Ultrasound Evaluation of the Changes of Ophthalmic Artery Doppler and Optic Nerve Sheath in Pregnant Women With FGR

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Objectives—This study aimed to compare changes in ultrasonic Doppler parameters, particularly the peak ratio (PR) of the ophthalmic artery (OA) and optic nerve sheath diameter (ONSD), in pregnancies complicated by fetal growth restriction (FGR). Furthermore, it sought to evaluate differences in these parameters across various subgroups and analyze the cut-off value of PR for predicting delivery within 1 week in pregnancies complicated by FGR.

Methods—A total of 62 pregnant women in the mid-to-late stages of gestation were enrolled, comprising 31 participants in the FGR group and 31 in the control group. The general conditions, pregnancy outcomes, Doppler parameters of the OA, and ONSD were compared between the two groups. Comparative analysis was performed to investigate differences in OA Doppler parameters and ONSD across FGR subgroups. The predictive value of PR for delivery within 1 week was assessed using the area under the receiver operating characteristic curve.

Results—The PR of the OA was significantly elevated in the FGR group compared to the control group, demonstrating a statistically significant difference. The threshold PR value for predicting delivery within 1 week was 0.565, with a sensitivity of 0.88 and a specificity of 0.58.

Conclusions—The PR value of the OA in pregnant women with FGR is significantly increased and may serve as a reliable predictor for pregnancies complicated by FGR.

Key Words—fetal growth restriction; ophthalmic artery; optic nerve sheath; ultrasonic Doppler

Cover image article

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Abbreviations
EDV, end-diastolic blood velocity; FGR, fetal growth restriction; OA, ophthalmic artery; ONSD, optic nerve sheath diameter; P1SV, P1 systolic peak blood velocity; P2SV, P2 peak blood velocity; PI, pulsation index; PR, peak ratio; RI, resistance index; S/D, P1 peak systolic velocity/end-diastolic velocity; TAMAX, time-averaged maximum velocities

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Fetal growth restriction (FGR) is a common complication of pregnancy and is associated with various adverse outcomes, including stillbirth, prematurity, neonatal morbidity and mortality, as well as endocrine and metabolic alterations.[1] The incidence of FGR ranges from 3% to 9%, with mortality rates between 5% and 20%.[2–4] FGR is defined as the failure to achieve the genetically determined potential size due to maternal, fetal, placental, and other pathological factors. It is most commonly manifested as a fetal ultrasound-estimated weight (EFW) or abdominal circumference below the 10th percentile for the corresponding gestational age and gender.[5] Given the complex and multifactorial etiology of FGR, current clinical management primarily focuses on accurate diagnosis, enhanced surveillance, and symptomatic interventions. These include monitoring fetal growth velocity and assessing Doppler blood flow in the umbilical artery, middle cerebral artery, and ductus venosus. Moreover, predicting fetal metabolic acidosis is essential to enable timely intervention and prevent irreversible organ damage or mortality. Therefore, it is crucial for clinicians to identify effective indicators that signal the occurrence and severity of FGR.

The ophthalmic artery (OA), anatomically and functionally similar to intracranial blood vessels, is easily accessible during Doppler ultrasound examinations. It can provide valuable insights into intracranial circulation, which is otherwise challenging to evaluate.[6] Compared to the Doppler waveforms of the uterine and umbilical arteries, the OA waveform includes a second systolic peak (P2), which results from pulse-wave (PW) reflection in the arterial system and its transmission to the cerebral circulation.[7] Since PW reflection is modulated by vascular constriction or dilation, the amplitude of P2 may increase or decrease.[8] Therefore, OA Doppler parameters not only reflect intracranial blood perfusion but also provide insights into the constriction and relaxation of small-to-medium arteries. The OA waveform is not influenced by maternal obesity, making it easy to obtain and advantageous for obstetric evaluations.[9,10] Notably, the ratio of the second systolic peak to the first systolic peak (P2SV/P1SV), known as the peak ratio (PR), has garnered increasing attention. Recent studies have demonstrated that the PR value is significantly elevated in pregnant women with preeclampsia.[6–8]

The optic nerve, classified as the second cranial nerve, is directly connected to the brain. Increases in intracranial pressure result in cerebrospinal fluid accumulation in the subarachnoid space surrounding the optic nerve, leading to the dilation of the optic nerve sheath.[11,12] Ultrasonic measurement of optic nerve sheath diameter (ONSD) is advantageous due to its convenience and non-invasive nature.

The pathogenesis of FGR is complex, with many cases associated with maternal factors. This study compared the OA Doppler parameters and ONSD measurements between pregnant women with FGR and those with normal pregnancies. The objective was to identify effective indicators that reflect the presence, severity, and prognosis of FGR.

Materials and Methods

This study was conducted between July 2022 and July 2024 at the Shanghai First Maternity and Infant Hospital. Women meeting the following criteria were recruited: (1) age over 18 years; (2) antenatal examination at our hospital; (3) singleton pregnancy; (4) absence of fetal malformations or chromosomal abnormalities; and (5) diagnosis of FGR. Exclusion criteria included a history of eye surgery.

The diagnostic criteria for FGR included a EFW or abdominal circumference below the 10th percentile for the corresponding gestational age.[13] Gestational age was determined based on fetal crown-rump length at 11–13 weeks or fetal head circumference at 19–24 weeks.[14,15] Severe FGR was defined as EFW or AC below the 3rd percentile for the corresponding gestational age. Early-onset FGR was defined as FGR manifesting before 32 weeks of gestation.

Ultimately, 31 women were included in the FGR group, of whom 24 had severe FGR and 7 had mild cases. Among these, 20 cases were classified as early-onset FGR, and 11 were categorized as late-onset FGR. The study was approved by the Ethics Committee of the Shanghai First Maternity and Infant Hospital Affiliated to Tongji University (KS22310).

Doppler Ultrasonic Parameter Measurement

Patients were positioned in the supine posture with the head of the bed elevated by less than 20°. All ultrasound examinations were performed using a GE Voluson E10 ultrasound machine (GE Healthcare, Zipf, Austria) equipped with a high-frequency linear array probe to minimize power output. The probe was coated with a thick layer of gel and gently placed on the patients' closed eyelids to avoid exerting pressure on the eyeball. When the two-dimensional image clearly displayed the dark region of the optic nerve posterior to the globe, the Doppler sampling frame was positioned 15–20 mm behind the eyeball to identify the red ribbon blood flow signal of the OA. The probe was then slightly adjusted to ensure the angle between the acoustic beam and the blood flow direction was less than 20°. Sampling was performed once the optimal spectrum was identified.

The P1 systolic peak blood velocity (P1SV), P2 peak blood velocity (P2SV), end-diastolic blood velocity (EDV), P1 peak systolic velocity/

end-diastolic velocity (S/D), time-averaged maximum velocity (TAMAX), resistance index (RI), and pulsatility index (PI) of the OA were measured, and the PR value was subsequently calculated. The Doppler parameters for both the left and right ophthalmic arteries were measured, and the average value was computed. Figure 1 illustrates the ultrasonic Doppler waveform of the OA.

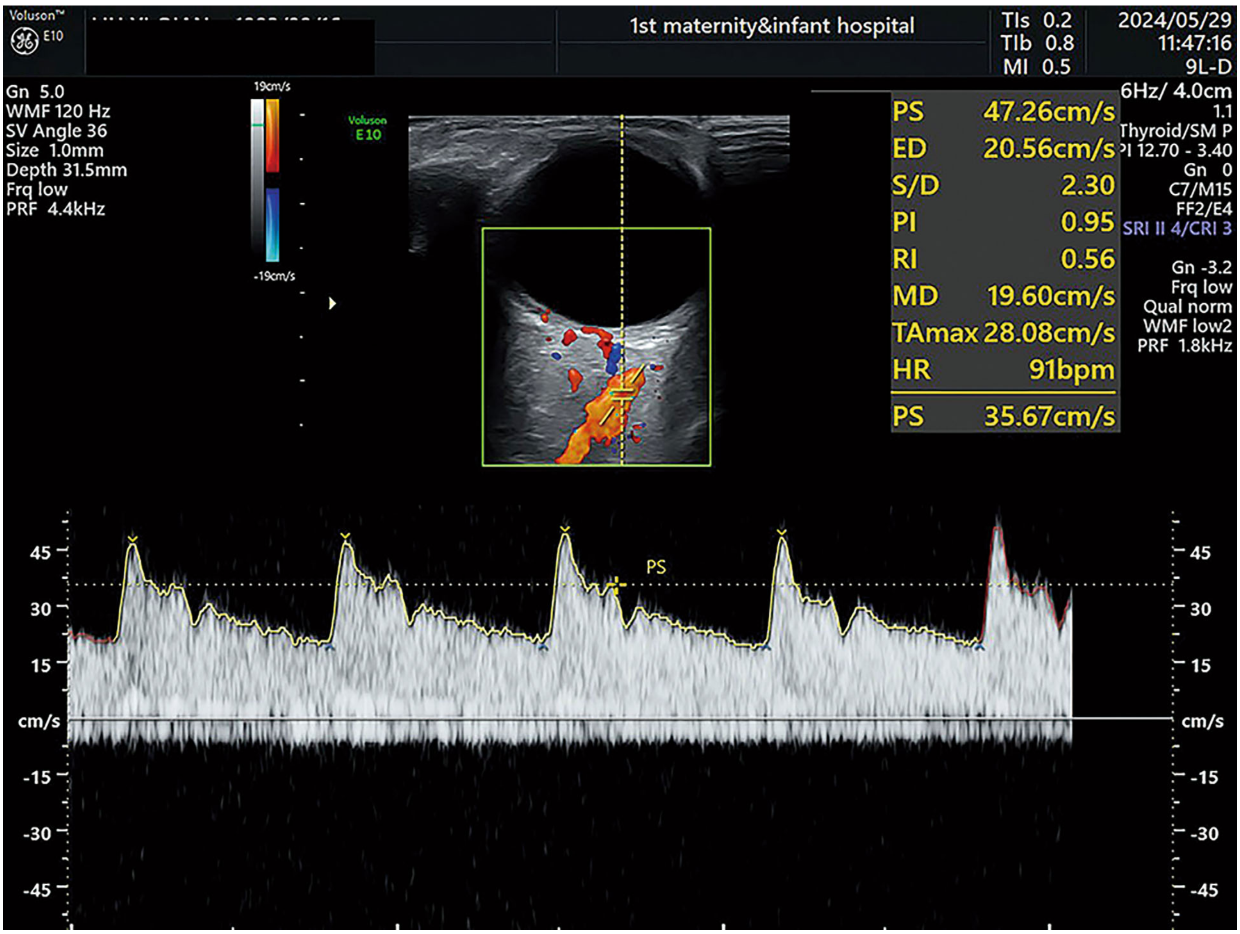
ONSD Measurement

Using the same patient positioning and probe, the ONSD was measured 3 mm posterior to the optic disc in both the sagittal and transverse planes of each eye. The average of these measurements was then calculated and recorded.

Statistical Analysis

Statistical analysis was performed using SPSS 26.0 software. Normality tests were conducted for all parameters. Quantitative data were presented as means ± standard deviations. For normally distributed data, *t* tests were applied to compare the two groups. For qualitative or quantitative data that did not meet the normality assumption, non-parametric tests were employed. The chi-square test was used to compare the abnormal rates of *Z*-scores. Pearson correlation analysis was utilized to evaluate the correlation between PR values, P2SV, and gestational age at the time of ultrasound. The predictive accuracy of delivery within 1 week in the FGR group, based on PR values, was assessed using the receiver operating characteristic (ROC) curve and the area under the

Figure 1. Ultrasonic Doppler waveform of the ophthalmic artery.



curve (AUC). A P-value of <.05 was considered statistically significant.

Results

Baseline Characteristics of the Study Subjects

The clinical data of pregnant women and neonates were compared between the FGR group and the control group. In the FGR group, gestational age at the time of ultrasound, gestational age at delivery, 1- and 5-minute Apgar scores, and neonatal weight were significantly lower compared to the control group. Conversely, the cesarean section rate, the proportion of neonates with complications, and the rate of neonatal intensive care unit (NICU) admissions were markedly higher in the FGR group. These differences were statistically significant. Refer to Table 1 for further details.

Comparison of Ultrasonic Doppler Parameters of the Ophthalmic Artery and ONSD Between the FGR and Control Groups

The analysis demonstrated that the P2SV and PR values in the FGR group were significantly elevated compared to those in the control group, with statistically significant differences observed ($P < .05$). However, no significant differences were noted for the other parameters. Refer to Table 2 for further details. Furthermore, the P2SV and PR values were analyzed for the overall population, as well as separately for the FGR and control groups, to explore their correlation with gestational age. The analysis revealed no significant correlation between PR values and gestational age at the time of imaging. However, a significant inverse correlation was observed between P2SV and gestational age, with a correlation coefficient of −0.301.

Comparison of Ultrasonic Doppler Parameters of the Ophthalmic Artery and ONSD Between the Mild and Severe FGR Groups

Among the 31 pregnancies complicated by FGR, 24 cases were classified as severe FGR, while 7 cases were categorized as mild FGR. Comparative analysis of the ultrasonic Doppler parameters of the OA and ONSD between the mild and severe FGR groups revealed no statistically significant differences. Refer to Table 3 for further details.

Comparison of Ultrasonic Doppler Parameters of the Ophthalmic Artery and ONSD Between the Early-Onset and Late-Onset FGR Groups

Among the 31 pregnancies complicated by FGR, 21 cases were classified as early-onset FGR, while 10 cases were classified as late-onset FGR. Comparative analysis of the ultrasonic Doppler parameters of the OA and ONSD between the early-onset and late-onset FGR groups revealed no statistically significant differences. Refer to Table 4 for further details.

Table 1. Comparison of Clinical Data Between the FGR Group and the Normal Group of Pregnant Women and Newborns

	FGR Group (n = 31)	Normal Group (n = 31)	*P*
Maternal age (year)	31.45 ± 3.491	30.323 ± 3.516	.209
Gravidity	1.71 ± 1.131	1.71 ± 0.902	1.000
Parity	0.19 ± 0.402	0.19 ± 0.402	1.000
BMI (kg/m^2)	21.51 ± 3.814	21.36 ± 2.753	.854
Gestational age at the time of ultrasound	33.39 ± 3.607	35.41 ± 3.962	.041*
Gestational weeks at delivery	35.73 ± 2.829	38.97 ± 1.292	.000*
Cesarean section	26 (83.9%)	15 (48.4%)	.003*
Newborn complication	15 (48.4%)	6 (19.4%)	.016*
Neonatal intensive care unit	16 (51.6%)	6 (19.4%)	.008*
Apgar score at 1 minute	8.79 ± 0.491	9.16 ± 0.374	.002*
Apgar score at 5 minute	9.41 ± 0.501	9.80 ± 0.402	.001*
Newborn weight (g)	2045.17 ± 566.667	3124.84 ± 356.068	.000*

Data are shown as mean ± SD or number of participants (%); *$P < .05$.

Table 2. Comparison of Ophthalmic Artery Doppler Ultrasound Parameters and Optic Nerve Sheath Diameter (ONSD) in Pregnant Women From the FGR Group Versus the Control Group

	FGR Group (n = 16)	Normal Group (n = 16)	*P*
P1SV (cm/s)	38.67 ± 13.928	36.10 ± 11.462	.432
P2SV (cm/s)	24.89 ± 10.671	20.13 ± 6.786	.040*
PR	0.65 ± 0.163	0.56 ± 0.086	.011*
S/D	3.88 ± 1.266	4.42 ± 1.256	.096
PI	1.55 ± 0.544	1.79 ± 0.422	.055
RI	0.72 ± 0.080	0.75 ± 0.075	.092
EDV (cm/s)	10.625 ± 4.130	8.66 ± 3.836	.056
TAMAX (cm/s)	17.52 ± 7.098	15.57 ± 5.436	.230
ONSD (mm)	3.17 ± 0.395	3.24 ± 0.299	.439

Data are shown as mean ± SD; **P* < .05.

Table 3. Comparison of Ophthalmic Artery Doppler Ultrasound Parameters and ONSD Between the Mild and Severe FGR Groups

	Severe Group (n = 24)	Mild Group (n = 7)	*P*
P1SV (cm/s)	39.07 ± 15.647	37.286 ± 5.337	.771
P2SV (cm/s)	25.20 ± 11.815	23.84 ± 5.702	.772
PR	0.65 ± 0.172	0.64 ± 0.138	.890
S/D	3.95 ± 1.341	3.63 ± 1.017	.570
PI	1.54 ± 0.586	1.56 ± 0.407	.938
RI	0.72 ± 0.079	0.70 ± 0.087	.675
EDV (cm/s)	10.51 ± 4.356	11.02 ± 3.510	.779
TAMAX (cm/s)	17.40 ± 7.910	17.90 ± 4.434	.874
ONSD (mm)	3.16 ± 0.412	3.19 ± 0.359	.884

Data are shown as mean ± SD.

Table 4. Comparison of Ophthalmic Artery Doppler Ultrasound Parameters and ONSD Between the Late-Onset and Early-Onset FGR Groups

	Early-Onset Group (n = 21)	Late-Onset Group (n = 10)	*P*
P1SV (cm/s)	40.31 ± 16.309	35.21 ± 5.999	0.350
P2SV (cm/s)	26.74 ± 12.161	20.99 ± 5.095	0.074
PR	0.67 ± 0.181	0.60 ± 0.106	0.144
S/D	3.80 ± 1.384	4.04 ± 1.021	0.628
PI	1.47 ± 0.603	1.72 ± 0.366	0.240
RI	0.71 ± 0.085	0.74 ± 0.066	0.359
EDV (cm/s)	11.31 ± 4.617	9.18 ± 2.467	0.105
TAMAX (cm/s)	18.43 ± 8.321	15.60 ± 2.836	0.174
ONSD (mm)	3.15 ± 0.433	3.20 ± 0.319	0.748

Data are shown as mean ± SD.

Comparison of Ultrasonic Doppler Parameters of the Ophthalmic Artery and ONSD Between FGR Cases With and Without Hypertension-Related Disorders

In the FGR cohort, 11 pregnant women had comorbidities associated with hypertension, while 15 exhibited no such comorbidities. Comparative analysis revealed that PR values were significantly elevated in the cohort with hypertension-related comorbidities compared to those without. Conversely, the S/D and PI values were significantly reduced in the former group, with these differences being statistically significant. Refer to Table 5 for further details.

Table 5. Comparison of Ophthalmic Artery Doppler Ultrasound Parameters and ONSD in Pregnant Women With FGR Associated With Hypertension-Related Disorders Versus Those Without Comorbidities

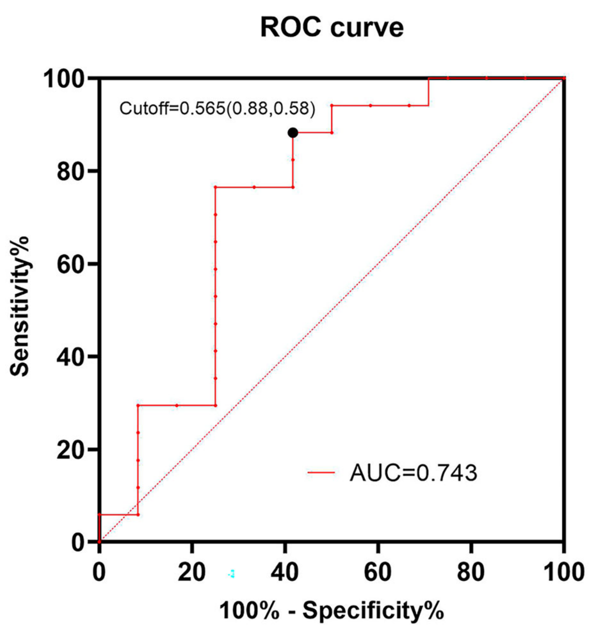
	HP Group (n = 11)	Control Group (n = 15)	*P*
P1SV (cm/s)	37.21 ± 9.820	37.79 ± 9.022	.878
P2SV (cm/s)	28.41 ± 9.573	21.86 ± 8.551	.079
PR	0.76 ± 0.119	0.58 ± 0.158	.004*
S/D	3.26 ± 0.753	4.34 ± 1.474	.025*
PI	1.21 ± 0.503	1.77 ± 0.499	.010*
RI	0.68 ± 0.064	0.74 ± 0.083	.052
EDV (cm/s)	11.75 ± 3.398	9.70 ± 4.111	.189
TAMAX (cm/s)	17.71 ± 7.855	16.74 ± 5.061	.703
ONSD (mm)	3.27 ± 0.518	3.05 ± 0.281	.186

Data are shown as mean ± SD; **P* < .05.

ROC Curve Analysis for Predicting Delivery Within 1 Week Using PR Values in Pregnant Women Over 28 Weeks Gestation

This study analyzed pregnancies complicated by FGR that were beyond 28 weeks of gestation. As illustrated in Figure 2, the ROC curve analysis demonstrated that the AUC for PR was 0.743. The predictive cut-off value for PR, indicating the likelihood of delivery within 1 week, was determined to be 0.565, with a sensitivity of 0.88 and a specificity of 0.58.

Figure 2. Receiver operating characteristic (ROC) curves of PR for pregnant women with FGR.



Discussion

The pathogenesis of FGR remains unclear, with multiple contributing factors involving the mother, fetus, and placenta. Some studies indicate that preterm infants and women with preeclampsia share similar pathophysiological characteristics, such as placental intrauterine damage and endothelial injury. Furthermore, women with these pregnancy complications are at an elevated long-term risk of developing cardiovascular diseases.[16–23] Notably, a significant proportion of women with preeclampsia also deliver infants with FGR, suggesting potential similarities in the underlying pathogenesis of these two conditions. Certain cardiovascular monitoring parameters applicable to preeclamptic women may, therefore, also be relevant for mothers with FGR.

The OA, a medium-sized vessel in the human arterial system, represents the first major branch of the internal carotid artery upon entering the cranial cavity. The Doppler ultrasound spectrum of the OA is characterized by two systolic peaks, P1 and P2. P1 is generated by ventricular contraction, which pumps blood from the aorta into the OA, while P2 results from blood reaching smaller, higher-resistance peripheral arteries and reflecting back to the heart via the aortic arch, with a portion of this wave entering the OA. The initial systolic peak, P1, like other arterial peaks, originates from ventricular contraction and reflects the magnitude of ventricular contractility. In contrast, P2SV is influenced by peripheral arterial compliance and resistance, closely associated with vascular compliance in medium-sized and small arteries, while P1SV depends more on cardiac output. Consequently, an elevated P2SV/P1SV ratio, or PR value, may suggest increased peripheral vascular resistance or reduced cardiac output.[8,24]

Numerous studies have demonstrated alterations in OA parameters among pregnant women with preeclampsia, including the pulsatility index (PI), resistance index (RI), peak systolic velocity (PSV), and PR. Notably, preeclamptic women exhibit a significant increase in PR values, whereas outcomes for other parameters vary across studies. However, there is a dearth of research investigating the relationship between OA parameters and FGR as assessed by Doppler ultrasound.

In a study by Abdel Azim et al, it was found that, in pregnant women between 35 and 36 + 6 weeks, the PR value among FGR mothers was significantly higher than that of normal mothers, albeit to a lesser degree than among preeclamptic mothers. It should be noted that this study focused exclusively on women at 35–36 + 6 weeks and compared only the P1SV, P2SV, and PR parameters of the OA.[25] A prospective study by Melo et al, involving 60 pregnant women with FGR, reported significantly lower PI and RI values in the FGR group compared to normal pregnancies, while the PR value was significantly elevated.[26] Abdel Azim and Arechvo et al compared FGR pregnancies without gestational hypertension or preeclampsia to other pregnancies and found that the PR values in the OA of FGR mothers were significantly higher. However, they did not exclude pregnant women with gestational diabetes from the control group, raising questions regarding the potential influence of this factor on the results.[27,28]

In the present study, pregnant women with FGR and normal pregnancies were enrolled and stratified based on the type and onset of FGR. The findings demonstrated a significantly elevated PR value and P2SV in the OA of the FGR group compared to the control group, whereas no significant differences were observed in PI, PR, and P1SV values between the two groups. These results suggest alterations in systemic microvascular conditions in FGR pregnancies, characterized by reduced peripheral vascular compliance and increased resistance, resembling changes observed in preeclampsia.

Further subgroup analysis was conducted based on the presence of hypertension-related (HR) disorders or the absence of maternal complications in pregnancies with FGR. The results revealed a significantly higher PR value in the HR group compared to the control group, along with markedly lower S/D and PI values, suggesting that hypertension influences vascular compliance. Additionally, analysis of the PR value in ophthalmic arteries of pregnant women beyond 28 weeks of gestation indicated that a PR value of 0.565 serves as an effective predictor for the likelihood of delivery within 1 week, with a sensitivity of 0.88 and specificity of 0.58.

Comparative analyses of mild versus severe FGR, as well as early-onset versus late-onset FGR, revealed no statistically significant differences. It is plausible that the limited sample size within each subgroup did not provide sufficient power to detect significant distinctions. Validation of potential subgroup differences will require larger-scale studies.

Furthermore, this study analyzed the ONSD in pregnant women with FGR and normal pregnancies. The results showed no statistically significant differences, indicating that FGR may not necessarily be associated with changes in intracranial pressure.

The limitations of this study should be acknowledged. Firstly, the absence of clear guidelines to differentiate between small-for-gestational-age (SGA) infants and those with FGR may have resulted in the inadvertent inclusion of healthy SGA infants. Second, the relatively small sample size highlights the need for larger-scale studies to confirm these findings. Additionally, the gestational ages of the subjects at the time of ultrasound were not matched between the two groups, potentially raising concerns regarding the comparability of the measured values. Nonetheless, a correlation analysis—conducted for the overall cohort and individual groups—revealed no significant correlation between PR values and gestational age at the time of imaging, supporting the comparability of the data. Nevertheless, matching gestational ages between groups would enhance the robustness of the results. Finally, P2SV demonstrated a slight negative correlation with gestational age within the FGR group, and this study does not fully establish that P2SV in the OA of FGR pregnancies differs from that of normal pregnancies.

Conclusion

Pregnant women with FGR demonstrate a significant increase in the PR value of the OA. This PR value possesses predictive significance for delivery within 1 week in late-stage pregnancies, with a cut-off value of 0.565. Therefore, the PR value may serve as a reliable indicator for identifying FGR fetuses and predicting the timing of delivery.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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