 741–748, doi: 10.1016/s1701-2163(15)30865-3.
2. ACOG Practice bulletin no. 134: fetal growth restriction. Obstet Gynecol. 2013; 121(5): 1122–1133, doi: 10.1097/01.AOG.0000429658.85846.f9, indexed in Pubmed: 23635765.
3. Barker DJ, Winter PD, Osmond C, et al. Weight in infancy and death from ischaemic heart disease. Lancet. 1989; 2(8663): 577–580, doi: 10.1016/s0140-6736(89)90710-1, indexed in Pubmed: 2570282.
4. Barker DJ, Osmond C, Simmonds SJ, et al. The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life. BMJ. 1993; 306(6875): 422–426, doi: 10.1136/bmj.306.6875.422, indexed in Pubmed: 8461722.
5. Salafia CM, Charles AK, Maas EM. Placenta and fetal growth restriction. Clin Obstet Gynecol. 2006; 49(2): 236–256, doi: 10.1097/00003081-200606000-00007, indexed in Pubmed: 16721104.
6. Haram K, Søfteland E, Bukowski R, et al. Intrauterine growth restriction. Int J Gynaecol Obstet. 2006; 93(1): 5–12, doi: 10.1016/j.ijgo.2005.11.011, indexed in Pubmed: 16469319.
7. Figueras F, Puerto B, Martinez JM, et al. Cardiac function monitoring of fetuses with growth restriction. Eur J Obstet Gynecol Reprod Biol. 2003; 110(2): 159–163, doi: 10.1016/s0301-2115(03)00123-4, indexed in Pubmed: 12969576.
8. Girsen A, Ala-Kopsala M, Mäkikallio K, et al. Cardiovascular hemodynamics and umbilical artery N-terminal peptide of proB-type natriuretic peptide in human fetuses with growth restriction. Ultrasound Obstet Gynecol. 2007; 29(3): 296–303, doi: 10.1002/uog.3934, indexed in Pubmed: 17323307.
9. Mäkikallio K, Vuolteenaho O, Jouppila P, et al. Ultrasonographic and biochemical markers of human fetal cardiac dysfunction in placental insufficiency. Circulation. 2002; 105(17): 2058–2063, doi: 10.1161/01.cir.0000015505.24187.fa, indexed in Pubmed: 11980685.
10. Watanabe S, Hashimoto I, Saito K, et al. Characterization of ventricular myocardial performance in the fetus by tissue Doppler imaging. Circ J. 2009; 73(5): 943–947, doi: 10.1253/circj.cj-08-0529, indexed in Pubmed: 19276611.
11. DeVore GR. Assessing fetal cardiac ventricular function. Semin Fetal Neonatal Med. 2005; 10(6): 515–541, doi: 10.1016/j.siny.2005.08.009, indexed in Pubmed: 16257825.
12. Hernandez-Andrade E, López-Tenorio J, Figueroa-Diesel H, et al. A modified myocardial performance (Tei) index based on the use of valve clicks improves reproducibility of fetal left cardiac function assessment. Ultrasound Obstet Gynecol. 2005; 26(3): 227–232, doi: 10.1002/uog.1959, indexed in Pubmed: 16116562.
13. Bilardo CM, Wolf H, Stigter RH, et al. Relationship between monitoring parameters and perinatal outcome in severe, early intrauterine growth restriction. Ultrasound Obstet Gynecol. 2004; 23(2): 119–125, doi: 10.1002/uog.965, indexed in Pubmed: 14770389.
14. Crispi F, Hernandez-Andrade E, Pelsers MM, et al. Cardiac dysfunction and cell damage across clinical stages of severity in growth-restricted fetuses. Am J Obstet Gynecol. 2008; 199(3): 254.e1–254.e8, doi: 10.1016/j.ajog.2008.06.056, indexed in Pubmed: 18771973.
15. Chaiworapongsa T, Espinoza J, Yoshimatsu J, et al. Subclinical myocardial injury in small-for-gestational-age neonates. J Matern Fetal Neonatal Med. 2002; 11(6): 385–390, doi: 10.1080/jmf.11.6.385.390, indexed in Pubmed: 12389653.
16. Seckl JR, Meaney MJ. Glucocorticoid "programming" and PTSD risk. Ann N Y Acad Sci. 2006; 1071: 351–378, doi: 10.1196/annals.1364.027, indexed in Pubmed: 16891583.

17. Vickers MH, Gluckman PD, Coveny AH, et al. Neonatal leptin treatment reverses developmental programming. Endocrinology. 2005; 146(10): 4211–4216, doi: 10.1210/en.2005-0581, indexed in Pubmed: 16020474.
18. Crispi F, Bijnens B, Figueras F, et al. Fetal growth restriction results in remodeled and less efficient hearts in children. Circulation. 2010; 121(22): 2427–2436, doi: 10.1161/CIRCULATIONAHA.110.937995, indexed in Pubmed: 20497977.
19. Kiserud T, Ebbing C, Kessler J, et al. Fetal cardiac output, distribution to the placenta and impact of placental compromise. Ultrasound Obstet Gynecol. 2006; 28(2): 126–136, doi: 10.1002/uog.2832, indexed in Pubmed: 16826560.
20. Tsyvian P, Malkin K, Wladimiroff JW. Assessment of fetal left cardiac isovolumic relaxation time in appropriate and small-for-gestational-age fetuses. Ultrasound Med Biol. 1995; 21(6): 739–743, doi: 10.1016/0301-5629(95)00016-k, indexed in Pubmed: 8571461.
21. Tsyvian P, Malkin K, Artemieva O, et al. Cardiac ventricular performance in the appropriate- for-gestational age and small-for-gestational age fetus: relation to regional cardiac non-uniformity and peripheral resistance. Ultrasound Obstet Gynecol. 2002; 20(1): 35–41, doi: 10.1046/j.1469-0705.2002.00734.x, indexed in Pubmed: 12100415.
22. Baschat AA, Cosmi E, Bilardo CM, et al. Predictors of neonatal outcome in early-onset placental dysfunction. Obstet Gynecol. 2007; 109(2 Pt 1): 253–261, doi: 10.1097/01.AOG.0000253215.79121.75, indexed in Pubmed: 17267821.
23. Schwarze A, Gembruch U, Krapp M, et al. Qualitative venous Doppler flow waveform analysis in preterm intrauterine growth-restricted fetuses with ARED flow in the umbilical artery--correlation with short-term outcome. Ultrasound Obstet Gynecol. 2005; 25(6): 573–579, doi: 10.1002/uog.1914, indexed in Pubmed: 15912468.
24. Ichizuka K, Matsuoka R, Hasegawa J, et al. The Tei index for evaluation of fetal myocardial performance in sick fetuses. Early Hum Dev. 2005; 81(3): 273–279, doi: 10.1016/j.earlhumdev.2004.07.003, indexed in Pubmed: 15814209.
25. Berkley E, Chauhan SP, Abuhamad A. Society for Maternal-Fetal Medicine Publications Committee. Doppler assessment of the fetus with intrauterine growth restriction. Am J Obstet Gynecol. 2012; 206(4): 300–308, doi: 10.1016/j.ajog.2012.01.022, indexed in Pubmed: 22464066.
26. Ho CY, Solomon SD. A clinician's guide to tissue Doppler imaging. Circulation. 2006; 113(10): e396–e398, doi: 10.1161/CIRCULATIONAHA.105.579268, indexed in Pubmed: 16534017.
27. Chan LYs, Fok WY, Wong JTh, et al. Reference charts of gestation-specific tissue Doppler imaging indices of systolic and diastolic functions in the normal fetal heart. Am Heart J. 2005; 150(4): 750–755, doi: 10.1016/j.ahj.2004.12.028, indexed in Pubmed: 16209978.
28. Kaya B, Tayyar A, Açar DK, et al. Comparison of fetal cardiac functions between small-for-gestational age fetuses and late-onset growth-restricted fetuses. J Perinat Med. 2019; 47(8): 879–884, doi: 10.1515/jpm-2019-0206, indexed in Pubmed: 31393834.
29. Alici Davutoglu E, Ozel A, Oztunc F, et al. Modified myocardial performance index and its prognostic significance for adverse perinatal outcome in early and late onset fetal growth restriction. J Matern Fetal Neonatal Med. 2020; 33(2): 277–282, doi: 10.1080/14767058.2018.1489534, indexed in Pubmed: 30033784.
30. Pérez-Cruz M, Cruz-Lemini M, Fernández MT, et al. Fetal cardiac function in late-onset intrauterine growth restriction vs small-for-gestational age, as defined by estimated fetal weight, cerebroplacental ratio and uterine artery Doppler. Ultrasound Obstet Gynecol. 2015; 46(4): 465–471, doi: 10.1002/uog.14930, indexed in Pubmed: 26112274.
31. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. Fetal Diagn Ther. 2014; 36(2): 86–98, doi: 10.1159/000357592, indexed in Pubmed: 24457811.
32. Schulman H, Fleischer A, Farmakides G, et al. Development of uterine artery compliance in pregnancy as detected by Doppler ultrasound. Am J Obstet Gynecol. 1986; 155(5): 1031–1036, doi: 10.1016/0002-9378(86)90340-6.