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Longitudinal Arterial and Venous Doppler Changes in Late-Onset Fetal Growth Restriction

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ABSTRACT

OBJECTIVE: This study aimed to evaluate longitudinal changes in arterial and venous Doppler parameters in late-onset fetal growth restriction and to investigate their association with NICU admission.

STUDY DESIGN: This prospective cohort study included singleton pregnancies diagnosed with LO-FGR at or beyond 32 weeks of gestation and followed at a tertiary perinatology center between August 2025 and February 2026. Serial Doppler assessments included measurements of the umbilical artery (UA), the middle cerebral artery (MCA), and the ductus venosus (DV). DV waveform-derived parameters, including pulsatility index for veins (PIV), preload index (PLI), peak velocity index for veins (PVIV), S/a ratio, and time-averaged maximum velocity (TAmax), were evaluated together with arterial Doppler indices and the cerebroplacental ratio (CPR). Neonatal intensive care unit (NICU) admission was used as the primary outcome.

RESULTS: Fifty-two pregnancies with LO-FGR were included. Longitudinal evaluation showed a significant decrease in MCA PI between the first and second examinations (p=0.026). In contrast, no significant changes were observed in DV Doppler parameters, including DV PIV, PLI, PVIV, S/a ratio, and TAmax. UA Doppler indices and CPR also remained stable over time. NICU admission occurred in 21.2% of neonates. Longitudinal changes in DV PIV and CPR were not significantly associated with NICU admission. In multivariable analysis, weekly change in CPR showed a borderline association with NICU admission (adjusted OR 0.04, 95% CI 0.002–1.08, p=0.056).

CONCLUSION: In LO-FGR, arterial Doppler parameters, particularly MCA PI, may show longitudinal change, whereas venous Doppler parameters remained relatively stable. These findings suggest that fetal adaptation in LO-FGR primarily manifests in the arterial circulation.

Keywords: Cerebroplacental ratio; Doppler ultrasonography; Ductus venosus; Late-onset fetal growth restriction; Perinatal outcome

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Introduction

Fetal growth restriction (FGR) is a major obstetric complication associated with increased perinatal morbidity and mortality (1). In most cases, FGR is associated with placental insufficiency, which leads to impaired placental perfusion and altered fetal circulation (2). Fetuses affected by FGR are at increased risk of adverse perinatal outcomes, including preterm birth, neonatal intensive care unit (NICU) admission, and long-term neurodevelopmental impairment (3). Therefore, close antenatal surveillance is essential to identify fetal deterioration and to optimize the timing of delivery.

Doppler ultrasonography has become an essential tool in the surveillance of pregnancies complicated by FGR, as it allows noninvasive evaluation of fetal and placental hemodynamics. Progressive placental insufficiency leads to characteristic changes in fetal circulation. Increased placental resistance may first be reflected by abnormalities in the umbilical artery (UA) Doppler indices (4). As fetal hypoxemia progresses, redistribution of blood flow toward the brain may

occur, resulting in a decrease in the middle cerebral artery pulsatility index (MCA PI) (5). In more advanced stages, Doppler abnormalities may also develop in the venous circulation, particularly in the ductus venosus (DV), reflecting increasing cardiac load and fetal compromise (6).

Early-onset and late-onset forms of FGR (EO-FGR and LO-FGR) represent distinct clinical and pathophysiological phenotypes. EO-FGR is typically associated with severe placental dysfunction resulting from abnormal placentation and impaired remodeling of the spiral arteries (2). This leads to marked increases in placental vascular resistance and more frequent abnormalities in UA Doppler indices, often followed by progressive deterioration in venous Doppler parameters during the course of the disease (7). In contrast, LO-FGR is usually associated with milder placental insufficiency that develops later in pregnancy (8). In these cases, UA Doppler findings may remain within normal limits, and fetal adaptation is more commonly reflected by redistribution of blood flow to the brain and changes in the cerebroplacental ratio (CPR) (9).

Although arterial Doppler parameters, such as MCA PI and CPR, have been widely investigated in the surveillance of LO-FGR, data on venous Doppler changes in this group remain limited (10). Most previous studies have primarily focused on DV pulsatility index for veins (DV PIV), while other DV waveform-derived parameters have been less frequently evaluated (11). In addition, the relationship between longitudinal changes in these venous Doppler parameters and perinatal outcomes has not been clearly established, particularly in comparison with arterial Doppler parameters (12).

Therefore, the aim of this study was to evaluate longitudinal changes in both arterial and venous Doppler parameters in pregnancies complicated by LO-FGR and to investigate their association with perinatal outcomes.

Materials and Methods

Study Design and Setting: This prospective cohort study was conducted at a tertiary perinatology center between August 2025 and February 2026. The study protocol was approved by the local Non-Interventional Ethics Committee (approval number: 2025/337) and was conducted in accordance with the ethical principles of the Declaration of Helsinki (as revised in 2024). The study was prospectively registered at ClinicalTrials.gov (Identifier: NCT07193381). Written informed consent was obtained from all participants before enrollment.

Study Population and Follow-up Protocol: Pregnant women diagnosed with FGR and followed in our perinatology unit were prospectively enrolled. FGR was defined as an estimated fetal weight (EFW) and/or abdominal circumference (AC) below the 10th percentile for gestational age. However, according to the Delphi consensus and the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines, fetal size alone is not sufficient to define fetal growth restriction, and additional parameters, particularly Doppler findings, are recommended to distinguish true FGR from constitutionally small fetuses (1,13). Only LO-FGR cases were included, and late-onset disease was defined as diagnosis at or beyond 32 weeks of gestation. EO-FGR cases diagnosed before 32 weeks were excluded to ensure a homogeneous cohort focused on late placental insufficiency. Gestational age was determined according to first-trimester crown–rump length (CRL) measurements. Only singleton pregnancies were included. Cases with major fetal structural anomalies, known chromosomal or genetic abnormalities, incomplete neonatal outcome data due to delivery at an external center, or withdrawal of maternal consent during follow-up were excluded from the final analysis.

After the diagnosis of FGR, each participant was followed longitudinally until delivery. Routine surveillance was scheduled every week. In accordance with the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) recommendations for the monitoring of late-onset fetal growth restriction, follow-up frequency was individualized based on Doppler findings and amniotic fluid status. Surveillance was intensified to twice weekly when there was evidence of progressive placental insufficiency, defined as umbilical artery pulsatility index (UA PI) above the 95th percentile for gestational age, CPR below the 5th percentile, DV waveform abnormalities including absent or reversed a-wave, and/or reduced amniotic fluid volume (amniotic fluid index (AFI) <5 cm or deepest vertical pocket (DVP) <2 cm). Clinical decision-making was based not only on isolated abnormal values but also on the overall trajectory of Doppler changes over time. This approach reflects routine clinical practice, where longitudinal trends are considered more informative than single measurements. Inclusion in the final analysis required a minimum of two serial DV Doppler assessments obtained at different gestational weeks, allowing evaluation of temporal changes within the same fetus. For statistical analysis, two time points were used to ensure standardized within-subject comparisons across all participants.

At the initial evaluation, a comprehensive Doppler assessment was performed, including bilateral uterine artery pulsatility index (UtA PI), UA PI, middle cerebral artery pulsatility index (MCA PI), and DV Doppler parameters. UtA Doppler was assessed exclusively at the baseline visit as part of the initial placental evaluation, whereas UA PI, MCA PI, and DV Doppler measurements were repeated longitudinally during follow-up. CPR was calculated as the ratio of MCA PI to UA PI. In addition, fetal biometric parameters, EFW and percentile values, AFI and DVP measurements were documented at each visit. Oligohydramnios was defined as AFI < 5 cm and/or DVP <2 cm.

Ultrasound and Doppler Assessment: All ultrasonographic examinations were performed using a Voluson E8 ultrasound system (GE Healthcare, Zipf, Austria) equipped with a 2-9 MHz convex transducer. Standard fetal biometric parameters, including biparietal diameter (BPD), head circumference (HC), AC, femur length (FL), and EFW, were obtained at each visit. Doppler assessments of the UA, MCA, and DV were performed during periods of minimal fetal activity and normal fetal heart rate.

DV was identified in a sagittal or oblique plane of the fetal abdomen using color Doppler imaging, demonstrating the characteristic aliasing pattern at the inlet. The pulsed Doppler sample volume (0.5-1.0 mm) was positioned at the isthmic region where the accelerated jet flow was visualized. The insonation angle was maintained below 30°, and only technically adequate recordings containing at least three consecutive cardiac cycles were accepted for analysis (Figure 1). Measurements were obtained in real time during the examination and prospectively recorded.

From the DV waveform, peak systolic velocity (S), diastolic velocity (D), atrial contraction velocity (a-wave), Time-Averaged maximum velocity (TAmax), S/a ratio, pulsatility index for veins (PIV), peak velocity index for veins (PVIV), and preload index (PLI) were recorded. The a-wave was classified as positive, absent/isosystolic, or reversed.

Arterial Doppler parameters included UA systolic/diastolic ratio (S/D) and PI, MCA PI and peak systolic velocity (PSV), as well as bilateral UtA PI (right and left) measured according to standard Doppler principles. All examinations were performed by the same experienced perinatology specialist to minimize measurement variability.

Outcomes: The primary outcome of the study was NICU admission following delivery. Given the multifactorial nature of neonatal morbidity in LO-FGR, a composite adverse neonatal outcome (CANO) variable was constructed to provide a broader assessment of neonatal compromise. CANO was considered present if at least one of the following occurred: NICU admission, 5-minute Apgar score <7, development of respiratory distress syndrome (RDS), or preterm birth before 37+0 weeks of gestation. RDS was diagnosed by the neonatology team based on compatible clinical findings requiring respiratory support with or without radiographic confirmation. However, due to the limited sample size and the low number of adverse events, analyses based on the composite outcome were not performed, and NICU admission was used as the primary outcome variable in the final analysis.

Secondary outcomes included gestational age at delivery, birth weight and birth weight percentile, development of oligohydramnios during follow-up, 1-minute and 5-minute Apgar scores, and umbilical cord arterial pH.

Neonatal outcome data were obtained from hospital electronic medical records and neonatal unit charts after delivery. All perinatal and neonatal variables were prospectively recorded in the institutional database and subsequently extracted for analysis. Outcome assessment was performed independently of the Doppler measurements.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics software (version 26.0; IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Shapiro-Wilk test and visual inspection of histograms. Normally distributed continuous variables were presented as mean ± standard deviation (SD), whereas non-normally dis-

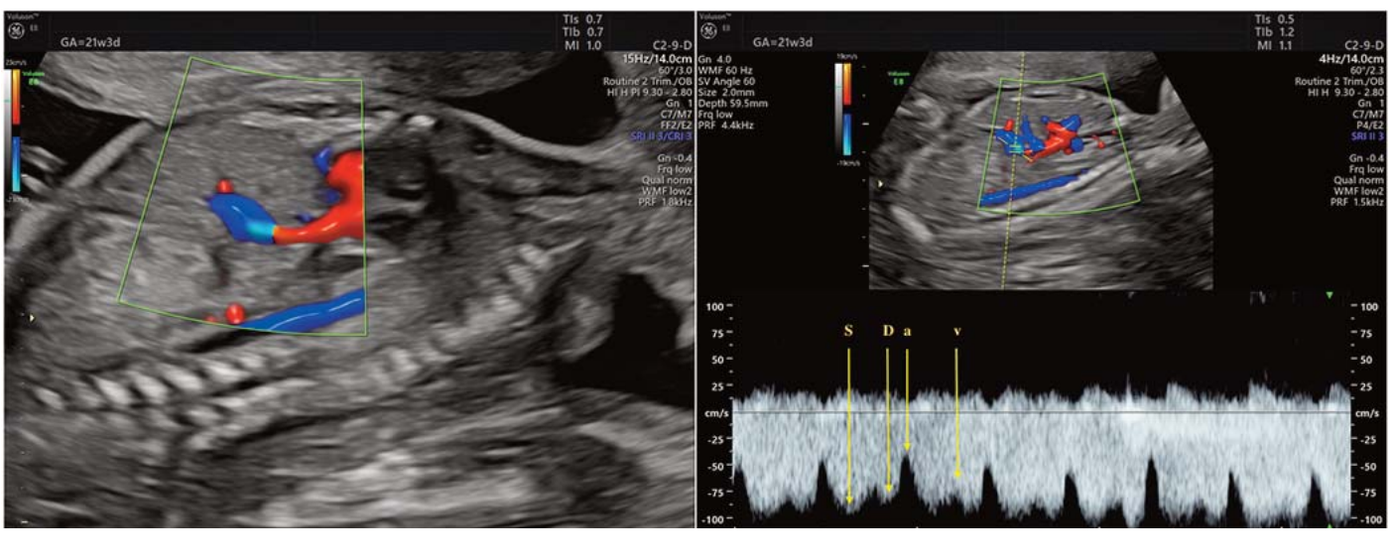

Figure 1: *Ultrasound images demonstrating ductus venosus Doppler assessment at 21 weeks and 3 days of gestation.*

The left panel shows color Doppler imaging of the ductus venosus, which connects the umbilical vein to the inferior vena cava. The right panel demonstrates the spectral Doppler waveform of the ductus venosus with the characteristic S (systolic), D (early diastolic), a (atrial contraction), and v waves indicated. These waveforms reflect the phasic changes in the fetal cardiac cycle and are used to evaluate fetal cardiovascular hemodynamics.

tributed variables were expressed as median (minimum–maximum). Categorical variables were summarized as numbers and percentages. For longitudinal evaluation, changes between the first and second Doppler assessments were calculated as the absolute difference (Δ = visit 2 - visit 1). Percentage change (%Δ) and weekly change (Δ per week) were also calculated by normalizing the absolute change to the time interval between visits. Comparisons between groups with and without NICU admission were performed using the independent samples t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Categorical variables were compared using Fisher's exact test. The relationship between longitudinal changes in DV PIV (ΔDV PIV) and CPR (ΔCPR) was assessed using Spearman correlation analysis. To identify independent predictors of NICU admission, multivariable logistic regression analysis was performed. Variables considered clinically relevant and those showing potential association in univariable analyses were included in the model. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated. A two-sided p-value <0.05 was considered statistically significant.

Results

A total of 52 pregnancies complicated by LO-FGR were included in the final analysis. The mean maternal age was 26.33 ± 4.69 years, and the mean BMI was 27.40 ± 5.10 kg/m². Smoking during pregnancy was reported in 22.0% of available cases, and 5.8% of pregnancies were conceived via in vitro fertilization. The remaining baseline demographic and obstetric characteristics of the study population are presented in Table I.

Table I: *Baseline demographic and obstetric characteristics of the study population (n = 52)*

Maternal age, years (mean ± SD)	26.33 ± 4.69
Gravidity, median (min-max)	2 (1-10)
Parity, median (min-max)	0 (0-4)
Living children, median (min-max)	0 (0-3)
History of abortion, n (%)	9 (17.3)
Smoking during pregnancy, n (%)	11 (22.0)*
IVF pregnancy, n (%)	3 (5.8)
BMI (kg/m²), mean ± SD	27.40 ± 5.10

Values are presented as mean ± SD, median (min-max), or number (%), as appropriate.
**Percentages calculated among available cases (n=50).*
BMI: Body mass index, IVF: In vitro fertilization

At diagnosis, the median gestational age was 34 (32-37) weeks. The median AC percentile was 1.7 (1.0-17.5), and the median HC percentile was 8.2 (1.0-71.9). The mean EFW percentile was 6.89 ± 4.60. EFW was below the 3rd percentile in 21.2% of fetuses and below the 10th percentile in 82.7%, while AC was below the 3rd percentile in 57.7% and below the 10th percentile in 96.2% of cases. Detailed fetal biometric findings are summarized in Table II.

Table II: *Fetal biometric characteristics of the study population (n=52)*

GA at diagnosis (weeks), median (min-max)	34 (32-37)
AC percentile, median (min-max)	1.7 (1.0-17.5)
HC percentile, median (min-max)	8.2 (1.0-71.9)
EFW percentile, mean ± SD	6.89 ± 4.60
HC/AC ratio, mean ± SD	1.11 ± 0.05
EFW <3rd percentile	11 (21.2)
EFW <10th percentile	43 (82.7)
AC <3rd percentile	30 (57.7)
AC <10th percentile	50 (96.2)

Values are presented as mean ± SD, median (min-max), or number (%), as appropriate.
GA: Gestational age, AC: Abdominal circumference, HC: Head circumference, EFW: Estimated fetal weight

Baseline Doppler findings are summarized in Table III. The median UtA PI was 0.32 (0.00-1.29). The mean UA PI was 1.07 ± 0.43, and the mean UA S/D ratio was 3.03 ± 1.08. The median MCA PI was 1.85 (1.46-3.39), and the median CPR was 1.67 (1.09-5.03). Regarding venous Doppler parameters, the mean DV PIV was 0.55 ± 0.23, PLI was 0.45 ± 0.22, and PVIV was 0.52 ± 0.36.

Table III: *Doppler characteristics of the study population (n= 52)*

Mean uterine artery PI, median (min-max)	0.32 (0.00-1.29)
Umbilical artery PI, mean ± SD	1.07 ± 0.43
Umbilical artery S/D ratio, mean ± SD	3.03 ± 1.08
MCA PI, median (min-max)	1.85 (1.46-3.39)
MCA PSV (cm/s), mean ± SD	52.99 ± 19.69
Cerebroplacental ratio (CPR), median (min-max)	1.67 (1.09-5.03)
Ductus venosus PIV, mean ± SD	0.55 ± 0.23
Ductus venosus PLI, mean ± SD	0.45 ± 0.22
Ductus venosus PVIV, mean ± SD	0.52 ± 0.36
Ductus venosus S/a ratio, median (min-max)	1.88(1.25-4.59)
Ductus venosus TAmax (cm/s), median (min-max)	52.29 (29.18-118.05)

Values are presented as mean ± SD, median (min–max), or number (%), as appropriate.
PI: Pulsatility index, S/D: Systolic/diastolic ratio, MCA: Middle cerebral artery, PSV: Peak systolic velocity, CPR: Cerebroplacental ratio, DV: Ductus venosus, PIV: Pulsatility index for veins, PLI: Preload index, PVIV: Peak velocity index for veins, TAmax: Time-averaged maximum velocity

Longitudinal Doppler evaluation between the first and second assessments showed a significant decrease in MCA PI over time (p=0.026). In contrast, no significant longitudinal changes were observed in any of the examined DV Doppler parameters, including DV PIV, PLI, PVIV, S/a ratio, and TAmax. Similarly, CPR, UA PI, UA S/D ratio, and MCA PSV did not change significantly between visits. Detailed longitudinal Doppler changes are shown in Table IV.

Regarding perinatal outcomes, the median gestational age at delivery was 37 (34-41) weeks, and the median birth weight was 2390 (1650-3720) g. Preterm birth before 37 weeks oc-

Table IV: Longitudinal changes in Doppler parameters between visit 1 and visit 2

GA at visit (weeks)	34 (32-37)	36 (34-39)	3 (2-4)	-	-	<0.001
DV PIV	0.54±0.26	0.61±0.46	0.09±0.52	18.31±64.1	0.01±0.32	0.230
DV PLI	0.44±0.17	0.47±0.22	0.04±0.26	11.32±50.1	-0.003±0.23	0.314
DV PVIV	0.48(0.20-1.64)	0.51 (0.18-1.53)	0.04 (-0.74-0.57)	3.73 (-74.65-190.91)	0.01 (-0.93-0.74)	0.240
DV S/a	1.79 (1.25-5.52)	1.76 (1.22-16.35)	0.06 (-3.25-10.83)	2.27 (-70.81-196.20)	0.02 (-2.82-3.43)	0.139
DV TAmax	46.68 (18.00-121.52)	53.27 (15.56-187.33)	2.29 (-70.50-149.97)	1.44 (-66.16-486.59)	0.70 (-123.38-262.45)	0.792
CPR	1.72 (0.93-5.03)	1.77 (0-4.17)	0.11 (-1.96–2.34)	-0.73 (-46.18-127.37)	-0.002 (-1.96-1.08)	0.361
UA PI	1.02±0.23	0.97±0.25	-0.06±0.27	-3.75±20.2	-0.01±0.21	0.315
UA S/D	2.87±0.63	2.76±0.75	-0.13±0.76	-3.02±20.8	0.03±0.61	0.185
MCA PI	1.78(1.093.39)	1.60 (0.98–3.63)	-0.12 (-1.06-1.85)	-5.65 (-47.03-103.93)	-0.07 (-1.24-2.00)	0.026
MCA PI	50.91±13.17	53.51±13.18	2.58±15.1	5.1±40.2	0.94±9.8	0.767

Percentage change and weekly change were not calculated for gestational age, as it is a time variable that advances proportionally to the inter-visit interval. Values are presented as mean ± SD, median (min–max), or number (%), as appropriate. Δ indicates the change between visit 2 and visit 1. Δ per week represents the change normalized to the time interval between visits. DV: Ductus venosus, PIV: Pulsatility index for veins, PLI: Preload index, PVIV: Peak velocity index for veins, TAmax: Time-averaged maximum velocity, CPR: Cerebroplacental ratio, UA: Umbilical artery, MCA: Middle cerebral artery, PSV: Peak systolic velocity

curred in 15 pregnancies (28.8%), whereas 37 cases (71.2%) were delivered at term. Eleven neonates (21.2%) required admission to the NICU, and among these, 9 (81.8%) remained hospitalized for more than 2 days. The median umbilical artery pH at birth was 7.31 (7.13-7.41). Perinatal outcome data are summarized in Table V.

Table V: *Perinatal outcomes of the study population (n=52)*

Gestational age at delivery, weeks, median (min-max)	37 (34-41)
Birth weight (g), median (min-max)	2390 (1650-3720)
Preterm birth (<37 weeks), n (%)	15 (28.8)
Term birth (≥37 weeks), n (%)	37(71.2)
NICU admission, n(%)	11 (21.2)
NICU admission >2 days*, n (%)	9 (81.8)
Umbilical artery pH, median (min-max)	7.31 (7.13-7.41)

** Among neonates admitted to the neonatal intensive care unit (NICU) (n=11). Values are presented as mean ± SD, median (min-max), or number (%), as appropriate. NICU: Neonatal intensive care unit*

Longitudinal Doppler changes were further analyzed according to NICU admission status. No significant difference was found between neonates with and without NICU admission in terms of absolute change in DV PIV (0.00 ± 0.36 vs 0.11 ± 0.40, p=0.433) or weekly change in DV PIV (0.01 ± 0.25 vs 0.06 ± 0.30, p=0.592). Likewise, the direction of change in DV PIV, categorized as increase or decrease, was not associated with NICU admission (p=0.873). Similar findings were observed for CPR. Neither absolute change in CPR (p=0.388), weekly change in CPR (p=0.100), nor the pattern of increase or decrease in CPR (p=0.519) differed significantly according to NICU admission status. These results are presented in Table VI.

The relationship between changes in DV PIV and CPR was also assessed. No significant correlation was observed between absolute changes in DV PIV and CPR (Spearman ρ=−0.022,

Table VI: *Association between longitudinal Doppler changes and NICU admission*

Ductus venosus parameters			
Δ DV PIV, mean ± SD	0.11 ± 0.40	0.00 ± 0.36	0.433
Δ DV PIV per week, mean ± SD	0.06 ± 0.30	0.01 ± 0.25	0.592
Decrease in DV PIV, n (%)	12 (37.5)	4 (40.0)	0.873
Increase in DV PIV, n (%)	20 (62.5)	6 (60.0)	
Cerebroplacental ratio parameters			
Δ CPR, median (min–max)	−0.058 (−1.957–2.337)	0.013 (−0.742–0.665)	0.388
Δ CPR per week, median (min–max)	−0.025 −1.957–1.074)	0.015 (−1.298–1.075)	0.100
Decrease in CPR, n (%)	17 (54.8)	4 (44.4)	0.519

Values are presented as mean ± SD, median (min-max), or number (%), as appropriate. Continuous variables were compared using the independent samples t-test or Mann-Whitney U test, and categorical variables using the Fisher's exact test, as appropriate. DV: Ductus venosus, PI: Pulsatility index, CPR: Cerebroplacental ratio, Δ: Change between visit 2 and visit 1, NICU: Neonatal intensive care unit Analyses were performed using complete-case data; therefore, subgroup totals may not equal the overall cohort size or the total number of NICU cases.

p=0.881). Similarly, weekly changes in these parameters were not correlated (Spearman's ρ = -0.031, p= 0.835). Correlation analysis results are shown in Table VII.

Table VII: *Correlation between longitudinal changes in DV PIV and CPR (n=47)*

Δ DV PIV vs Δ CPR	−0.0220.881
Δ DV PIV per week vs Δ CPR per week	−0.0310.835

Spearman correlation analysis was performed in cases with complete paired DV, PIV, and CPR measurements; therefore, the sample size differs from other analyses due to variable-specific missing data. DV: ductus venosus, PIV: pulsatility index for veins, CPR: cerebroplacental ratio, Δ: change between visit 2 and visit 1

Finally, multivariable logistic regression analysis was performed to identify independent predictors of NICU admission. Maternal age, BMI, gestational age at delivery, absolute change in CPR, and weekly change in DV PIV were not independently associated with NICU admission. Weekly change in CPR was associated with NICU admission at the borderline level (adjusted OR 0.04, 95% CI 0.002-1.08, p=0.056). The full regression model is presented in Table VIII.

Discussion

In this study, the longitudinal changes in arterial and venous Doppler parameters were evaluated in pregnancies complicated by fetal growth restriction, and the relationship between these changes and perinatal outcomes was investigated. The main findings of the study can be summarized under several points. First, a significant decrease in MCA PI values was observed during the follow-up period between the two evaluations. Second, no significant change was observed between the two measurements in any of the ductus venosus Doppler parameters examined. Third, no statistically significant association was found between changes in Doppler parameters and NICU admission. Additionally, no statistically significant association was observed between weekly changes in CPR and NICU admissions.

The progression of Doppler changes over time in fetal growth restriction has previously been described in several studies. In particular, longitudinal studies by Baschat et al. demonstrated that fetal hemodynamic deterioration related to placental insufficiency follows a characteristic sequence (14,15). According to these studies, changes in the fetal circulation occur before deterioration in the biophysical profile; first, an increase in placental resistance develops in the umbilical artery, followed by redistribution in the cerebral circulation as an adaptation to fetal hypoxemia, resulting in a decrease in the MCA PI (14). In the later stages of the disease, Doppler abnormalities may develop in venous structures, such as the ductus venosus and umbilical vein, reflecting cardiac overload and myocardial dysfunction (15). Similarly, in a larger longitudinal cohort study conducted by Turan et al., deterioration in Doppler parameters typically progressed in the same sequence and occurred at progressively shorter intervals (4).

Studies from the Barcelona group have shown that early- and late-onset fetal growth restriction represent different clinical phenotypes from a hemodynamic perspective (7,8). In EO-FGR, impairment in the umbilicoplacental circulation is more pronounced, and venous Doppler changes occur more frequently following arterial Doppler abnormalities during disease progression (5). In contrast, placental insufficiency in late-onset FGR is usually milder; umbilical artery Doppler findings may often remain normal, and fetal adaptation more commonly appears as redistribution in the cerebral circulation (8,9). For this reason, arterial Doppler parameters, such as the MCA and the CPR, are considered more sensitive indicators for the clinical surveillance of LO-FGR (10,14).

The TRUFFLE (Trial of Randomized Umbilical and Fetal Flow in Europe) study has also provided important data regarding fetal surveillance and timing of delivery, particularly in EO-FGR (3). In this multicenter randomized trial, it was shown that surveillance strategies combining ductus venosus Doppler findings with computerized cardiotocography (cCTG) in pregnancies diagnosed with EO-FGR between 26 and 32 weeks may improve perinatal and neonatal outcomes (3). Subsequent analyses also emphasized that the combined evaluation of Doppler findings and cCTG is important in clinical surveillance when determining the optimal timing of delivery in EO-FGR (16,17).

Since the study population consisted entirely of cases with LO-FGR, the findings are consistent with the pathophysiological model described in the literature (18). The significant decrease observed in MCA PI values during the follow-up period can be interpreted as an indicator of cerebral redistribution in the fetal circulation. In the presence of placental in-

Table VIII: *Multivariable logistic regression analysis for NICU admission*

Maternal age	1.01	0.80-1.26	0.958
BMI	1.07	0.84-1.35	0.601
Gestational age at delivery (weeks)	1.08	0.99-1.19	0.098
Δ CPR	7.28	0.77-68.57	0.083
Δ CPR per week	0.04	0.002-1.08	0.056
Δ DV PIV per week	0.65	0.01-29.05	0.822

Multivariable logistic regression analysis was performed to identify independent predictors of NICU admission. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) are presented. OR: odds ratio, CI: confidence interval, DV: ductus venosus, PIV: pulsatility index for veins, CPR: cerebroplacental ratio

sufficiency, the fetus develops a decrease in cerebral vascular resistance in order to preserve blood flow to vital organs, which appears as a decrease in MCA PI values on Doppler examination (19). Previous studies have also shown that a decrease in MCA PI, along with the associated reduction in the cerebroplacental ratio, represents an early sign of fetal adaptation in FGR (19). Therefore, it is generally accepted that arterial Doppler changes occur earlier than venous Doppler changes, and the significant decrease in MCA PI observed in our study supports the notion that fetal adaptation in LO-FGR primarily occurs at the arterial level. Previous longitudinal studies in late-onset FGR and SGA fetuses, particularly those from the Barcelona group, have demonstrated that cerebral Doppler changes may precede other hemodynamic alterations, supporting the concept that arterial redistribution is an early adaptive mechanism in these cases (7).

In contrast, the absence of a significant longitudinal change in DV parameters in our study may suggest that advanced cardiac decompensation had not yet developed in a substantial proportion of the fetuses. From a pathophysiological perspective, changes in DV flow patterns are generally associated with increased cardiac afterload, myocardial dysfunction, and fetal acidemia, reflecting the decompensation phase of fetal circulation (7). For this reason, venous Doppler abnormalities usually appear in later stages when fetal hypoxia progresses, and cardiovascular compensatory mechanisms begin to fail. In LO-FGR, placental insufficiency generally follows a milder course; therefore, fetal adaptation usually remains at the level of arterial redistribution, while marked Doppler changes in the venous system are observed less frequently (2). The absence of significant changes in ductus venosus parameters may reflect either a true physiological finding in late-onset FGR or limited statistical power.

In most studies, ductus venosus assessment has been limited to PI alone, whereas in our study, in order to provide a more comprehensive evaluation of the venous circulation, different venous Doppler parameters such as PLI, PVIV, S/a ratio, and TAmax were analyzed in addition to DV PIV, and no significant change over time was observed. The literature reports that these parameters may reflect different aspects of fetal cardiac hemodynamics (6,18,19). In particular, waveform-derived indices such as PLI and PVIV are considered to be sensitive to preload and afterload changes in the right heart and may be useful parameters for evaluating fetal right heart function (11). In addition, the S/a ratio reflects the relationship between ventricular systole and atrial contraction phases and may provide additional information about fetal cardiac filling pressures and diastolic function (21). Classical studies on fetal venous circulation have shown that the DV waveform closely follows the cardiac cycle, and that the S, D, and a waves reflect the ventricular systole, ventricular diastole, and atrial contraction phases, respectively (20). Moreover, TAmax and other velocity parameters are used to evaluate the velocity profile along the DV and the distribution of flow energy within this vessel, and have been described in detail in studies investigating the hemodynamic role of the DV in fetal circulation (6). A more detailed evaluation of venous Doppler parameters in this manner may contribute to a more comprehensive assessment of circulatory adaptations that occur in FGR and other hemodynamic stress conditions (20).

When longitudinal Doppler changes were evaluated in our study, no significant difference was found between cases with and without NICU admission in terms of DV PIV change and weekly DV PIV change. Similarly, no statistically significant association was detected between CPR change and NICU admission. Weekly changes in CPR were not significantly associated with NICU admission, although the magnitude of the observed effect suggests a possible association warranting further investigation. This finding suggests that evaluating hemodynamic changes over time rather than relying on a single measurement may be more informative for predicting fetal hypoxia and adverse perinatal outcomes; however, it should be interpreted cautiously given the limited sample size.

When the relationship between DV and CPR changes was evaluated, no significant correlation was found between the two parameters. This may suggest that arterial and venous circulations do not always change in parallel during fetal adaptation. Indeed, it is known that circulatory adaptation in placental insufficiency usually begins with arterial redistribution, whereas venous Doppler changes appear in more advanced stages of hemodynamic deterioration (4). Morales et al. also reported that arterial and venous Doppler parameters may change at different times in FGR and that these parameters reflect different stages of fetal hemodynamic deterioration (10).

Our study has several strengths. First, the longitudinal evaluation of arterial and venous Doppler parameters enabled a more dynamic assessment of fetal hemodynamic adaptation. In addition, simultaneous evaluation of multiple ductus venosus parameters enabled a more comprehensive assessment of venous circulation. Furthermore, relating Doppler changes to perinatal outcomes increases the clinical relevance of the study.

However, the study also has several limitations. First, the absence of a healthy control group limits the ability to assess the specificity of the observed Doppler findings. Second, although the study was designed as a longitudinal cohort, analyses were based on two time points, and variability in follow-up intervals, despite normalization using weekly change, may have introduced measurement bias. Third, NICU admission was used as the primary outcome, which represents a heterogeneous endpoint influenced by gestational age and clinical management, and the predefined composite outcome could not be analyzed due to the limited number of events. In addition, although a priori power estimation based on previous studies suggested an adequate sample size, the relatively small num-

ber of NICU admissions may have reduced the effective statistical power, particularly for outcome-based and multivariable analyses, and increased the risk of overfitting, as reflected by wide confidence intervals. Furthermore, the definition of LO-FGR based on EFW and/or AC <10th percentile may have introduced heterogeneity by including constitutionally small fetuses. These limitations should be considered when interpreting the findings. Future studies with larger multicenter cohorts, more frequent longitudinal assessments, and integration with additional monitoring tools such as computerized cardiotocography may further clarify the clinical role of arterial and venous Doppler changes in LO-FGR.

Conclusion

In conclusion, this study showed that arterial Doppler parameters may change over time in pregnancies complicated by LO-FGR, whereas venous Doppler parameters may remain relatively stable. In addition, a potential association was observed, suggesting that changes in CPR over time may be associated with perinatal outcomes. These findings suggest that longitudinal assessment of Doppler parameters rather than a single measurement may be clinically valuable in evaluating fetal hemodynamic adaptation. However, these findings are not sufficient for direct clinical decision-making and should be validated in larger prospective studies.

Declarations

Data Availability Statement: Data are not publicly available due to ethical restrictions. Further inquiries can be directed to the corresponding author.

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Conflict of Interest Disclosure: The authors declare that they have no conflicts of interest.

Ethics Approval Statement: This study complied with all relevant national regulations, institutional policies, and the principles of the Helsinki Declaration (as revised in 2024). The study protocol was reviewed and approved by the local Non-Interventional Ethics Committee (approval number: 2025/337). The study was prospectively registered at Clinical Trials.gov (identifier: NCT07193381).

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