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Prognostic value of foramen ovale morphology and hemodynamics in late-onset fetal growth restriction: a 3D ultrasonography-based study

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Abstract

Objective To assess the structural and hemodynamic characteristics of the foramen ovale (FO) in fetuses with late-onset fetal growth restriction (LO-FGR) using three-dimensional (3D) ultrasonography and Doppler imaging, and to examine their associations with Doppler parameters in FGR and composite adverse perinatal outcomes (CAPO).

Methods This case-control study included 40 fetuses with LO-FGR and 40 matched controls exhibiting appropriate-for-gestational-age (AGA) between 34 and 37 weeks. FO area was measured using 3D spatio-temporal image correlation (STIC) imaging, and FO width and pulsatility index (PI) were evaluated using 2D and Doppler ultrasonography. FO parameters were compared between the groups, and partial correlation analyses adjusted for gestational age to assess their associations with FGR and CAPO. Additionally, Receiver Operating Characteristic (ROC) curve analysis was conducted to evaluate the predictive value of FO parameters for CAPO within the FGR group.

Results FO area ($p < 0.001$), FO width ($p < 0.001$), left atrial (LA) width ($p = 0.029$), FO/LA ratio ($p < 0.001$), and FO/RA ratio ($p = 0.024$) were significantly reduced in the FGR group compared to the controls. Among FGR fetuses, those who developed CAPO had lower FO area ($p = 0.009$), FO width ($p = 0.001$), LA width ($p = 0.006$), FO/LA ratio ($p < 0.001$), and FO/RA ratio ($p = 0.041$). In ROC analysis, the FO/LA ratio exhibited the highest predictive value for predicting CAPO (AUC: 0.851, $p < 0.001$).

Conclusion Alterations in FO morphology are significantly associated with adverse perinatal outcomes in LO-FGR. The FO/LA ratio may serve as a reliable and noninvasive parameter for risk stratification. Incorporating advanced fetal cardiac morphometry could improve prenatal surveillance in FGR.

Keywords Foramen ovale, Fetal growth restriction, Composite adverse perinatal outcome, Three-dimensional ultrasonography, Fetal hemodynamics

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Introduction

Fetal growth restriction (FGR) refers to a condition in which the fetus fails to reach its genetically determined growth potential, most commonly due to placental insufficiency [1, 2]. This condition is associated with increased perinatal morbidity and mortality, developmental delays, and a higher risk of cardiovascular and metabolic diseases in adulthood [2, 3]. Impaired placental function limits the transfer of oxygen and nutrients to the fetus, leading to chronic hypoxia and triggering circulatory adaptations known as the "brain-sparing" effect, which prioritizes oxygen delivery to vital organs such as the brain and heart [4, 5].

The foramen ovale (FO) plays a central role in fetal circulation by enabling oxygenated blood to pass from the right atrium (RA) to the left atrium (LA), effectively bypassing the fetal lungs. This shunt is crucial for ensuring optimal cerebral and coronary perfusion during fetal life, so the morphology and flow dynamics of the FO may reflect the overall fetal cardiovascular status [6, 7]. In recent years, novel echocardiographic parameters such as the FO width, FO area, and FO pulsatility index (FO PI) have been developed to assess the structural and functional characteristics of the FO [6–8]. Furthermore, advanced imaging techniques, such as three-dimensional ultrasonography (3D US), have revolutionized the evaluation of the FO by enabling more precise measurements and detailed analysis of flow dynamics [9, 10].

Despite prior research detailing normative alterations in FO dimensions across gestational age [6], the potential significance of FO characteristics in the pathophysiology of FGR remains inadequately comprehended. Previous studies have indicated affected FO area or PI values in growth-restricted fetuses [8, 11, 12]; however, a thorough evaluation of FO structure and function utilizing advanced imaging modalities and its possible association with composite adverse perinatal outcomes (CAPO) has not been adequately explored. Addressing this gap may yield novel insights into cardiovascular adaptation in FGR and offer supplementary tools for prenatal risk stratification.

Therefore, this study aims to assess FO morphology, including FO area, width, FO/LA and FO/RA ratios, and FO PI in pregnancies complicated by FGR. The FO area was quantified using 3D US with the spatio-temporal image correlation (STIC) technique in rendering mode, while other parameters were evaluated using standard two-dimensional ultrasonography (2D US). Furthermore, we examined the correlations among FO parameters, obstetric Doppler results, and CAPO to evaluate the clinical significance of FO measurements in the context of FGR surveillance.

Materials and methods

This case-control study was conducted between January and May 2025 at the Department of Perinatology, Ankara Etlik City Hospital, a tertiary referral center. The study protocol was approved by the Ankara Etlik City Hospital Ethics Committee (approval number: AESH-BADEK-2025-0074). and written informed consent was obtained from all participants. The study adhered to the ethical principles outlined in the Declaration of Helsinki.

FGR was diagnosed based on the Delphi consensus criteria, with inclusion limited to fetuses whose abdominal circumference (AC) and/or estimated fetal weight (EFW) measured below the 3rd percentile [13]. Fetuses with biometric measurements between the 3rd and 10th percentiles were excluded. The appropriate-for-gestational-age (AGA) group included fetuses with an EFW above the 10th percentile and normal Doppler parameters. All participants were in the third trimester, between 34 and 37 weeks of gestation.

Exclusion criteria included fetuses fetuses with chromosomal abnormalities or structural anomalies, as well as pregnancies complicated by gestational diabetes mellitus (GDM), pregestational diabetes mellitus (type 1 or type 2), hypertensive disorders, maternal anemia, or other chronic systemic maternal diseases.

Gestational age was determined using the first day of the last menstrual period (LMP) and confirmed by first-trimester crown–rump length (CRL) measurement via ultrasound. In cases where the ultrasound-based dating differed from the LMP by more than seven days, gestational age was adjusted according to the ultrasound findings. All ultrasound examinations were performed transabdominally using a 3.5-MHz convex transducer on a Voluson S10 Expert system (GE Healthcare, Milwaukee, WI) by a maternal-fetal medicine specialist (Ö.V.A.). While operator consistency reduces inter-observer variability, the examiner was not blinded to group allocation (FGR vs. AGA) due to real-time clinical assessment settings. To address reproducibility, intra-observer variability was assessed for key FO measurements, including FO area and FO width, using intraclass correlation coefficients (ICCs). A subset of 15 randomly selected cases underwent repeated measurements one week apart under identical conditions. The reproducibility of 3D STIC-based cardiac measurements has been demonstrated in previous studies, such as Pontes et al. (2023), and our protocol followed similar methodological standards [9]. Intra-observer reproducibility for FO area measurement using 3D STIC was excellent, with a concordance correlation coefficient (CCC) of 0.97 and inter-observer reproducibility, as reported by Pontes et al. in a similar context, also demonstrated high reliability (CCC = 0.94).

Ultrasound assessments were performed in accordance with the guidelines of the International Society

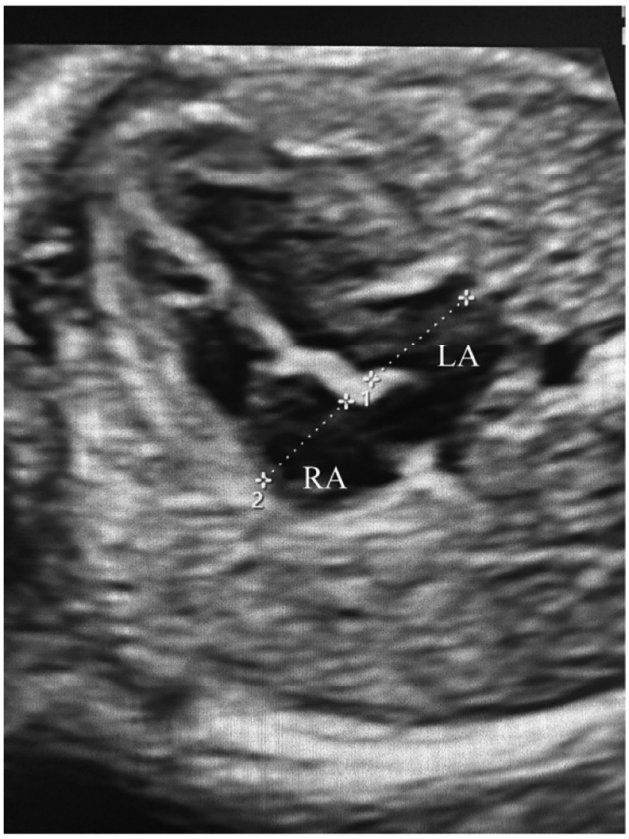

Fig. 1 Measurement of Right and Left Atrial Widths in the Four-Chamber View. Ultrasound image illustrating the measurement of maximal transverse diameters of the left atrium (LA) and right atrium (RA) in a lateral four-chamber view

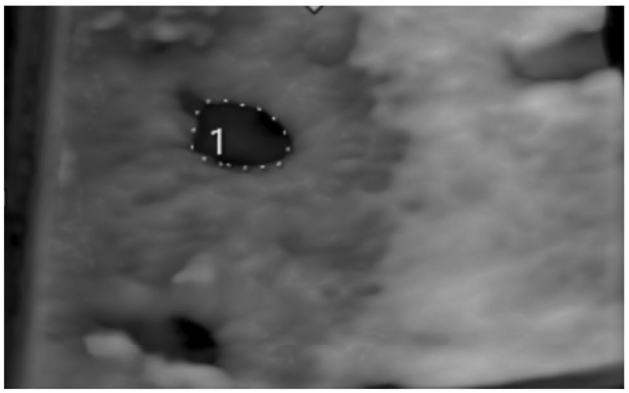

Fig. 2 Three-dimensional Spatiotemporal Image Correlation (STIC) image showing the measurement of the foramen ovale (FO) area. The contour of the FO area was manually traced on the plane providing optimal visualization for area calculation

of Ultrasound in Obstetrics and Gynecology (ISUOG) [14, 15]. All Doppler evaluations were conducted in the absence of fetal movements to minimize variability. The following parameters were measured: estimated fetal weight (EFW), abdominal circumference (AC), biparietal diameter (BPD), head circumference (HC), maximum vertical pocket (MVP), and Doppler indices of the umbilical artery (UA), uterine artery (UtA), and middle cerebral artery (MCA). UA Doppler measurements were obtained from free-floating loops of the umbilical cord. UtA Doppler indices were recorded at the crossover point of the uterine artery and the external iliac artery, using a longitudinal transducer orientation and color flow mapping. MCA Doppler measurements were performed at the location where the artery crosses the sphenoidal wing near the circle of Willis. The cerebroplacental ratio (CPR) was calculated as the ratio of the MCA to UA pulsatility indices (PI). The cerebroplacental-uterine ratio (CPUR) was calculated by dividing the CPR by the mean UtA-PI. Cardiac measurements included the maximum transverse diameters of the LA and RA, obtained in the lateral four-chamber view just above the atrioventricular valve orifices at end-systole, measured from inner edge to inner edge (Fig. 1). The FO area was measured using the STIC technique. In the 3D four-chamber view generated by STIC, the FO was visualized, and its area was calculated by manually tracing the contour of the FO flap at the plane of maximal visibility (Fig. 2). The FO width was measured in the four-chamber view using two-dimensional echocardiography. A single frame was selected in which the foramen ovale flap (FOF) was clearly visible, and the maximal width was measured from the most prominent point of the FOF to the interatrial septum, following the method described by Vena et al. [16]. In most cases, the FOF was clearly visualized due to favorable fetal positioning and adequate amniotic fluid. In instances where the FOF was not adequately visualized on initial imaging, the scan was repeated within one week. The maximum width of the FO flap was then measured from the outer edge of the most prominent part of the flap to this line (Fig. 3). Additionally, pulsed-wave Doppler assessments were obtained from the same anatomical location. FO PI was measured using pulsed-wave Doppler in the apical four-chamber view. The Doppler sample volume was placed at the mid-portion of the foramen ovale flap, ensuring the beam was aligned as parallel as possible to the direction of blood flow through the FO, with an insonation angle kept below 30°. The sample gate was set to 2 mm. Measurements were obtained during fetal quiescence, avoiding respiratory motion or fetal activity. At least three uniform waveforms were recorded and averaged for each fetus. The FO PI was calculated using the standard formula: PI = Peak systolic velocity – End-diastolic velocity/Mean velocity over the cardiac cycle.

All pregnant participants were followed prospectively until delivery. Data collected included gestational age at birth, birth weight (BW), Apgar scores at 1 and 5 min, and neonatal intensive care unit (NICU) admission. A composite adverse perinatal outcome (CAPO)

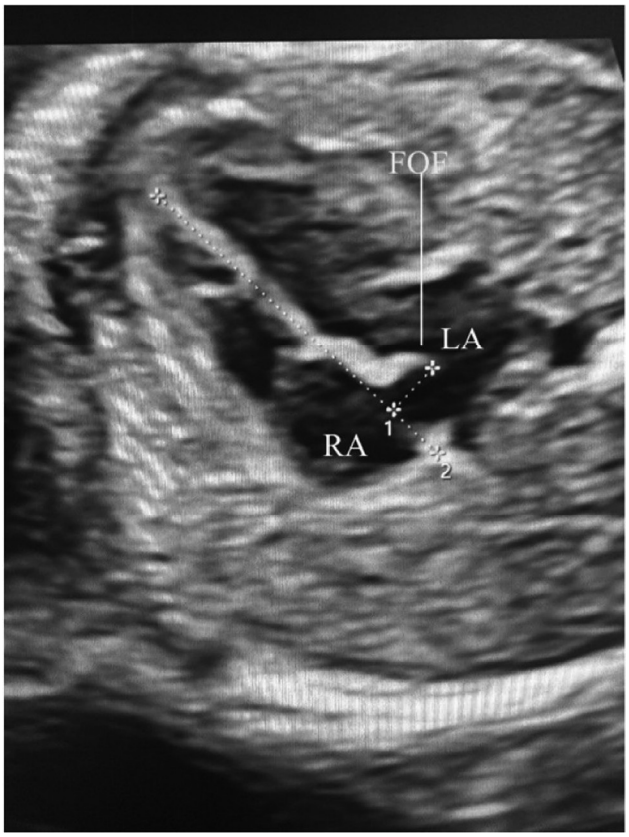

Fig. 3 Two-dimensional ultrasound image illustrating the measurement of foramen ovale (FO) width from the most prominent point of the foramen ovale flap (FOF) to the interatrial septum

was defined as the occurrence of any of the following: cesarean delivery due to fetal distress, a 5-minute Apgar score ≤ 7, or NICU admission.

Sample Size Calculation

A priori power analysis was conducted using G*Power 3.1.9.7 software to ascertain the minimal sample size necessary for detecting a statistically significant difference between two independent means, employing a two-tailed Independent samples t-test. The effect size (Cohen's d) computed from the means and standard deviations reported by Nader et al. was 1.18 [11]. With a significance level (α) of 0.05 and a desired power (1−β) of 0.95, the minimum necessary sample size was established at 40 participants, consisting of 20 fetuses with FGR and 20 gestational age–matched controls exhibiting AGA growth.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed data were presented as mean ± standard deviation (SD), while non-normally distributed data were expressed as median with interquartile range (IQR). Categorical variables were summarized as frequencies and percentages. Comparisons between the FGR and AGA groups 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 the Chi-square test or Fisher's exact test, as appropriate. Partial correlation analysis, controlling for gestational age at booking, was used to evaluate the relationships between foramen ovale morphometric parameters and Doppler indices. Receiver operating characteristic (ROC) curve analysis was employed to assess the predictive performance of fetal cardiac morphometric parameters and Doppler indices for the occurrence of CAPO among fetuses with growth restriction. A p-value < 0.05 was considered statistically significant.

Results

A total of 80 fetuses were included, 40 with FGR and 40 with AGA. There were no statistically significant differences between the groups in terms of maternal age, gravidity, nulliparity, or maternal body mass index (BMI). Significant differences were observed in Doppler parameters between the groups. Fetuses in the FGR group exhibited higher umbilical artery pulsatility index (UA PI) ($p = 0.032$), lower MCA PI ($p = 0.005$), as well as significantly reduced CPR and CPUR (both $p < 0.001$). In addition, EFW and AC percentiles were significantly lower in the FGR group (both $p < 0.001$), accompanied by a reduced MVC of amniotic fluid ($p = 0.027$). The incidence of CAPO was also significantly higher among FGR fetuses compared to AGA controls ($p = 0.010$). (Table 1).

In terms of FO morphology and atrial dimensions, fetuses with FGR demonstrated significantly smaller FO area (0.450 ± 0.069 cm^2 vs. 0.616 ± 0.126 cm^2, $p < 0.001$) and FO width (5.85 ± 1.04 mm vs. 6.97 ± 0.97 mm, $p = 0.007$) compared to the AGA group Both right and left atrial widths were also significantly reduced in the FGR group (12.72 ± 1.88 mm vs. 14.06 ± 1.66 mm, $p < 0.001$; and 12.81 ± 2.03 mm vs. 13.82 ± 2.07 mm, $p = 0.029$, respectively). Additionally, the FO/RA and FO/LA width ratios were significantly lower in the FGR group (0.463 vs. 0.498, $p = 0.024$; and 0.458 vs. 0.504, $p < 0.001$, respectively). The FO PI was significantly higher in the FGR group compared to the AGA group (1.895 ± 0.455 vs. 1.139 ± 0.292, $p < 0.001$). (Table 2).Among fetuses with FGR ($n = 40$), CAPO were observed in 15 cases (37.5%). There were no significant differences between the CAPO and non-CAPO groups in terms of maternal age, gravidity, parity, or body mass index ($p > 0.05$ for all comparisons). Similarly, UA and MCA PI values did not differ significantly between the two groups. However, fetuses

Table 1 Comparison of demographic, ultrasonographic, and neonatal characteristics between fetuses with FGR and the AGA

Variables	FGR (*n*:40)	AGA (*n*:40)	*p*-value
Demographics			
Maternal age (years)	26.1 ± 3.1	26.5 ± 2.7	0.527[a]
Gravida	2.0 (1.0–2.0)	2.0 (1.0-2.2)	0.315[b]
Nulliparity	23 (57.5%)	18 (45.0%)	0.263[b]
Maternal body mass index (kg/m2)	28.1 ± 4.0	28.3 ± 2.5	0.818[a]
Ultrasonographic findings at scan			
Gestational age at ultrasound examination (weeks)	35.0 (34.0–37.0)	35.5 (34.0–37.0)	0.674[b]
Umbilical artery PI	0.93 ± 0.22	0.84 ± 0.12	0.032[a]
Middle cerebral artery PI	1.65 ± 0.48	1.89 ± 0.20	0.005[a]
Cerebroplacental ratio (CPR)	1.83 ± 0.55	2.29 ± 0.39	< 0.001[a]
Uterine artery PI	0.85 ± 0.24	0.76 ± 0.12	0.039[a]
Cerebroplacental-uterine ratio (CPUR)	2.37 ± 1.05	3.06 ± 0.63	< 0.001[a]
Estimated fetal weight (grams)	1920 ± 246	2700 ± 289	< 0.001[a]
Estimated fetal weight centile (%)	1.0 (1.0–1.0)	61.0 (69.0-85.3)	< 0.001[b]
Abdominal circumference centile (%)	2.0 (1.0–2.0)	61.0 (45.3–77.8)	< 0.001[b]
Amniotic fluid MVC (mm)	43.4 ± 7.8	47.6 ± 8.7	0.027[a]
Postnatal findings			
Gestational age at birth (weeks)	37.0 (37.0–37.0)	39.0 (38.0–39.0)	< 0.001[b]
Birthweight (grams)	2319 ± 178	3286 ± 294	< 0.001[a]
Fetal Distress	8 (20.0%)	2 (5.0%)	0.043[c]
5th minute Apgar Score ≤ 7	4 (10.0%)	-	0.116[c]
NICU admission	13 (32.5%)	4 (10.0%)	0.014[c]
Composite adverse Perinatal outcome	15 (37.5%)	5 (12.5%)	0.010[c]

FGR Fetal Growth Restriction, *AGA* Appropriate for Gestational Age, *PI* Pulsatility Index, *MVC* Maximum Vertical Pocket, *NICU* Neonatal Intensive Care Unit

[a] Independent samples t-test was used for comparisons between groups. Data are presented as mean ± standard deviation

[b] The Mann–Whitney U test was used for comparisons between groups. Data are presented as median (interquartile range)

[c] Categorical variables were compared using the Chi-square or Fisher's exact test, as appropriate. Results are shown as n, (%)

Table 2 Morphometric and hemodynamic differences in foramen ovale and right Atria between FGR and AGA fetuses

Variables	FGR (*n*:40)	AGA (*n*:40)	*p*-value
FO Area (cm^2)	0.450 ± 0.069	0.616 ± 0.126	< 0.001[a]
FO Width (mm)	5.85 ± 1.04	6.97 ± 0.97	< 0.001[a]
Right Atrium Width (mm)	12.72 ± 1.88	14.06 ± 1.66	0.001[a]
Left Atrium Width (mm)	12.81 ± 2.03	13.82 ± 2.07	0.029[a]
FO/LA width ratio	0.458 (0.445–0.466)	0.504 (0.500-0.508)	< 0.001[b]
FO/RA width ratio	0.463 ± 0.076	0.498 ± 0.057	0.024[a]
FO PI	1.895 ± 0.455	1.139 ± 0.292	< 0.001[a]

FGR Fetal Growth Restriction, *AGA* Appropriate for Gestational Age, *FO* Foramen Ovale, *LA* Left Atrium, *RA* Right Atrium, *PI* Pulsatility Index

[a] Independent samples t-test was used for comparisons between groups. Data are presented as mean ± standard deviation

[b] The Mann–Whitney U test was used for comparisons between groups. Data are presented as median (interquartile range)

in the CAPO group demonstrated significantly lower CPR and CPUR values ($p = 0.038$ and $p = 0.012$, respectively). In addition, the CAPO group had a significantly smaller FO area (0.410 vs. 0.500 cm^2, $p = 0.009$), narrower FO width (5.20 ± 1.08 mm vs. 6.23 ± 0.81 mm, $p = 0.001$), and reduced left atrial width (11.70 ± 2.24 mm vs. 13.47 ± 1.59 mm, $p = 0.006$). Both FO/LA and FO/RA width ratios were also significantly lower in the CAPO group ($p < 0.001$ and $p = 0.041$, respectively). No significant difference was observed in the FO pulsatility index between the groups ($p = 0.472$). (Table 3).

A partial correlation analysis, controlling for gestational age, was performed to evaluate the association between composite adverse perinatal outcomes (CAPO) and foramen ovale (FO) characteristics, along with Doppler indices within the FGR group (Table 4). Substantial negative associations were observed between CAPO and FO width ($r = -0.542$, $p < 0.001$), FO area ($r = -0.447$, $p = 0.004$), left atrial (LA) width ($r = -0.478$, $p = 0.002$), FO/left atrium (FO/LA) ratio ($r = -0.581$, $p < 0.001$), and FO/right atrium (FO/RA) ratio ($r = -0.333$, $p = 0.038$). while no significant correlation was seen regarding RA Width, FO PI and CAPO ($p = 0.061$ and $p = 0.095$, respectively). A notable negative connection was seen between CAPO and the CPR ($r = -0.345$, $p = 0.032$). In contrast, the CPUR was not correlated with CAPO ($p = 0.102$).

Partial correlation analysis, controlling for gestational age, was performed to evaluate the relationships between foramen ovale (FO) parameters, Doppler indices, and fetal growth restriction status. As presented in Supplementary Table 1, FGR was significantly and negatively correlated with FO area ($r = -0.707$, $p < 0.001$), FO width ($r = -0.604$, $p < 0.001$), left atrial width ($r = -0.303$, $p = 0.007$), and FO/LA ratio ($r = -0.881$, $p < 0.001$), while positively correlated with FO PI ($r = 0.832$, $p < 0.001$). Additionally, significant correlations were observed between FO parameters and CPR, CPUR, and uterine artery PI.

Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the predictive performance of fetal cardiac morphometric parameters and Doppler indices for identifying composite adverse perinatal outcomes (CAPO) among fetuses with FGR. The FO/LA width ratio exhibited the highest predictive accuracy, with an area under the curve (AUC) of 0.851 (95% CI: 0.702–0.943, $p < 0.001$), achieving a sensitivity of 93.3% and a specificity of 76.0% at a cut-off value of ≤ 0.458. FO width and the CPUR also showed strong predictive utility, with AUCs of 0.780 ($p = 0.003$) and 0.739 ($p = 0.023$), respectively. Additional significant predictors included FO area (AUC: 0.745, $p = 0.003$), left atrial width (AUC:

Table 3 Comparison of demographic, ultrasonographic, and foramen ovale parameters between FGR fetuses with and without composite adverse perinatal outcomes (CAPO)

Variables	CAPO (*n*:15)	Non-CAPO (*n*:25)	*p*-value
Demographics			
Maternal age (years)	27.1 ± 2.3	25.5 ± 3.5	0.080[a]
Gravida	1 (1–2)	2 (1–2)	0.422[b]
Parity	0 (0–1)	0 (0–1)	0.699[b]
Maternal body mass index (kg/m2)	28.93 ± 3.96	27.68 ± 4.10	0.349[a]
Ultrasonographic findings at scan			
Gestational age at ultrasound examination (weeks)	35.2 ± 1.4	35.4 ± 1.4	0.724[a]
Umbilical artery PI	0.91 (0.82–1.13)	0.87 (0.75–1.01)	0.201[b]
Middle cerebral artery PI	1.51 (1.28–1.62)	1.64 (1.46–2.08)	0.133[b]
Cerebroplacental ratio (CPR)	1.603 ± 0.618	1.976 ± 0.474	0.038[a]
Uterine artery PI	1.05 (0.70–1.15)	0.75 (0.70–0.83)	0.069[b]
Cerebroplacental-uterine ratio (CPUR)	1.748 (0.774–2.349)	2.446 (2.117–3.114)	0.012[b]
Estimated fetal weight (grams)	1889 ± 264	1940 ± 240	0.532[a]
Estimated fetal weight centile (%)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	0.956[b]
Abdominal circumference centile (%)	2.00 (1.00–2.00)	1.70 (1.00–2.00)	0.740[b]
Amniotic fluid MVC (mm)	45.3 ± 7.5	42.3 ± 8.1	0.248[a]
FO Area (cm^2)	0.410 (0.360–0.450)	0.500 (0.420–0.520)	0.009[b]
FO Width (mm)	5.20 ± 1.08	6.23 ± 0.81	0.001[a]
Right Atrium Width (mm)	12.14 ± 1.88	13.07 ± 1.83	0.129[a]
Left Atrium Width (mm)	11.70 ± 2.24	13.47 ± 1.59	0.006[a]
FO/LA width ratio	0.446 (0.440–0.457)	0.464 (0.458–0.469)	< 0.001[b]
FO/RA width ratio	0.432 ± 0.075	0.482 ± 0.072	0.041[a]
FO PI	1.98 (1.77–2.10)	1.95 (1.32–2.15)	0.472[b]

PI Pulsatility Index, *MVC* Maximum Vertical Pocket, *FO* Foramen Ovale

[a] Independent samples t-test was used for comparisons between groups. Data are presented as mean ± standard deviation

[b] The Mann–Whitney U test was used for comparisons between groups. Data are presented as median (interquartile range)

0.744, $p = 0.012$), FO/RA ratio (AUC: 0.712, $p = 0.017$), and CPR (AUC: 0.709, $p = 0.024$). (Table 5; Fig. 4).

Discussion

This study evaluated the morphometric and hemodynamic characteristics of the foramen ovale in fetuses with late-onset fetal growth restriction (LO-FGR) and explored their association with composite adverse perinatal outcomes (CAPO). Our findings revealed that FO area was significantly reduced in fetuses with LO-FGR, while FO pulsatility index (PI) was elevated, suggesting altered intracardiac hemodynamics. Notably, receiver operating characteristic (ROC) analysis demonstrated that FO morphometric parameters—particularly the FO/LA ratio—were strong predictors of CAPO. These results suggest that structural and functional alterations in the FO may be not only associated with the presence of FGR but also serve as prognostic markers for adverse perinatal outcomes.

Table 4 Partial correlation analysis between composite adverse perinatal outcomes (CAPO), foramen ovale parameters, and doppler indices in the FGR group, adjusted for gestational age

Variables	*r*	*p*-value
FO Width (mm)	−0.542	< 0.001
FO Area (cm^2)	−0.447	0.004
Left Atrium Width (mm)	−0.478	0.002
Right Atrium Width (mm)	−0.303	0.061
FO/LA width ratio	−0.581	< 0.001
FO/RA width ratio	−0.333	0.038
FO PI	0.271	0.095
CPR	−0.345	0.032
CPUR	−0.265	0.102

FO Foramen Ovale, *LA* Left Atrium, *RA* Right Atrium, *PI* Pulsatility Index, *CPR* Cerebroplacental Ratio, *CPUR* Cerebroplacental-Uterine Ratio

During fetal life, the FO is crucial for delivering oxygenated blood to the brain and heart by facilitating the passage of oxygen-rich blood from the ductus venosus from the right atrium to the left atrium under normal physiological conditions [17, 18]. Kiserud et al. found that the FO width increases with advancing gestational age, whereas the FO to RA ratio remains reasonably stable until the 32nd week of gestation, after which it slightly decreases [6]. Numerous alterations in FO structure and hemodynamics have been documented in the literature concerning cases of FGR [8, 11, 12]. Notable among these alterations are a reduction in FO area and an elevation in PI. Research has demonstrated that these anatomical and functional disparities signify cardiac adaptations particular to FGR.

In the research by Kiserud et al., cases of FGR exhibited significantly reduced FO width and FO/RA ratio, which was particularly pronounced before the 32nd week of gestation. Furthermore, the FO/RA ratio diminished progressively with the escalation of the severity of Doppler abnormalities. Nonetheless, the RA width exhibited no significant change between the FGR and control groups [12]. In our present investigation, the FO area, FO width, and FO/RA ratio were significantly diminished in the FGR group. The results indicate that alterations in the morphology and hemodynamics of the foramen ovale may arise even in instances with LO-FGR, and these characteristics could serve as indications of fetal adaptation processes. In contrast to Kiserud et al., the RA width was markedly reduced in the FGR group in our investigation. The discrepancy could be due to Kiserud et al.

Table 5 Receiver operating characteristic (ROC) analysis of foramen ovale morphometric and doppler parameters for predicting composite adverse perinatal outcomes (CAPO) in fetuses with fetal growth restriction

Variables	Cut-off	AUC	95% CI	Sensitivity (%)	Spesifity (%)	+LR	-LR	*p*-value
FO Area	≤ 0.41	0.745	0.583–0.870	53.3	88.0	4.44	0.53	0.003
FO Width	≤ 5.28	0.780	0.621–0.895	73.3	92.0	9.17	0.29	0.003
LA Width	≤ 11.51	0.744	0.582–0.869	66.7	92.0	8.33	0.36	0.012
FO/LA	≤ 0.458	0.851	0.702–0.943	93.3	76.0	3.89	0.09	< 0.001
FO/RA	≤ 0.443	0.712	0.547–0.844	73.3	72.0	2.62	0.37	0.017
CPR	≤ 1.692	0.709	0.544–0.842	60.0	84.0	3.75	0.48	0.024
CPUR	≤ 1.986	0.739	0.576–0.864	73.3	84.0	4.58	0.32	0.023

AUC Area Under the Curve, *CI* Confidence Interval, *+LR* Positive Likelihood Ratio, *-LR* Negative Likelihood Ratio, *FO* Foramen Ovale, *LA* Left Atrium, *RA* Right Atrium, *CPR* Cerebroplacental ratio, *CPUR* Cerebroplacental-uterine ratio

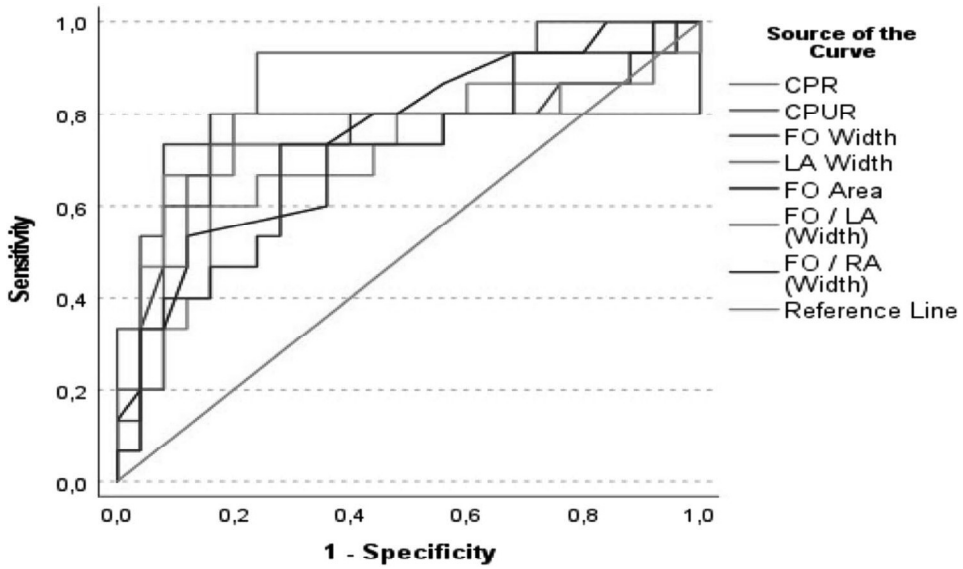

Fig. 4 Receiver Operating Characteristic (ROC) Curves of Foramen Ovale Morphometric and Doppler Parameters for Predicting Composite Adverse Perinatal Outcomes (CAPO) in Fetuses With Fetal Growth Restriction

encompassing a broader gestational age range (24–39 weeks), not distinguishing between late- and early-onset FGR, and exclusively including cases with EFW below the 5th percentile, while our study focused on late-onset FGR cases within a more restricted gestational age range (34–37 weeks) and cases with EFW below the 3rd percentile. In a different study, Nader et al. found that fetuses with FGR had higher FO PI, which they suggested might be caused by a decline in left ventricular diastolic functioning [11]. Likewise, Faraji et al. indicated that FO PI levels were elevated in the FGR cohort, and this parameter demonstrated robust predictive capability with an AUC of 0.91 for diagnosing FGR [8]. The substantial elevation of FO PI in the FGR group in our study aligns with existing literature and corroborates that hemodynamic alterations in FO indicate the cardiac implications of FGR.

Considering that the width and area of the FO expand with advancing gestational age, we performed a partial correlation analysis controlling for gestational age, demonstrating robust associations between FGR and FO characteristics. It indicates that FO undergoes morphological shortening and increases hemodynamic resistance in FGR. A positive association was identified between FO PI and UA PI ($r = 0.334$, $p = 0.003$), while a negative but weak relationship was observed with MCA PI ($r = -0.201$, $p = 0.075$). These findings are broadly consistent with existing literature indicating that FO PI significantly correlates positively with UA PI [8, 11]. These data indicate that FO characteristics are correlated not only with the occurrence of FGR but also with circulatory alterations identified by Doppler.

This study significantly contributes to the literature by doing subgroup analyses based on the development of CAPO within the FGR group. Our data indicate that the FO area, width, and FO/LA ratio were markedly reduced in FGR patients with CAPO, although FO PI remained comparable. In addition, partial correlation analysis, adjusted for gestational age, indicated that FO morphometric characteristics, including FO area, width, LA width, and the FO/LA and FO/RA ratios, exhibited

a negative relationship with CAPO, irrespective of gestational age. Among the Doppler indices, CPR exhibited a significant albeit weaker relationship with CAPO, whereas CPUR failed to achieve statistical significance. The data indicate that structural changes in the FO may signify inadequate cardiovascular adaptation and could act as early markers of fetal impairment. Faraji et al. stated that FO PI has good sensitivity and specificity in diagnosing FGR; however, they did not establish a direct correlation between FO PI and short-term perinatal outcomes [8]. In another study, Nader et al. similarly demonstrated that FO PI is essential for diagnosing FGR but did not assess its correlation with perinatal morbidity [11]. In our investigation, the morphological parameters of the FO were determined to be at least comparable to classical Doppler indices in predicting the development of CAPO in cases of FGR, and superior in certain parameters (FO area [AUC: 0.745], FO Width [AUC: 0.780], and FO/LA [AUC: 0.851]). The findings indicate that alterations in FO structure and hemodynamics could be an early indicator of fetal hemodynamic stress and adverse perinatal outcomes. Interestingly, our study found that the FO/LA width ratio had the highest predictive value for composite adverse perinatal outcomes (CAPO), surpassing both traditional Doppler indices and the FO/RA ratio. This finding differs from previous reports, such as those by Kiserud et al., which emphasized the prognostic importance of the FO/RA ratio, particularly in early-onset FGR [12]. Several factors may account for this discrepancy. First, our study focused exclusively on late-onset FGR (34–37 weeks), whereas prior studies often included a broader gestational range or primarily early-onset cases. As gestation advances, the fetal left atrium undergoes maturational changes that may increase its sensitivity to volume and pressure shifts, possibly making FO/LA a more responsive marker in this later window of pregnancy. Second, the use of both two-dimensional and 3D STIC imaging in our study may have provided more consistent anatomical delineation of the left atrium compared to the right atrium, whose shape and volume can be more variable due to venous inflow patterns and positioning. Third, the composite outcome we evaluated (CAPO) primarily reflects short-term neonatal compromise, which may be more closely associated with left-sided cardiac adaptation and output redistribution, particularly in the setting of late gestational hypoxemia. These distinctions suggest that FO/LA and FO/RA ratios may reflect different aspects of fetal cardiovascular adaptation depending on the timing, severity, and nature of growth restriction. Future studies comparing both ratios across early- and late-onset FGR cohorts, with long-term neonatal outcome data, are warranted to further clarify their respective prognostic roles.

This research has several limitations. First, the relatively small sample size, while sufficient to demonstrate statistical significance in primary analyses, limits the generalizability of the findings and may reduce the robustness of subgroup comparisons—particularly those assessing the predictive value of foramen ovale parameters for adverse outcomes. Larger, multicenter studies are essential to confirm these results and enhance their applicability across diverse populations. Second, the single-center design may introduce institutional bias, further limiting external validity. Third, although all ultrasonographic assessments were performed by an experienced operator to ensure consistency, the absence of blinding may increase the risk of observer bias. Additionally, this study exclusively evaluated late-onset FGR, and thus, the applicability of these findings to early-onset cases remains unknown. FO measurements were not correlated with postnatal cardiac function or long-term outcomes, limiting insight into their enduring clinical relevance. Finally, neonatal outcomes were based on a limited set of clinical parameters, precluding a comprehensive evaluation of short- and long-term neonatal morbidity.

Conclusion

In conclusion, notable alterations were detected in foramen ovale hemodynamics and morphology, as assessed by the STIC approach, in fetuses experiencing late-onset fetal growth restriction. Specifically, structural parameters, including FO area, FO width, and FO/LA ratio, were considerably diminished in the FGR group, whereas FO PI was elevated. The FO/LA ratio demonstrated superior predictive capability relative to traditional Doppler indices in forecasting CAPO development, indicating its potential as a noninvasive indicator of fetal distress and early neonatal outcomes. These findings highlight the potential clinical value of FO morphometric evaluation as a noninvasive marker for fetal compromise and neonatal prognosis in LO-FGR. Further large-scale, prospective studies incorporating comprehensive functional cardiac assessments are warranted to validate and expand upon these observations.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
ÖVA: Project administration, Writing – original draft. RTA: Writing – review & editing, Formal Analysis. COU: Methodology, Formal Analysis. AK: Data curation, Resources. KC: Data curation, Investigation. ZVY: Supervision, Project administration.

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Data availability
Due to hospital policies, patient data and study materials cannot be shared. However, the data are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ankara Etlik City Hospital Ethics Committee (approval number: AESH-BADEK-2025-0074). and written informed consent was obtained from all participants. The study adhered to the ethical principles outlined in the Declaration of Helsinki.

Consent for publication
Not applicable. This study does not contain any individual person's data in any form (including any individual details, images, or videos) that would require consent for publication.

Competing interests
The authors declare no competing interests.

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