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Original Article

A multiparameter model combining ultrasound and maternal serum biomarkers accurately predicts late-onset fetal growth restriction

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Abstract: Objectives: Late-onset fetal growth restriction (FGR) in pregnancy is frequently encountered and is linked to adverse perinatal results. This investigation aimed to evaluate the clinical use of a multiparameter model combining ultrasound features and maternal serum biomarkers for late-onset FGR. Methods: A retrospective investigation was conducted on 350 pregnant women in their third trimester who received standard prenatal care between January 2021 and December 2025. Participants were divided into a late-onset FGR group (n = 175) and a normal fetal development group (n = 175) according to the Chinese expert consensus criteria. Ultrasound findings including fetal biometry and Doppler flow indices were measured. Maternal serum levels of soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PLGF) were quantified through enzyme-linked immunosorbent assay. Subsequently, the sFlt-1 to PLGF ratio (sFlt-1/PLGF) was calculated. Results: Among the 350 enrolled women, the FGR group exhibited markedly reduced abdominal circumference, estimated fetal weight, cerebroplacental ratio, and elevated uterine artery-pulsatility index and sFlt-1/PLGF compared to those in the normal group (all $P < 0.05$). The multiparameter evaluation model achieved an area under the curve of 0.977, demonstrating a sensitivity of 91.4% and specificity of 92.6% at the optimal threshold. Conclusions: The multiparameter model integrating ultrasound features and maternal serum biomarkers demonstrated excellent predictive performance for late-onset FGR, supporting its clinical use for early identification and management.

Keywords: Late-onset fetal growth restriction, ultrasound features, maternal serum biomarkers, multiparameter model

Introduction

Fetal growth restriction (FGR) affects around 5-10% of pregnancies globally and represents a major contributor to perinatal illness and death worldwide [1]. Unlike early-onset FGR, which is often linked with significant placental dysfunction and identifiable structural or chromosomal anomalies, late-onset FGR (identified at or after 32 weeks of gestation) comprises 70-80% of all FGR cases and frequently presents with more subtle clinical features [2]. This subgroup is particularly challenging to detect antepartum because affected fetuses often have normal or borderline growth measurements until the third trimester, yet they remain at heightened risk for adverse neurodevelopmental outcome, stillbirth, and neonatal complications [3]. Current routine prenatal surveillance, based largely on serial fundal height measurements and standard ultrasound biometry, has limited sensitivity for identifying late-onset FGR, leading to delayed recognition and missed opportunities for timely intervention [4].

Doppler ultrasound has substantially improved the assessment of fetoplacental hemodynamics. In late-onset FGR, typical findings include increased umbilical artery-pulsatility index (UA-PI) reflecting placental vascular resistance, and decreased middle cerebral artery-PI (MCA-PI) indicating cerebral vasodilation - the so-called

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brain-sparing effect [5]. The cerebroplacental ratio (CPR), determined by the formula MCA-PI/UA-PI, has emerged as a sensitive predictor of adverse outcome even when UA-PI remains within the normal range [6]. However, Doppler findings alone may not fully capture the underlying pathophysiology. Uterine artery (UtA) Doppler abnormalities, suggestive of impaired spiral artery remodeling, are less prominent in late-onset than in early-onset FGR, limiting their standalone predictive value. Consequently, reliance on a single ultrasound finding often yields suboptimal accuracy for identifying late-onset FGR [7, 8].

Parallel advances in angiogenic biomarker research have provided complementary insights. A dysregulation between the pro-angiogenic placental growth factor (PLGF) and the anti-angiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) plays a key driver of placental dysfunction [9]. In pregnancies destined to develop late-onset FGR, maternal serum PLGF levels tend to decline while sFlt-1 levels rise, resulting in a higher sFlt-1/PLGF several weeks before any clinical or sonographic manifestations appear [10]. Nevertheless, biomarker thresholds vary across populations and gestational ages, and their predictive value when used in isolation remains moderate [11].

Given that late-onset FGR arises from a complex interplay of suboptimal placentation, hemodynamic redistribution, and impaired fetal growth, a multiparameter approach integrating ultrasound features with maternal serum biomarkers holds promise for improving identification accuracy [12]. Such a model could capture both structural (biometric) and functional (Doppler and angiogenic) dimensions of the disorder, potentially overcoming the limitations of single-marker strategies [13]. However, the systematic evaluation of the clinical value of combining these modalities specifically for late-onset FGR has not been conducted in a large-scale cohort [2].

Consequently, this study sought to develop and validate a multiparameter evaluation model incorporating ultrasound features (fetal biometry and Doppler indices) and maternal serum biomarkers (sFlt-1, PLGF, and their ratio), and to assess its predictive performance for late-onset FGR in third-trimester pregnancies.

Materials and methods

Patients

A retrospective analysis was conducted on 350 pregnant women in their third trimester who were regularly admitted for prenatal assessments at The Fourth Hospital of Shijiazhuang from January 2021 to December 2025. Of these, 175 cases were identified with late-onset FGR (FGR group), while 175 cases had normal fetal development during the same period (Normal group). The inclusion criteria for the study were: (a) singleton pregnancy with a gestational age of 32 weeks or more; (b) FGR group met the diagnostic criteria for FGR [14]; (c) Normal group showed normal findings on ultrasound examination; (d) regular prenatal checkups were maintained; (e) maternal mental status and communication abilities were normal; (f) complete clinical data. Exclusion criteria included: (a) fetal structural malformations or chromosomal abnormalities; (b) maternal cardiac, thyroid, liver, or renal insufficiency; (c) diagnosed autoimmune diseases or congenital infections; (d) twin or multiple pregnancies. This research was performed in compliance with the Declaration of Helsinki and received approval from the Institutional Review Board (IRB) at The Fourth Hospital of Shijiazhuang. Due to the retrospective design of the study and the utilization of anonymized data, the IRB waived the need for written informed consent.

According to the “Chinese Expert Consensus on Fetal Growth Restriction” [14], the diagnostic criteria for late-onset FGR are as follows: fetal growth abnormalities occurring at or after 32 weeks of gestation, with an abdominal circumference (AC) and/or estimated fetal weight (EFW) below the 3rd percentile, or meeting at least two out of these three conditions: (a) AC and/or EFW below the 10th percentile; (b) a decreasing trend in AC and/or EFW growth compared to the previous examination, with a difference exceeding 50% in percentiles; (c) a CPR below the 5th percentile or an UA-PI above the 95th percentile.

Instruments and methods

(1) Ultrasound examination: A color Doppler ultrasonic diagnostic instrument (Voluson E8, GE Healthcare, USA) was used with a convex

array probe frequency set at 3.5-5.0 MHz. Pregnant women were comforted to calm their emotions and guided to lie in a supine position. The basic fetal conditions (placenta, fetal heart rate, umbilical cord) were first observed, followed by measurements of fetal growth and development parameters [head circumference (HC), biparietal diameter (BPD), AC, femur length (FL), and EFW]. Subsequently, the UtA, UA, and MCA were examined to obtain blood flow indices [PI, resistance index (RI), and end-systolic peak flow velocity to end-diastolic peak flow velocity ratio (S/D)]. The MCA-PI to UA-PI ratio was calculated as the CPR.

(2) Serological testing: Two enzyme-linked immunosorbent assay (ELISA) kits (BMS268-3, EHPGF, Thermo Fisher Scientific, USA) were used to measure sFlt-1 and serum PLGF. The sFlt-1 to PLGF ratio (sFlt-1/PLGF) was then calculated.

Statistical processing

Statistical analyses were performed employing SPSS statistical software (Version 29.0, SPSS Inc., USA). The normality of continuous variables was evaluated with the Shapiro-Wilk test, while homogeneity of variances was assessed by Levene's test. Normally distributed data were reported as mean ± standard deviation (M±SD), and non-normally distributed data as median (interquartile range). For group comparisons, the independent samples t-test or the Mann-Whitney U test was applied as appropriate. Categorical variables were presented as frequencies and percentages [n (%)] and compared between groups utilizing the χ^2 test. To identify independent influencing factors of late-onset FGR, both univariate and multivariate logistic regression analyses were conducted. Candidate variables for multivariable logistic regression were selected based on univariate analysis ($P < 0.10$) and clinical relevance. To prevent multicollinearity, variance inflation factors (VIF) were calculated, and variables with a VIF > 5 were excluded. The final model selection used a stepwise forward selection procedure (entry criterion $P < 0.05$, removal criterion $P > 0.10$). The diagnostic utility of ultrasound characteristics and maternal serum biomarkers, assessed separately and in combination, was assessed through receiver operating characteristic (ROC) curves for late-onset FGR. A *P*-value less than 0.05 was considered significant.

Results

General information

No notable differences were observed between the two groups regarding maternal age, gestational age at examination, gravidity, BMI, conception method, or GDM (all $P > 0.05$, **Table 1**). However, the incidence of hypertensive disorders of pregnancy (HDP) was markedly higher in the FGR group compared to the normal group (28.00% vs. 10.29%, $P < 0.001$).

Ultrasound features

In comparison to the normal group, the FGR group demonstrated notably lower values for BPD ($P = 0.027$), HC ($P = 0.013$), AC ($P < 0.001$), FL ($P = 0.013$), and EFW ($P < 0.001$). These results suggest that fetuses in the FGR group exhibit smaller measurements across all assessed anatomic dimensions relative to those in the normal group, highlighting a broad effect on fetal growth (**Table 2**).

For UtA, both PI ($P = 0.011$), RI ($P = 0.002$), and S/D ($P = 0.004$) were markedly higher in the FGR group compared to the normal group. Similarly, for UA, PI was also markedly higher in the FGR group ($P = 0.005$), although RI did not show a notable difference ($P = 0.480$). The UA S/D was also markedly elevated in the FGR group ($P = 0.006$). Conversely, MCA measurements indicated that PI was lower in the FGR group ($P = 0.011$), whereas RI was significantly reduced as well ($P = 0.002$). Furthermore, the CPR was markedly lower in the FGR group ($P < 0.001$). These findings suggest an increased resistance to blood flow in both the UtA and UA in pregnancies affected by FGR, alongside a relative decrease in resistance in the MCA, indicating potential compensatory mechanisms in fetal blood flow distribution (**Table 3**).

Maternal serum biomarkers

The levels of sFlt-1 were markedly elevated in the FGR group ($P < 0.001$), whereas PLGF levels were markedly reduced ($P < 0.001$). Consequently, the sFlt-1/PLGF was markedly elevated in the FGR group compared to the normal group ($P < 0.001$). These findings suggest that

Table 1. Comparison of general information between the two groups

Item	Normal group (n = 175)	FGR group (n = 175)	t/χ^2	P
Age (years)	*31.28 ± 3.15*	*31.67 ± 3.42*	*1.084*	*0.279*
Gestational age (weeks)	*34.32 ± 1.08*	*34.47 ± 1.21*	*1.271*	*0.205*
Gravidity (times)	*1.63 ± 0.46*	*1.55 ± 0.43*	*1.771*	*0.077*
BMI (kg/m^2)	*21.06 ± 2.85*	*20.78 ± 3.01*	*0.889*	*0.375*
Method of conception [n (%)]			*2.685*	*0.101*
Assisted conception	*98 (56.00%)*	*113 (64.57%)*		
Natural conception	77 (44.00%)	62 (35.43%)		
GDM [n (%)]	*51 (29.14%)*	*38 (21.71%)*	*2.546*	*0.111*
HDP [n (%)]	*18 (10.29%)*	*49 (28.00%)*	*17.739*	*< 0.001*

FGR, Fetal Growth Restriction; BMI, Body Mass Index; GDM, Gestational Diabetes Mellitus; HDP, Hypertensive Disorders of Pregnancy.

Table 2. Comparison of fetal development indicators between the two groups

Indicator	Normal group (n = 175)	FGR group (n = 175)	t	P
BPD (cm)	*8.72 ± 0.91*	*8.51 ± 0.88*	*2.226*	*0.027*
HC (cm)	*30.05 ± 3.28*	*29.21 ± 2.96*	*2.495*	*0.013*
AC (cm)	*29.88 ± 3.45*	*25.15 ± 3.07*	*13.552*	*< 0.001*
FL (cm)	*6.23 ± 1.02*	*5.96 ± 0.98*	*2.502*	*0.013*
EFW (g)	*3056.41 ± 458.73*	*2457.89 ± 462.15*	*12.159*	*< 0.001*

FGR, Fetal Growth Restriction; BPD, Biparietal Diameter; HC, Head Circumference; AC, Abdominal Circumference; FL, Femur Length; EFW, Estimated Fetal Weight.

Table 3. Comparison of blood flow indicators between the two groups

Indicator	Normal group (n = 175)	FGR group (n = 175)	t	P
UtA				
PI	*0.84 ± 0.14*	*0.89 ± 0.19*	*2.547*	*0.011*
RI	*0.42 ± 0.07*	*0.45 ± 0.11*	*3.078*	*0.002*
S/D	*2.69 ± 0.24*	*2.77 ± 0.28*	*2.883*	*0.004*
UA				
PI	*0.82 ± 0.15*	*0.86 ± 0.14*	*2.826*	*0.005*
RI	*0.56 ± 0.06*	*0.57 ± 0.08*	*0.707*	*0.480*
S/D	*2.33 ± 0.28*	*2.41 ± 0.25*	*2.764*	*0.006*
MCA				
PI	*1.79 ± 0.23*	*1.73 ± 0.21*	*2.544*	*0.011*
RI	*0.76 ± 0.08*	*0.74 ± 0.05*	*3.056*	*0.002*
CPR	*2.21 ± 0.19*	*2.01 ± 0.22*	*9.012*	*< 0.001*

FGR, Fetal Growth Restriction; UtA, Uterine Artery; PI, Pulsatility Index; RI, Resistance Index; S/D, End-Systolic Peak Flow Velocity to End-Diastolic Peak Flow Velocity Ratio; UA, Umbilical Artery; MCA, Middle Cerebral Artery; CPR, Cerebroplacental Ratio.

pregnancies complicated by FGR are characterized by an imbalance between angiogenic and anti-angiogenic factors, with increased sFlt-1 and decreased PLGF levels leading to a higher sFlt-1/PLGF (**Figure 1**).

Univariate logistic regression analysis

The univariate logistic regression analysis revealed multiple significant influencing factors for late-onset FGR. HDP significantly increased the odds of late-onset FGR ($P < 0.001$, odds ratio [OR] = 3.392). Among fetal biometric parameters, BPD ($P = 0.028$, OR = 0.765), HC ($P = 0.014$, OR = 0.918), AC ($P < 0.001$, OR = 0.646), and FL ($P = 0.014$, OR = 0.763) were inversely associated with late-onset FGR. EFW also showed a significant inverse association ($P < 0.001$, OR = 0.997). For blood flow parameters, UtA-PI ($P = 0.012$, OR = 4.989), UtA-RI ($P = 0.003$, OR = 39.875), S/D ($P = 0.005$, OR = 3.247), UA-PI ($P = 0.006$, OR = 7.931), and UA-S/D ($P = 0.007$, OR = 3.087) were positively associated with late-onset FGR. Conversely, MCA-PI ($P = 0.012$, OR = 0.290) and MCA-RI ($P = 0.003$, OR = 0.007) were inversely linked to late-onset FGR. Additionally, the CPR was strongly inversely linked to late-onset FGR ($P < 0.001$, OR = 0.011). Maternal serum biomarkers sFlt-1 ($P <$

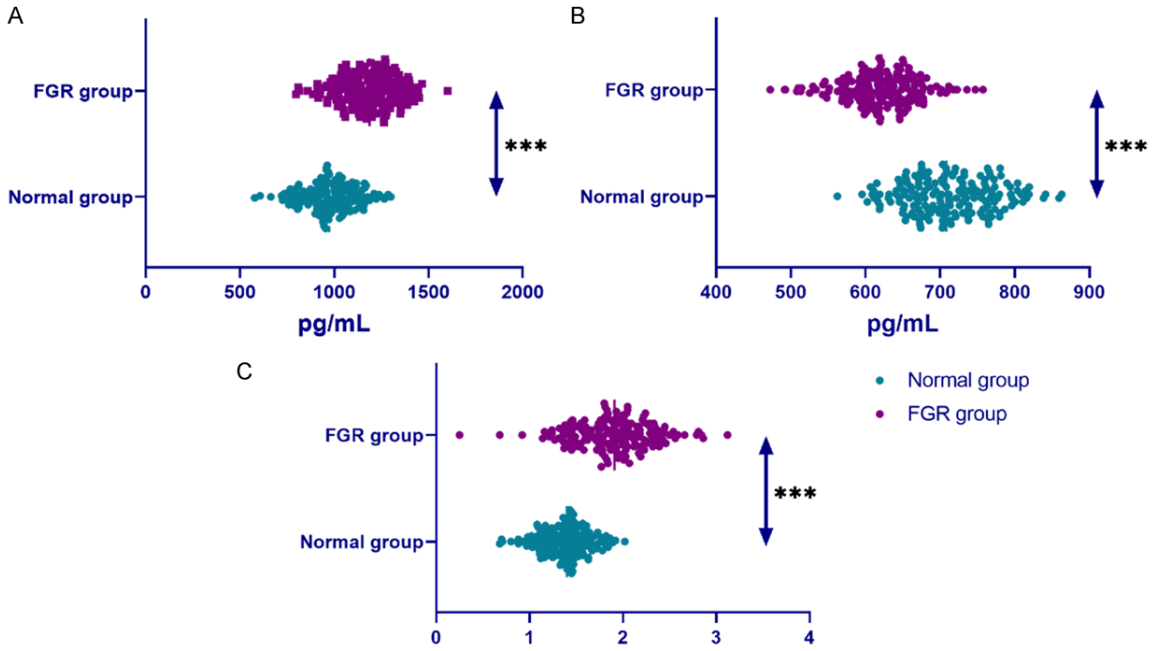

Figure 1. Comparison of maternal serum biomarkers between two groups. A. sFlt-1; B. PLGF; C. sFlt-1/PLGF. FGR, Fetal Growth Restriction; sFlt-1, Soluble Vascular Endothelial Factor Receptor-1; PLGF, Placental Growth Factor; ***: P < 0.001.

Table 4. Univariate logistic regression analysis of influencing factors of late-onset FGR

Indicator	Coefficient	Std Error	Wald	P	OR	95% CI
HDP	*1.221*	*0.30*	*4.065*	*< 0.001*	*3.392*	*1.913-6.250*
BPD	*-0.268*	*0.122*	*2.202*	*0.028*	*0.765*	*0.601-0.969*
HC	*-0.086*	*0.035*	*2.457*	*0.014*	*0.918*	*0.856-0.982*
AC	*-0.436*	*0.048*	*9.109*	*< 0.001*	*0.646*	*0.585-0.706*
FL	*-0.270*	*0.110*	*2.463*	*0.014*	*0.763*	*0.613-0.944*
EFW	*-0.003*	*0.000*	*8.700*	*< 0.001*	*0.997*	*0.996-0.998*
UtA-PI	*1.607*	*0.641*	*2.507*	*0.012*	*4.989*	*1.442-17.910*
CPR	*-4.553*	*0.611*	*7.456*	*< 0.001*	*0.011*	*0.003-0.033*
sFlt-1/PLGF	*4.668*	*0.507*	*9.208*	*< 0.001*	*106.474*	*41.661-305.455*

FGR, Fetal Growth Restriction; OR, Odds Ratio; CI, Confidence Interval; HDP, Hypertensive Disorders of Pregnancy; BPD, Biparietal Diameter; HC, Head Circumference; AC, Abdominal Circumference; FL, Femur Length; EFW, Estimated Fetal Weight; UtA, Uterine Artery; PI, Pulsatility Index; CPR, Cerebroplacental Ratio; sFlt-1, Soluble Vascular Endothelial Factor Receptor-1; PLGF, PLGF, Placental Growth Factor.

0.001, OR = 1.009) and PLGF (P < 0.001, OR = 0.967) as well as their ratio (sFlt-1/PLGF) (P < 0.001, OR = 106.474) demonstrated significant associations with late-onset FGR. These findings highlight the multifactorial nature of late-onset FGR, involving maternal vascular health, fetal growth measurements, and angiogenic balance (**Table 4**).

Multivariate logistic regression analysis

In the multivariate logistic regression analysis of influencing factors for late-onset FGR, several measures showed significant associations (**Table 5**). AC (P < 0.001, OR = 0.589), EFW (P < 0.001, OR = 0.997), and CPR (P < 0.001, OR = 0.003) were significantly linked to a reduced risk of late-onset FGR. UtA-PI (P = 0.044, OR = 15.692) and sFlt-1/PLGF (P < 0.001, OR = 177.176) showed strong associations with an increased risk of late-onset FGR.

ROC analysis

Among the single measurements, sFlt-1/PLGF (area under the curve [AUC] = 0.863) had the

Table 5. Multivariate logistic regression analysis of influencing factors of late-onset FGR

Indicator	Coefficient	Std Error	Wald Stat	P	OR	OR CI Lower	OR CI Upper
AC	-0.529	0.086	-6.141	< 0.001	0.589	0.498	0.698
EFW	-0.003	0.001	-5.273	< 0.001	0.997	0.996	0.998
UtA-PI	2.753	1.369	2.011	0.044	15.692	1.072	229.603
CPR	-5.849	1.165	-5.019	< 0.001	0.003	0.000	0.028
sFlt-1/PLGF	5.177	0.800	6.470	< 0.001	177.176	36.924	850.154

FGR, Fetal Growth Restriction; OR, Odds Ratio; CI, Confidence Interval; HDP, Hypertensive Disorders of Pregnancy; BPD, Biparietal Diameter; HC, Head Circumference; AC, Abdominal Circumference; FL, Femur Length; EFW, Estimated Fetal Weight; UtA, Uterine Artery; PI, Pulsatility Index; CPR, Cerebroplacental Ratio; sFlt-1, Soluble Vascular Endothelial Factor Receptor-1; PLGF, PLGF, Placental Growth Factor.

Table 6. ROC curve analysis of ultrasound features and maternal serum biomarkers for the independent diagnostic efficacy of late-onset FGR

Indicator	Best_threshold	Sensitivities	Specificities	AUC	Youden_index	F1_score
AC	28.060	0.851	0.697	0.845	0.548	0.756
EFW	2655.910	0.669	0.840	0.821	0.509	0.305
UtA-PI	0.995	0.320	0.863	0.576	0.183	0.439
CPR	2.105	0.680	0.714	0.748	0.394	0.315
sFlt-1/PLGF	1.735	0.709	0.926	0.863	0.635	0.795

FGR, Fetal Growth Restriction; AUC, Area Under the Curve; HDP, Hypertensive Disorders of Pregnancy; BPD, Biparietal Diameter; HC, Head Circumference; AC, Abdominal Circumference; FL, Femur Length; EFW, Estimated Fetal Weight; UtA, Uterine Artery; PI, Pulsatility Index; CPR, Cerebroplacental Ratio; sFlt-1, Soluble Vascular Endothelial Factor Receptor-1; PLGF, PLGF, Placental Growth Factor.

highest predicted AUC for late-onset FGR, followed by AC (AUC = 0.845), and EFW (AUC = 0.821). The CPR showed an AUC of 0.748. The predictive performance of UtA-PI was relatively low (AUC = 0.576). **Table 6** lists the detailed optimal threshold, sensitivity, specificity, Youden index, and F1 score.

Multiparameter evaluation model

Logit(P) = -5.124 + (-0.529 × AC) + (-0.003 × EFW) + (2.753 × UtA-PI) + (-5.849 × CPR) + (5.177 × sFlt-1/PLGF)

The multiparametric evaluation model combining ultrasound features and maternal serum biomarkers demonstrated high predictive performance for late-onset FGR, as illustrated by the ROC curve. The AUC was 0.977, indicating excellent discriminatory performance between cases with and without late-onset FGR. At the optimal cutoff value of 0.475, the model achieved a sensitivity of 91.4% and a specificity of 92.6%, suggesting strong accuracy in identifying affected pregnancies while minimizing false positives. The mean AUC from cross-validation was 0.892, slightly lower than the original AUC but remaining in the "excellent" discriminatory range. Bootstrap correction yielded an optimism-corrected AUC of 0.876. Additionally, calibration curve indicated a strong agreement between predicted and observed probabilities. Decision curve analysis also revealed a clinical net benefit across various threshold probabilities (**Figure 2**).

Discussion

In this retrospective study of 350 third-trimester pregnancies, we found that a multiparameter model integrating ultrasound features and maternal serum biomarkers achieved high predictive accuracy for late-onset FGR. The model outperformed any single parameter, underscoring the complementary value of combining biometry, Doppler indices, and angiogenic markers. Our results provide evidence that late-onset FGR is characterized by a multidimensional phenotype involving reduced fetal size, increased fetoplacental vascular resistance, cerebral vasodilation, and an anti-angiogenic state.

HDP were more prevalent in the FGR group compared to the normal group at baseline. This association aligns with the established rela-

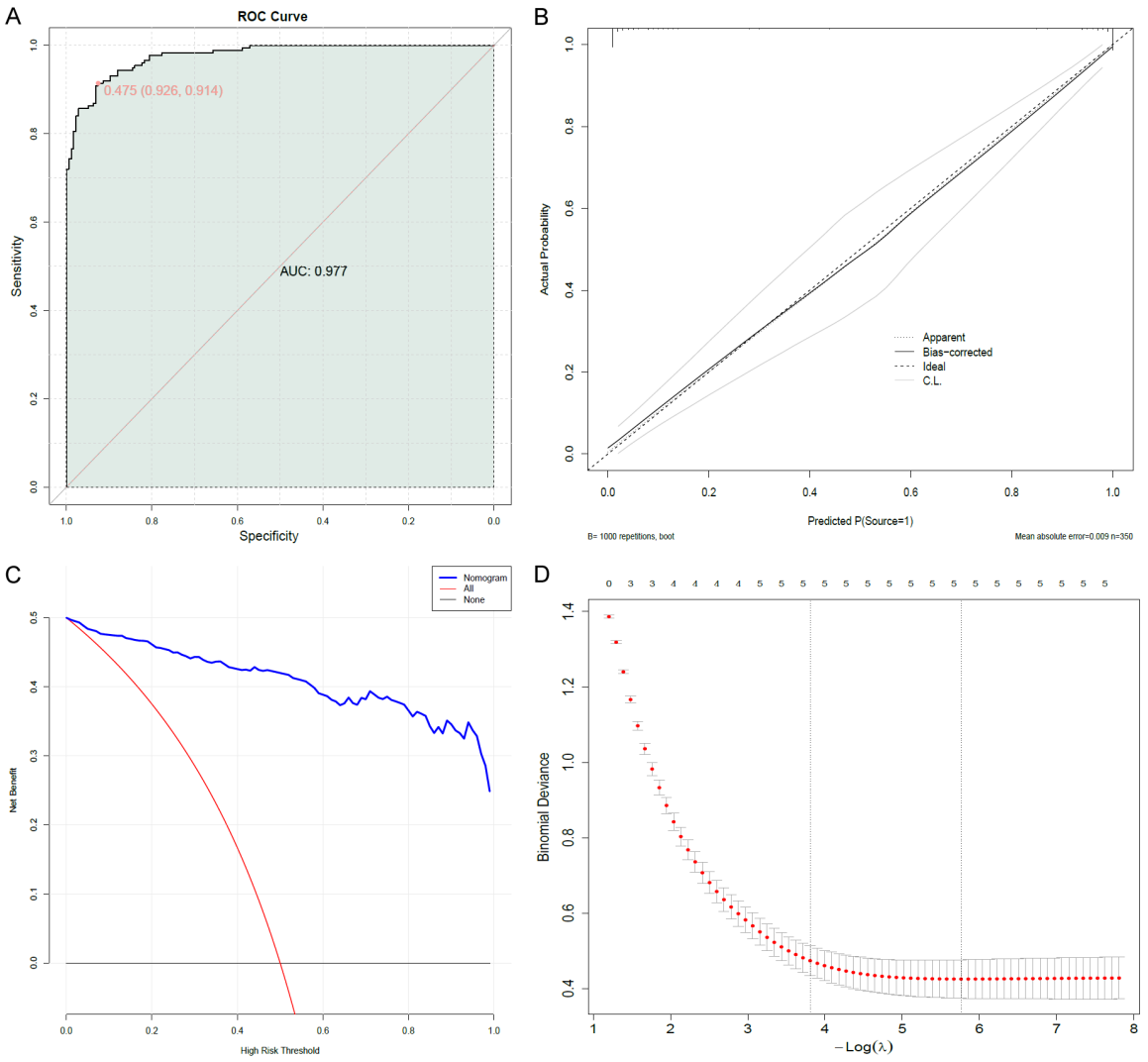

Figure 2. The diagnostic value of a multiparametric evaluation model combining ultrasound features and maternal serum biomarkers for late-onset FGR. A. ROC analysis; B. Calibration curve; C. Decision curve analysis; D. Cross-validation. FGR, Fetal Growth Restriction; ROC, Receiver Operating Characteristic; AUC, Area Under the Curve.

tionship between maternal hypertension and impaired placentation, where inadequate spiral artery remodeling reduces uteroplacental blood flow [15]. However, in multivariate analysis, HDP lost its independent association with late-onset FGR, suggesting that its effect may be mediated through variables directly reflecting placental perfusion and endothelial function, such as UtA Doppler indices or angiogenic biomarkers. Prior studies have reported similar attenuation of HDP's contribution after adjusting for UtA-PI and sFlt-1/PLGF [16, 17].

Regarding fetal biometry, the FGR group showed lower BPD, HC, AC, FL, and EFW compared to the normal group. Among these, AC and EFW displayed the largest between-group differences and remained independent predictors in multivariate analysis. This pattern reflects the pathophysiology of late-onset FGR, where nutrient restriction preferentially affects viscera and subcutaneous fat, resulting in asymmetric growth restriction with relative head sparing. The reduction in AC indicates decreased liver glycogen stores and abdominal fat deposition, sensitive markers of chronic nutrient deprivation. EFW, derived from AC and other measures, naturally follows this trend [18]. Although BPD, HC, and FL were also lower in the FGR group, these measures did not maintain independent significance following adjustments, likely because they are less sensitive to

nutritional compromise in late gestation. Our findings align with established criteria prioritizing AC and EFW over head measurements for identifying late-onset FGR [19, 20].

Doppler flow measurements revealed increased impedance in UtA and UA and reduced impedance in the MCA. For UtA, the FGR group had higher PI, RI, and S/D, indicating persistent high resistance in the uterine circulation reflecting incomplete spiral artery transformation [21, 22]. Although UtA abnormalities are classically linked to early-onset disease, our results suggest a subset of late-onset FGR also exhibits impaired uterine perfusion, representing a milder or later manifestation of similar placental pathology. Comparable observations have been reported by others. UA Doppler showed higher PI and S/D in the FGR group, whereas RI did not differ. This discrepancy may arise because PI and S/D are more sensitive than RI to subtle increases in downstream resistance, especially when resistance is not markedly elevated - a common scenario in late-onset FGR [23].

The MCA Doppler revealed lower PI and RI in the FGR group, indicative of cerebral vasodilation - the brain-sparing effect [24]. This compensatory response redirects cardiac output toward the brain in the presence of hypoxemia [25]. However, brain sparing does not fully protect against neurodevelopmental harm; even in late-onset FGR, subtle alterations in cerebral perfusion have been linked to long-term cognitive and behavioral deficits [26]. The CPR, which integrates UA and MCA information, was substantially lower in the FGR group. CPR has gained recognition as a predictor of adverse perinatal outcomes because it detects brain sparing even when UA-PI remains within normal limits. In our cohort, CPR showed a strong inverse association with late-onset FGR, reinforcing its clinical relevance [27, 28].

Maternal serum biomarkers demonstrated an anti-angiogenic shift in the FGR group, with increased sFlt-1, decreased PLGF, and an elevated sFlt-1/PLGF [29]. sFlt-1 neutralizes PLGF and VEGF, leading to endothelial dysfunction. The decrease in PLGF reflects reduced placental synthesis and increased consumption. This imbalance is a final common pathway in placental insufficiency syndromes, including preeclampsia and FGR. Our results agree with previous reports that the sFlt-1/PLGF is elevated in both early- and late-onset FGR, although the magnitude is generally smaller in late-onset disease [30].

The multiparameter model combining ultrasound features (AC, EFW, UtA-PI, CPR) and maternal serum biomarkers (sFlt-1/PLGF) produced a higher AUC, which was superior to any individual parameter. This improvement is expected because late-onset FGR arises from a combination of factors, including maternal vascular malperfusion, fetal hemodynamic adaptation, and dysregulation of angiogenic factors, rather than a single defect. The model demonstrated high sensitivity and specificity in our cohort, suggesting potential for clinical utility pending validation in independent, multi-center prospective studies [31]. Several previous attempts to construct predictive models for FGR have used either ultrasound or biomarkers alone. For example, the TRUFFLE study focused on Doppler parameters for management, while others have used sFlt-1/PLGF for prediction of preeclampsia [32, 33]. Our study extends these efforts by demonstrating that a combined model yields better performance than either modality alone.

Several limitations must be recognized. Firstly, this study was a single-center retrospective analysis, potentially introducing selection bias and limiting its generalizability. Although we performed rigorous internal validation using 1,000-iteration bootstrap resampling and 5-fold cross-validation to correct for optimistic bias, external validation was not conducted. The model was developed and validated using data from a single center with a relatively homogeneous population, possibly limiting its applicability to broader clinical settings or populations with different demographic characteristics (e.g., varying prevalence of hypertensive disorders or ethnic backgrounds). External validation in a prospective, multicenter cohort is needed. Second, biomarkers were measured only once during the third trimester; repeated measurements might improve predictive accuracy. Third, the study population comprised Chinese women; applicability to other ethnic groups requires investigation. Fourth, maternal factors such as parity, smoking, or prior pregnancy history were not included, and could further refine the model. Fifth, the reference stan-

dard for FGR was based on ultrasound criteria; some cases may have been constitutionally small rather than truly growth-restricted. Placental pathology or postnatal growth follow-up would help distinguish these entities. Finally, neonatal outcomes were not assessed, so the model's ability to predict adverse events beyond identifying FGR remains unknown.

Conclusion

The multiparameter evaluation model combining ultrasound features (fetal development indicators and blood flow parameters) and maternal serum biomarkers (sFlt-1/PLGF) demonstrated excellent predictive performance for late-onset FGR during the third-trimester pregnancies. This integrated approach outperforms any single measurement, reflecting the multifactorial pathophysiology of the condition. The model holds promise as a clinically useful tool for early identification of affected pregnancies, enabling timely surveillance and intervention. Prospective validation across diverse populations is warranted before routine implementation.

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Disclosure of conflict of interest

None.

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