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Original Article

Early identification of fetal growth restriction using ultrasound biometrics and biochemical markers: a comprehensive diagnostic approach

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Abstract: Objective: To evaluate whether ultrasound biometrics improve the identification and early treatment of fetal growth restriction (FGR). Methods: This retrospective study analyzed 240 pregnant women admitted to a Ji'nan Maternity and Child Care Hospital over a five-year period starting from January 2021. The study population comprised 120 women with fetal growth restriction (FGR group) and 120 women with normal pregnancies (Control group). The diagnosis of FGR was based on ultrasound measurements, with estimated fetal weight (EFW) and abdominal circumference (AC) both below the 10th percentile. Clinical data on, including maternal risk factors, ultrasound scans, and fetal data (e.g., weight, health status, ultrasound measurements such as weight estimates, skull size, bone development, and head size), were analyzed. Results: The FGR group exhibited significantly lower EFW ($P < 0.001$), smaller AC ($P < 0.001$), shorter femur length (FL) ($P < 0.001$), and smaller biparietal diameter (BPD) ($P < 0.001$) compared to the control group. The head circumference to abdominal circumference ratio (HC/AC) was significantly higher in the FGR group ($P < 0.001$), reflecting abnormal growth patterns. Doppler ultrasound revealed significantly lower velocities and higher resistance indices in both the middle cerebral artery (MCA) and umbilical artery (UA) in the FGR group ($P < 0.001$). Additionally, biochemical markers such as beta-hCG were significantly higher ($P < 0.001$), while AFP and PAPP-A were significantly lower in the FGR group ($P < 0.001$). These findings highlight the importance of using ultrasound and specific biomarkers for effective detection of FGR. Conclusion: Early identification of fetal growth restriction (FGR) using a combination of ultrasound biometric indicators, Doppler blood flow measurements, and biochemical markers significantly enhances diagnostic accuracy, facilitates timely interventions, and enhances both maternal and fetal outcomes.

Keywords: Fetal growth restriction, ultrasound biometrics, diagnostic indicators, early detection

Introduction

Fetal growth restriction (FGR) is a serious condition that affects approximately 5-10% of pregnancies and is associated with numerous complications, including preterm birth, stillbirth, and long-term developmental and health issues for the child [1]. FGR occurs when the fetus fails to reach expected growth due to a variety of factors, including placental insufficiency, maternal health conditions, or genetic factors [2-4]. This condition is a leading cause of perinatal morbidity and mortality, as FGR fetuses are at a significantly higher risk of preterm birth or intrauterine death. Additionally, FGR is often associated with adverse outcomes in childhood, such as cognitive impairment, cardiovascular issues, and metabolic disorders [5-7].

Early and accurate detection of FGR is crucial for improving maternal and fetal outcomes. Ultrasound has become the primary diagnostic tool for FGR, with clinicians assessing fetal growth through biometric measurements such as abdominal circumference (AC), head circumference (HC), femur length (FL), and estimated fetal weight (EFW) [8, 9]. However, despite the widespread use of these biomarkers, there is no consensus on the most effective combination of measurements for diagnosing FGR reliably. Current methods can be difficult to inter-

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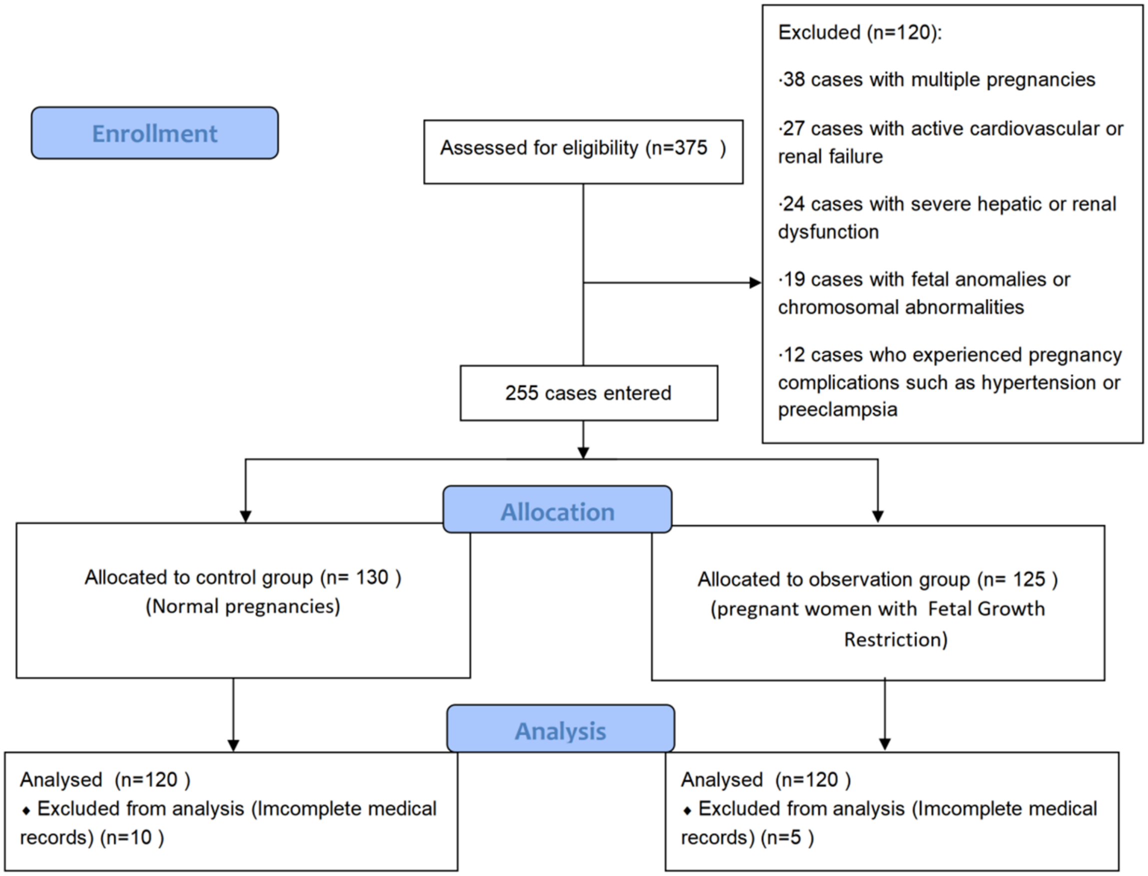

Figure 1. Flow diagram detailing patient selection in this study.

pret, particularly in borderline cases where fetal growth may fall within the normal range but still cause concern.

While previous studies have examined individual biometric measurements, few have explored the use of multiple ultrasound parameters in a comprehensive diagnostic approach. Moreover, there is limited research on the integration of additional diagnostic markers, such as biochemical markers and Doppler flow measurements, which could enhance the sensitivity and specificity of FGR detection. The innovation of this study lies in its comprehensive approach, which combines various ultrasound measurements with biochemical markers like beta-hCG, AFP, and PAPP-A, to develop a more robust and accurate diagnostic model. By integrating these diverse biomarkers, we hope to establish clearer diagnostic criteria for FGR and provide a more reliable tool for early assessment of fetal well-being. The clinical significance of this research is substantial, as early identification of FGR can facilitate timely interventions, reducing the risk of adverse pregnancy outcomes and improving long-term health for both the mother and the child.

Methods

Patients' selection

This study conducted a retrospective analysis of 240 pregnant women admitted to Ji'nan Maternity and Child Care Hospital between January 2021 and January 2025. The study participants were divided into two groups: the observation group (Fetal Growth Restriction, FGR; n = 120) and the control group (normal pregnancies; n = 120) according to the presence of FGR. The flowchart of the experimental design is shown in **Figure 1**. Ethical approval for the study was obtained from Ji'nan Maternity and Child Care Hospital.

Inclusion criteria: (1) women carrying singleton pregnancies between 28-40 weeks of gestational age; (2) pregnancy confirmed through routine prenatal assessments, including ultrasound; (3) complete medical records. The Observation Group consisted of women diagnosed with FGR, based on criteria such as fetal weight below the 10th percentile for gestational age, abnormal Doppler ultrasound results, and other indications of growth restriction [10]. The Control Group included healthy women with uncomplicated pregnancies and normal fetal development.

Exclusion criteria: pre-existing medical conditions (e.g., hypertension, diabetes, renal disease, cardiovascular disorders); multiple pregnancies (e.g., twins or triplets); fetal anomalies or chromosomal abnormalities; pregnancy complications such as hypertension or preeclampsia; incomplete medical records or unclear ultrasound data; or discontinued medical care before delivery.

Data extraction

In the FGR group, pregnancies with evidence of IUGR were identified when ultrasound-measured EFW and AC scores fell below the 10th percentile for gestational age. The control group consisted of healthy, uncomplicated pregnancies with normal EFW and AC values, indicating no evidence of growth restriction. To ensure comparability, both groups were matched for maternal age, parity, gestational age at entry, and other key demographic variables. Data collection involved gathering detailed pregnancy-related information, including maternal weight changes, any pre-existing medical conditions, and obstetric history. Routine ultrasound scans were performed during pregnancy to measure EFW, AC, BPD, FL and HC of the fetus. Additionally, Doppler studies were conducted on the middle cerebral artery (MCA), umbilical artery (UA), and placental vascular resistance indices. Biochemical markers, including Beta-hCG, AFP, and PAPP-A, were measured using maternal blood samples.

Outcome measures

Various ultrasound measurements, Doppler flow examinations, fetal heart variability, movement analysis, and biochemical markers were defined as primary outcomes for diagnosing FGR. The primary ultrasound measurements, including Estimated Fetal Weight (EFW), Abdominal Circumference (AC), Biparietal Diameter (BPD), Femur Length (FL), and Head Circumference (HC), were measured at regular intervals during pregnancy (i.e., 12, 20, 28, 32, and 36 weeks gestation). Additionally, the HC/AC ratio was used to assess abnormal growth patterns. Doppler ultrasound (Model: Voluson E8, Manufacturer: GE Healthcare, Chicago, IL, USA) was used to evaluate blood flow through the Middle Cerebral Artery (MCA) and Umbilical Artery (UA), by assessing S- and D-velocities and calculating the Resistance Index (RI) at 20, 28, and 36 weeks gestation to monitor changes in fetal circulation.

Secondary outcomes included tracking fetal health by monitoring heart rate and movement patterns, measured at regular intervals (e.g., 20, 28, and 36 weeks), as well as maternal weight gain during all trimesters. Maternal serum biochemical markers including β-hCG, AFP, and PAPP-A, were quantitatively assessed at 12, 20, and 32 weeks of gestation to evaluate placental function and its association with FGR. Blood samples were collected via venipuncture and processed within 2 hours. Levels of β-hCG (Cat. No. BKHCG-100), AFP (Cat. No. BKAFP-100), and PAPP-A (Cat. No. BKPAPPA-96) were measured using enzyme-linked immunosorbent assay (ELISA) kits (Manufacturer: Bioswamp Life Science, Wuhan, China) according to the manufacturer's instructions. Absorbance was read using a Thermo Scientific Multiskan FC Microplate Reader and quantified against standard curves.

Statistical analysis

Data analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize baseline information for both study groups, reporting average age, birth order, gestational age at enrollment, and the distribution of various pregnancy traits. To compare baseline characteristics between the FGR group and the control group, independent t-tests or chi-square tests were applied, as appropriate, with a significance level set at $P < 0.05$.

Independent t-tests were used to compare the means of ultrasound biometric indicators, Doppler parameters, fetal biochemical markers, and other continuous variables between the two groups. Z-score for each of the EFW, AC

Table 1. Comparison of baseline characteristics between the two groups

Characteristics	Observation Group (n = 120 cases)	Control Group (n = 120 cases)	t/X^2	*P*-value
Maternal Age (years)	29.35 ± 4.13	30.24 ± 4.22	1.654	0.099
Parity			0.067	0.796
Nulliparous	58	60		
Multiparous	62	60		
Gestational Age at Enrollment (weeks)	32.63 ± 2.23	32.47 ± 2.27	0.544	0.587
BMI (kg/m^2)	24.44 ± 3.48	24.47 ± 3.53	0.066	0.947
Hypertension (%)	12.5%	11.6%	0.046	0.831
Diabetes (%)	8.3%	9.2%	0.064	0.800
Smoking (%)	5.0%	4.2%	0.116	0.733
Previous Obstetric Complications (%)	15.0%	14.2%	0.040	0.841
Ethnicity			0.310	0.857
Caucasian	45	47		
Asian	35	37		
Other	40	36		

Note: BMI: Body mass index.

and FL values were calculated using reference values, and difference between groups were assessed using independent t-tests.

To identify risk factors for fetal growth restriction, multivariate logistic regression analysis was conducted. Variables that showed significant associations with FGR in the univariate analysis (P < 0.05) were included in the multivariate model. A stepwise approach was used for variable selection, with both forward and backward elimination processes considered. Variables such as Beta-hCG, AFP, PAPP-A, portal vein systolic velocity, and hepatic artery resistance index were chosen based on their significant associations with FGR. The final model included these variables, and odds ratios (OR) with 95% confidence intervals (CI) were computed to assess the strength and direction of their associations with FGR. *P*-values < 0.05 were considered statistically significant for all analyses. Receiver operating characteristic (ROC) curves were constructed to assess the diagnostic performance of significant variables, and the area under the curve (AUC) was calculated for each. *P*-values < 0.05 were considered statistically significant.

Results

Baseline characteristics of patients

No significant differences were observed between the two groups in key demographic and clinical parameters. Specifically, maternal age (P = 0.099), parity (P = 0.796), and gestational age at enrollment (P = 0.587) showed no significant differences between the groups. Additionally, there were no differences in body mass index (P = 0.947), the prevalence of hypertension (P = 0.831), diabetes (P = 0.800), smoking status (P = 0.733), or previous obstetric complications (P = 0.841). Ethnic distribution was also comparable between the two groups (P = 0.857) (**Table 1**). These findings confirm that the two groups were well-matched at baseline, ensuring that the subsequent analysis of ultrasound biometric indicators was not influenced by demographic or clinical confounding variables.

Comparison of ultrasound biometrics between the two groups

Mean EFW values in the FGR group were approximately 700 grams lower than those in the control group (P < 0.001). Similarly, AC was significantly reduced in the FGR group (P < 0.001), further supporting the diagnosis of growth restriction. FGR fetuses exhibited a smaller biparietal diameter than those in the control group, indicating delayed head development, which is common in FGR (P < 0.001). FL was also significantly shorter in the FGR group (P < 0.001), suggesting impaired skeletal growth. The head circumference to abdominal circumference ratio (HC/AC) was significantly

Table 2. Comparison of ultrasound parameters between the two groups

Ultrasound Indicator	Observation Group (n = 120 cases)	Control Group (n = 120 cases)	t	*P*-value
Estimated Fetal Weight (g)	2227.94 ± 322.08	2903.06 ± 385.57	14.721	< 0.001
Abdominal Circumference (cm)	29.08 ± 3.12	33.86 ± 3.79	10.672	< 0.001
Biparietal Diameter (cm)	7.98 ± 0.38	8.46 ± 0.60	7.473	< 0.001
Femur Length (cm)	6.23 ± 0.60	7.17 ± 0.72	10.942	< 0.001
Head Circumference (cm)	30.87 ± 2.70	33.06 ± 2.64	5.352	< 0.001
Head Circumference to Abdominal Circumference Ratio (HC/AC)	1.43 ± 0.07	1.00 ± 0.07	46.645	< 0.001
Placental Thickness (cm)	3.64 ± 0.71	3.73 ± 0.51	1.150	0.251
Amniotic Fluid Index (cm)	9.12 ± 2.00	11.94 ± 2.17	10.470	< 0.001

Table 3. Comparison of Z-score, middle cerebral artery, and umbilical artery blood flow parameters between the two groups

Parameter	Observation Group (n = 120 cases)	Control Group (n = 120 cases)	t	*P*-value
Z-score for Estimated Fetal Weight (EFW)	-2.32 ± 0.37	0.33 ± 0.18	71.179	< 0.001
Z-score for Abdominal Circumference (AC)	-1.80 ± 0.49	0.42 ± 0.18	47.046	< 0.001
Z-score for Femur Length (FL)	-1.53 ± 0.64	0.41 ± 0.31	29.957	< 0.001
Middle Cerebral Artery (MCA) Systolic Velocity (cm/s)	54.52 ± 9.12	61.70 ± 6.98	6.850	< 0.001
Middle Cerebral Artery (MCA) Diastolic Velocity (cm/s)	18.13 ± 4.20	21.71 ± 4.68	6.236	< 0.001
Middle Cerebral Artery (MCA) Resistance Index (RI)	0.81 ± 0.08	0.73 ± 0.07	7.491	< 0.001
Umbilical Artery (UA) Systolic Velocity (cm/s)	45.40 ± 7.62	56.98 ± 10.58	9.677	< 0.001
Umbilical Artery (UA) Diastolic Velocity (cm/s)	21.98 ± 5.47	25.64 ± 4.95	5.430	< 0.001
Umbilical Artery (UA) Resistance Index (RI)	0.76 ± 0.12	0.66 ± 0.10	7.486	< 0.001

higher in the FGR group ($P < 0.001$), reflecting abnormal growth patterns typically observed in growth-restricted fetuses. Although the placenta in the FGR group was thicker on average compared to the control group, the difference was not significant. Finally, the amniotic fluid index (AFI) was significantly lower in the FGR group ($P < 0.001$), further emphasizing the association between FGR and oligohydramnios (**Table 2**). These findings highlight that ultrasound biometrics, including EFW, AC, FL, and HC/AC ratio, play a key role in diagnosing fetal growth restriction.

Comparison of the Z-score values, middle cerebral artery, and umbilical artery blood flow parameters between the two groups

A detailed comparison of the FGR group and the control group revealed significant differences in all three measures. Z-scores for EFW, AC, and FL were markedly lower in the FGR group, indicating substantial growth restriction in these fetuses ($P < 0.001$ for all). Doppler ultrasound assessments of the MCA and UA revealed that blood flow was significantly affected by growth restriction. Specifically, MCA systolic and diastolic velocities were reduced in the FGR group ($P < 0.001$ and $P < 0.001$, respectively), with a higher MCA resistance index (RI) observed in the FGR group ($P < 0.001$), reflecting impaired cerebral perfusion, which is commonly associated with fetal growth restriction. Similarly, UA blood flow parameters, including systolic and diastolic velocities, were significantly lower in the FGR group ($P < 0.001$ for both), and the UA resistance index (RI) was significantly higher ($P < 0.001$) (**Table 3**), indicating compromised placental blood flow. These findings suggest that Z-scores and Doppler blood flow parameters are valuable tools for managing fetal growth restriction.

Comparison of fetal heart rate variability and fetal movement patterns between the two groups

Growth-restricted fetuses exhibited a lower baseline FHR than those with normal growth ($P < 0.001$), indicating changes in autonomic

Table 4. Comparison of fetal heart rate and fetal movement patterns between the two groups

Parameter	Observation Group (n = 120 cases)	Control Group (n = 120 cases)	t	*P*-value
Baseline Fetal Heart Rate (bpm)	135.37 ± 8.49	145.70 ± 5.25	10.470	< 0.001
Fetal Heart Rate Variability (bpm)	10.13 ± 3.00	15.60 ± 2.30	15.850	< 0.001
Frequency of Fetal Movements (per hour)	12.07 ± 4.47	18.36 ± 5.23	10.026	< 0.001
Number of Acceleration Episodes (per day)	3.09 ± 1.24	5.04 ± 1.61	10.477	< 0.001

Table 5. Comparison of placental vascular resistance and Doppler indices between the two groups

Parameter	Observation Group (n=120 cases)	Control Group (n=120 cases)	t	*P*-value
Uterine Artery Resistance Index (UtARI)	0.86 ± 0.09	0.66 ± 0.07	19.355	< 0.001
Placental Blood Flow (cm/s)	31.88 ± 7.38	41.75 ± 6.16	11.241	< 0.001
Absence of End-Diastolic Flow (Yes, %)	18.2%	5.0%	8.303	0.004
Reversed End-Diastolic Flow (Yes, %)	8.5%	1.2%	6.737	0.009

regulation. Additionally, fetal heart rate variability (FHRV) was markedly reduced in the FGR group (P < 0.001), indicating impaired fetal well-being. The frequency of fetal movements was significantly lower in the FGR group compared to the control group (P < 0.001), which is consistent with reduced fetal activity often observed in growth-restricted pregnancies. Furthermore, the number of acceleration episodes per day was also significantly lower in the FGR group (P < 0.001) (**Table 4**), suggesting abnormal fetal cardiovascular function. These findings suggest that atypical changes in fetal heart rate or movement patterns may signal fetal growth restriction, necessitating additional monitoring and care.

Comparison of placental vascular resistance and Doppler indices between the two groups

Higher resistance was noted in the uterine artery resistance index (UtARI) in the FGR group (P < 0.001), suggesting that the increased resistance is a typical feature of this condition. Placental blood flow was significantly lower in the FGR group (P < 0.001), further supporting the hypothesis of compromised placental function in growth-restricted fetuses. Doppler measurements of the final diastolic flow phase showed that more fetuses in the FGR group showed no end-diastolic flow (P = 0.004), indicating poor blood flow to the placenta in these infants. Reversed flow during the diastole phase was more common in the FGR group (P = 0.009), a major indicator of severe placental insufficiency (**Table 5**). This study supports the importance of using Doppler indices such as the UtARI and the presence of abnormal end-diastolic flow, to spot signs of placental dysfunction and fetal growth restriction.

Comparison of fetal biochemical markers between the two groups

As shown in **Figure 2**, the FGR group had significantly higher levels of beta-hCG (P < 0.001), which is typically associated with altered placental function and fetal growth restriction. In contrast, maternal serum levels of AFP and PAPP-A were significantly lower in the FGR group (P < 0.001 for both), indicating impaired fetal liver and placental function, respectively. These differences highlight the potential of these biochemical markers as diagnostic tools for identifying FGR, with lower levels of AFP and PAPP-A and elevated beta-hCG serving as biomarkers of poor fetal growth and placental insufficiency.

Comparison of maternal weight gain during pregnancy between the two groups

As seen in **Table 6**, the FGR group exhibited significantly lower weight gain than the control group. The observation group gained an average of 9.43 ± 2.38 kg, whereas the control group gained 13.77 ± 2.98 kg (P < 0.001). This pattern was consistent across all trimesters, with the observation group exhibiting lower weight gain in the first, second, and third trimesters (P < 0.001 for all). Specifically, weight

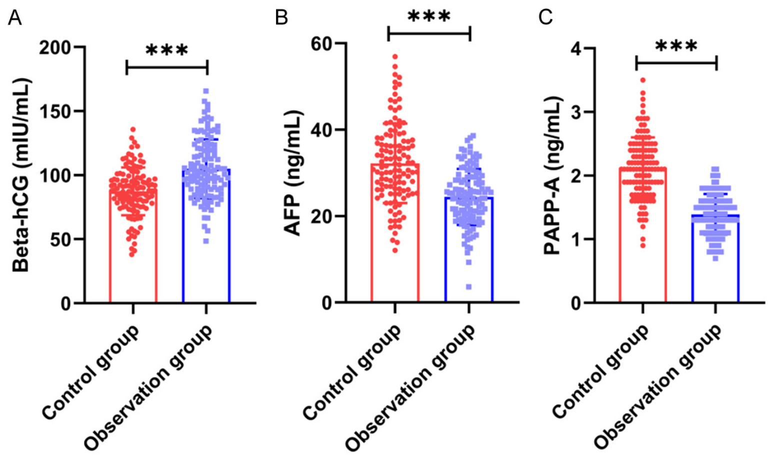

Figure 2. Comparison of fetal biochemical markers between the two groups. (A) Beta-hCG, (B) AFP, (C) PAPP-A. ***P < 0.001. Note: AFP: Alpha-fetoprotein, PAPP-A: Pregnancy-Associated Plasma Protein-A.

gain in the first trimester was 2.22 ± 0.96 kg in the observation group compared to 3.65 ± 1.20 kg in the control group (P < 0.001), and in the second trimester, it was 3.03 ± 1.27 kg in the observation group versus 4.67 ± 1.24 kg in the control group (P < 0.001). Similarly, weight gain in the third trimester was also significantly lower in the observation group (P < 0.001). Moreover, low weight gain was more common in the observation group (18.5%) compared to the control group (5.2%) (P = 0.002). In contrast, there was no significant difference between the two groups in the incidence of excessive weight gain (P = 0.841). Research shows that when a mother gains less weight beyond ideal ranges, it can be linked to fetal growth restriction and may help detect pregnancies on the path to FGR.

Comparison of fetal hepatic blood flow parameters between the two groups

The velocity of blood flow through the umbilical vein was significantly lower in fetuses with FGR than healthy fetuses (P < 0.001) (**Figure 3A**). The umbilical vein diastolic velocity was also markedly reduced in the FGR group (P < 0.001) (**Figure 3B**), suggesting insufficient blood return, which typically accompanies placental deficiency in FGR pregnancies. Furthermore, the portal vein systolic velocity was significantly lower in the FGR group (P < 0.001) (**Figure 3C**), indicating altered hepatic circulation due to the compromised placental function and fetal oxygenation. Finally, the hepatic artery resistance index was significantly higher in the FGR group (P < 0.001) (**Figure 3D**), reflecting increased vascular resistance in the fetal liver, a well-known marker of placental insufficiency and fetal compromise. These findings emphasize the importance of monitoring hepatic blood flow parameters as a tool for identifying abnormal fetal growth patterns and understanding the pathophysiology of FGR.

Multivariate regression analysis of influencing factors for fetal growth restriction

Multivariate regression analysis revealed that several factors were significantly associated with FGR, including Beta-hCG (OR: 0.957, 95% CI: 0.934-0.981, P = 0.001), AFP (OR: 1.093, 95% CI: 1.022-1.169, P = 0.009), and PAPP-A (OR: 49.446, 95% CI: 13.372-18). The results indicate that lower beta-hCG levels increase the likelihood of FGR, while higher AFP and PAPP-A levels are associated with an increased risk of FGR.

Other factors found to be significant in the multivariate model included portal vein systolic velocity (OR: 1.113, 95% CI: 1.012-1.267, P = 0.029) and hepatic artery resistance index (OR: 10.026, P = 0.463), with higher readings linked to a higher chance of FGR. However, the development of FGR seemed to be more closely related to hepatic artery resistance (OR: 1.403, 95% CI: 1.180-1.669, P <0.001) compared to any other factors (**Table 7**). These findings highlight the importance of monitoring these biomarkers in the medical care of a woman with suspected FGR, allowing for early detection of potential issues and timely intervention.

ROC curve analysis for risk variables in predicting FGR

To further evaluate the diagnostic performance of the significant variables identified through logistic regression analysis, ROC curves were plotted with the AUC values calculated (**Figure 4**). Among the individual biomarkers, the hepat-

Table 6. Comparison of maternal weight gain during pregnancy between the two groups

Parameter	Observation Group (n = 120 cases)	Control Group (n = 120 cases)	t	*P*-value
Total Maternal Weight Gain (kg)	9.43 ± 2.38	13.77 ± 2.98	12.487	< 0.001
Weight Gain in First Trimester (kg)	2.22 ± 0.96	3.65 ± 1.20	10.219	< 0.001
Weight Gain in Second Trimester (kg)	3.03 ± 1.27	4.67 ± 1.24	1.122	< 0.001
Weight Gain in Third Trimester (kg)	4.06 ± 1.34	5.58 ± 1.80	7.442	< 0.001
Insufficient Weight Gain (%)	18.5%	5.2%	9.280	0.002
Excessive Weight Gain (%)	14.2%	15.0%	0.040	0.841

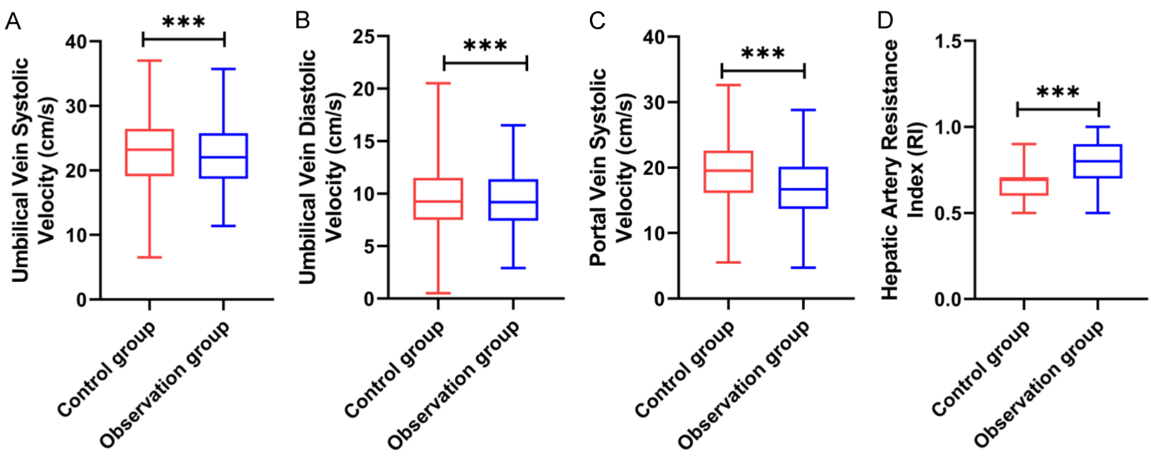

Figure 3. Comparison of fetal hepatic blood flow parameters between the two groups. A. Umbilical vein systolic velocity; B. Umbilical vein diastolic velocity; C. Portal vein systolic velocity; D. Hepatic artery resistance index. ***P < 0.001.

Table 7. Multivariate regression analysis of influencing factors for fetal growth restriction (FGR)

Variable	B	SE	Wald	P	OR	95% CI
Beta-hCG	-0.044	-0.013	12.030	0.001	0.957	0.934-0.981
AFP	0.089	0.034	6.803	0.009	1.093	1.022-1.169
PAPP-A	3.901	0.667	34.180	< 0.001	49.446	13.372-18.847
Portal Vein Systolic Velocity	0.124	0.057	4.739	0.029	1.133	1.012-1.267
Hepatic Artery Resistance Index	-11.940	2.868	17.335	< 0.001	1.403	1.180-1.669
Constant	2.305	3.139	0.539	0.463	10.026	-

Note: B: Coefficient; SE: Standard Error; Wald: Wald Statistic; P: *p*-value; OR: Odds Ratio; 95%CI: 95% Confidence Interval. The variable assignments: Beta-hCG: Actual value; AFP: Actual value; PAPP-A: Actual value; Portal Vein Systolic Velocity: Actual value; Hepatic Artery Resistance Index: Actual value. AFP: Alpha-fetoprotein, PAPP-A: Pregnancy-Associated Plasma Protein-A.

ic artery resistance index showed the highest diagnostic accuracy for FGR, with an AUC of 0.824 (95% CI: 0.765-0.883), indicating excellent discriminative ability. PAPP-A also demonstrated good predictive value, with an AUC of 0.731 (95% CI: 0.666-0.796), followed by beta-hCG, which had a moderate AUC of 0.661 (95% CI: 0.593-0.729). In contrast, AFP and portal vein systolic velocity showed limited diagnostic utility, with relatively low AUCs of 0.312 (95% CI: 0.244-0.379) and 0.387 (95% CI: 0.317-0.458), respectively. These findings suggest that AFP and portal vein measurements alone may not serve as reliable diagnostic markers for FGR. Importantly, when combining all significant variables into a composite model, the diagnostic performance improved, with the combined AUC reaching 0.828 (95% CI: 0.774-0.882). This underscores the value of a multiparametric approach incorporating biochemical markers and hemodynamic indicators for more accurate and early identification of FGR.

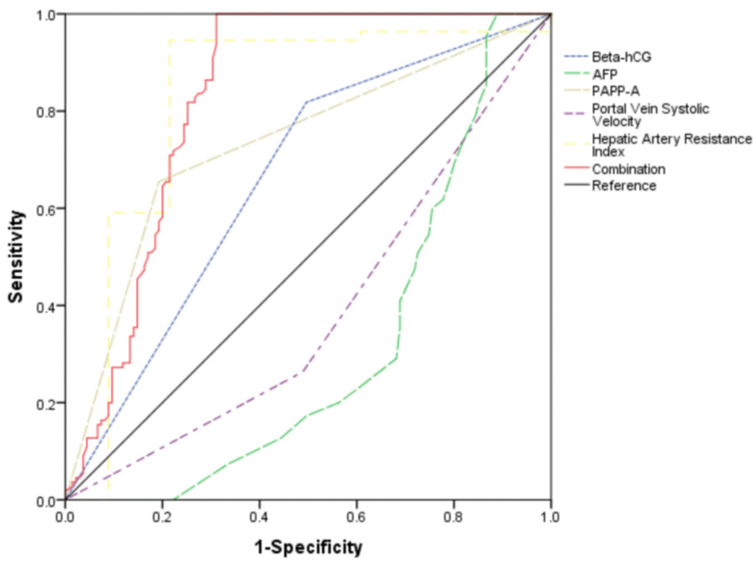

Figure 4. ROC curves for risk factor in predicting FGR. FGR: fetal growth restriction.

The ROC curve analysis supports the clinical feasibility of integrating these markers into prenatal screening protocols to improve diagnostic sensitivity and specificity.

Typical images from both groups

Figure 5 illustrates typical ultrasound images representing key fetal biometric measurements in both normal and growth-restricted pregnancies. The images showcase the biparietal diameter (BPD), abdominal circumference (AC), and femur length (FL) of fetuses from both groups. In the control group, these measurements reflect normal fetal growth, while in the FGR group, significant reductions in all parameters are observed. Specifically, the BPD, AC, and FL in the FGR group are notably smaller, indicating restricted fetal growth. These differences emphasize the diagnostic significance of ultrasound in detecting fetal growth abnormalities, with specific attention to how ultrasound biometrics can help clinicians differentiate between normal and growth-restricted fetuses. The clear disparity between the two groups underlines the importance of early identification and monitoring of fetal growth to improve clinical decision-making and outcomes.

Discussion

In this study, we explored a multiparametric diagnostic model for FGR by combining fetal biometric indicators, Doppler hemodynamics, maternal serum biochemical markers, and functional fetal parameters. Our results support and extend previous evidence regarding the complex pathophysiological mechanisms of FGR, particularly emphasizing the role of placental insufficiency and fetal compensatory adaptation.

Previous studies have suggested a significant reduction of EFW, AC, BPD, and FL in the fetuses with intrauterine growth restriction [11-13]. Such deficiencies are characteristic of fetuses with growth restriction and signify impaired somatic and skeletal development. Notably, the increased HC/AC ratio observed in the FGR group indicates an asymmetric development, which is often related to brain-sparing mechanism [14, 15]. This mechanism, validated in Doppler studies, involves a compensatory redistribution of blood flow, directing more blood to the brain at the expense of other organs such as the liver and extremities, in reaction to prolonged hypoxia [16]. Our findings support the clinical usefulness of these parameters in both detecting and differentiating between symmetric and asymmetric forms of FGR, which may have distinct outcomes.

The effects of changes in fetal and uteroplacental circulation were demonstrated using Doppler ultrasound. The FGR group demonstrated significantly lower systolic and diastolic velocities in MCA and UA, along with a raised resistance indices (RI), which is consistent with earlier studies associating an augmented vascular impedance with the risk of placental insufficiency [17-20]. Such hemodynamic changes reflect impaired oxygen and nutrient transport, which is central to FGR pathogenesis. Specifically, the high MCA RI value indicates reduced cerebral perfusion, contrasting with decreased cerebral resistance in a brain-sparing mechanisms. This can be seen as a threshold value beyond which compensatory mechanisms may no longer be effective, potentially indicating more severe or chronic hypoxia. The-

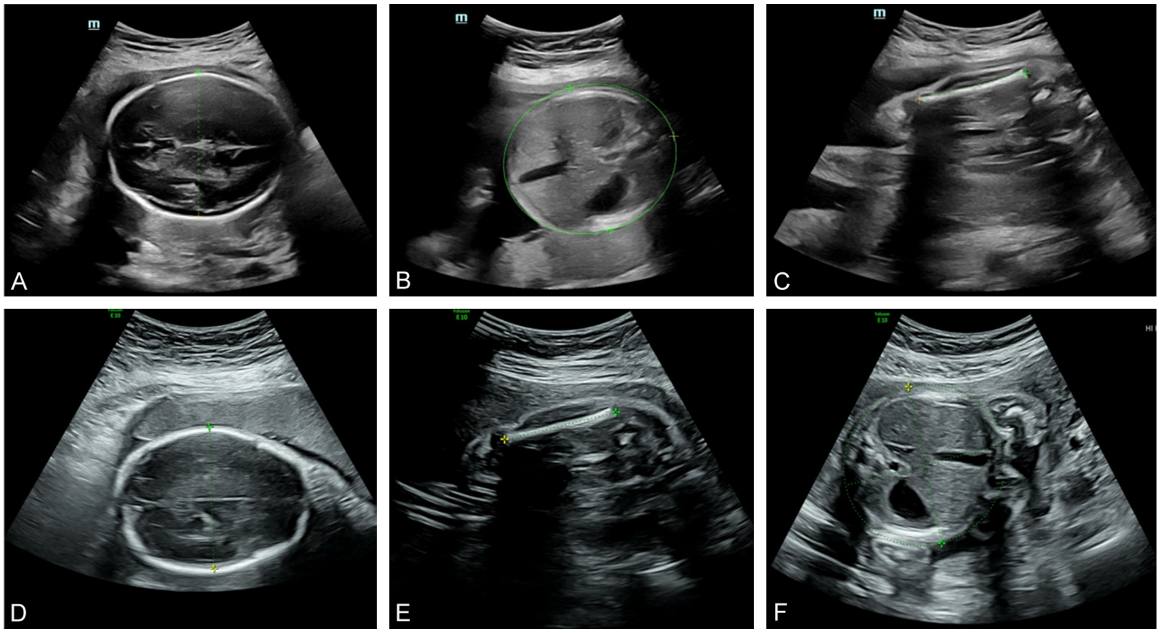

Figure 5. Typical images from two groups. A. The biparietal diameter (BPD) of a fetus from a normal pregnancy (control group); B. The abdominal circumference (AC) of a fetus from a normal pregnancy (control group); C. The femur length (FL) of a fetus from a normal pregnancy (control group); D. The biparietal diameter (BPD) of a fetus from a fetal growth restriction (FGR) pregnancy (observation group); E. The abdominal circumference (AC) of a fetus from a fetal growth restriction (FGR) pregnancy (observation group); F. The femur length (FL) of a fetus from a fetal growth restriction (FGR) pregnancy (observation group).

re was structural and vascular compromise in addition to functional evidence of fetal compromise. The degradation of autonomic regulation and fetal reactivity was evident from the lower baseline FHR, reduced FHR variability (FHRV), and diminished fetal movement power [21, 22]. These findings are critical, as they serve as precursors to clinical deterioration and can be useful to predict negative outcomes. Previous studies have associated reduced FHRV to both acute perinatal adverse events and subsequent neurodevelopmental outcomes [23].

The biochemical analysis demonstrated that, in cases of FGR, β-hCG concentrations were elevated, while AFP and PAPP-A levels were decreased compared to healthy pregnancies, correlating with the previous research [24-26]. These markers suggest abnormalities in trophoblast functioning, imperfect vascular remodeling, and disparities in AFP and PAPP-A levels, reflecting poor syncytiotrophoblast activity with limited nutrient exchange [27]. The diagnostic potential of these markers is highlighted by the fact that they are independent predictors in our multivariate model, especially when used together with imaging results.

Our study also included hepatic blood flow measurements, which showed that the portal vein flow and hepatic artery resistance were lower in the FGR group. These observations align with new observations on fetal circulatory adaptation beyond a brain-sparing model. In placental insufficiency, hepatic perfusion remains intact to maintain cerebral perfusion, but this dysfunction could relate to abnormal liver metabolism and postnatal morbidity under the circumstance of placental insufficiencies. This aspect has not been extensively studied in FGR literature and warrants further investigation. Collectively, our results depict the interrelationship between placental, hepatic, and cerebral circulatory adaptations in FGR. The evidence supports a hypothesis that poor placental perfusion triggers a hormonal, hemodynamic, and metabolic cascade aimed at maintaining fetal viability, which ultimately fails in severe cases. The presenting features of aberrant Doppler flow and disturbances in the biometric relationships along with variations on the biochemical markers provide a durable signature of this pathophysiology.

Though most of our findings align with existing literature, there are still some points that are worth discussing. For instance, while some reports suggest that the resistance index in MCA is reduced in brain-sparing, our study found it to be elevated in FGR [19]. This discrepancy could be attributed to factors such as gestational age, severity of growth restriction, or the breakdown of compensatory mechanisms. Similarly, β-hCG levels were elevated in our study compare to other reports indicating lower values. This could be attributed to differences in the temporal dynamics of trophoblastic activity or population-specific variation.

There are several limitations to our study. First, being a retrospective analysis, it is prone to information and selection bias, and causality cannot be determined. Second, while the inclusion of multiple parameters enhances internal validity, the reproducibility of our findings may be limited across institutions with different equipment or assay kits. Third, the absence of long-term neonatal outcome measurements prevents an assessment of the predictive value of our markers for postnatal development. Lastly, the study did not systematically examine the possible confounders, such as maternal diet, environmental exposure, and placental pathology. Future research should focus on validating these findings in prospective, multicentric cohorts using homogenized imaging and biochemical methods. The inclusion of angiogenesis markers (e.g., PIGF, sFlt-1), metabolomics, or placental MRI could further improve early detection of FGR. Further, longitudinal follow-up of neonates would be valuable in determining the prognostic value of the prenatal markers in assessing long-term health outcomes.

In conclusion, this study presents a comprehensive diagnostic approach to FGR that integrates biometric, hemodynamic, biochemical, and behavioral fetal indicators. This multi- faceted assessment offers superior diagnostic value compared to traditional models, facilitating earlier intervention and more individualized perinatal care. Our findings affirm the complex interplay between placental dysfunction, fetal adaptive physiology, and systemic regulation in the pathogenesis of FGR. These insights lay a solid foundation for further clinical and mechanistic investigations.

Disclosure of conflict of interest

None.

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