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ORIGINAL RESEARCH

Prediction of Fetal Growth Restriction Using Serum PlGF Combined with PAPP-A in Early Pregnancy

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Objective: This study aimed to assess the predictive capacity of placenta growth factor (PlGF) and pregnancy-associated plasma protein-A (PAPP-A) levels in the serum of pregnant women during early pregnancy (11–13^{+6} weeks) for fetal growth restriction (FGR).

Patients and Methods: A retrospective cohort study was conducted involving 1602 pregnant women who gave birth at The Second Nanning People's Hospital between March 2018 and September 2019. Serum concentrations of PlGF and PAPP-A were measured during early pregnancy for all participants. Based on pregnancy outcomes, participants were categorized into the FGR group (n = 94) and the normal control group (n = 1508). Clinical characteristics, serum PAPP-A, and PlGF levels during early pregnancy (11–13^{+6} weeks) were compared between the two groups using *t*-tests and one-way analysis of variance. Receiver operating characteristic (ROC) curves were generated to assess the predictive value of each biomarker.

Results: The overall incidence of FGR in the study cohort was 5.86%. Pregnant women in the FGR group exhibited significantly lower serum levels of PlGF and PAPP-A compared to the control group (both $p<0.05$). Correlation analysis revealed that PAPP-A levels were inversely associated with maternal age, pre-pregnancy body mass index (BMI), platelet count, and fibrinogen (all $p<0.05$). ROC analysis demonstrated that the area under the curve (AUC) for predicting FGR was 0.734 (95% CI: 0.677–0.790) for PlGF and 0.729 (95% CI: 0.676–0.781) for PAPP-A, which indicates a certain individual predictive value. When combined, the predictive efficiency slightly improved (AUC=0.742).

Conclusion: Serum levels of PlGF and PAPP-A in early pregnancy can effectively predict FGR, with slightly improved predictive accuracy when used together, presenting a new method for early FGR screening.

Keywords: fetal growth restriction, pregnancy-associated plasma protein-A, PLACENTA growth factor, predictive value

Introduction

Fetal growth restriction (FGR) is a prevalent complication in obstetrics, with an incidence rate ranging from 5–10%, ranking it as the second leading cause of perinatal mortality. FGR frequently leads to preterm birth and neonatal asphyxia.[1] At the same time, children affected by FGR face an elevated risk of neurodevelopmental delays, behavioral issues in childhood, and an increased susceptibility to cardiovascular and metabolic diseases in adulthood.[2–4]

Ultrasonic monitoring is the primary method for diagnosing FGR. However, cases identified late in pregnancy often miss the optimal intervention window, necessitating the identification of early predictive biomarkers. In cases of FGR without fetal congenital abnormalities, genetic anomalies, or infections, uteroplacental circulation disorders are typically implicated, with placental insufficiency being the core pathological mechanism.[5,6] Early changes in placental-derived biomarkers may offer a breakthrough in predicting FGR,[7] as adequate uteroplacental blood vessel dilation and placental development are crucial for normal fetal growth and development. Insufficient spiral artery remodeling is a significant factor in FGR. Placenta growth factor (PlGF), a vascular genesis regulatory factor, reflects placental vascular remodeling impairment when decreased, closely linking

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to the onset of preeclampsia and FGR.[8] Pregnancy-associated plasma protein-A (PAPP-A), secreted by trophoblast cells, indicates poor placental implantation when levels are low, with multiple studies confirming its association with an increased risk of FGR.[9] While single biomarkers have limited predictive efficacy for FGR, combining multiple indicators may enhance predictive accuracy.[10] For example, the PROGNOSIS study demonstrated the significant predictive value of the sFlt-1/PLGF ratio for preeclampsia.[11] However, research on the early combined prediction of FGR is lacking. This study aims to investigate the predictive value of serum PLGF and PAPP-A testing alone and in combination during early pregnancy (11–13^{+6} weeks) for FGR, providing evidence-based identification of high-risk pregnant women.

Clinical Data and Research Methods

Study Population

With approval from the Ethics Committee of the Second Nanning People's Hospital, a retrospective analysis was conducted on the medical records of 1602 pregnant women who delivered at the hospital between March 2018 and September 2019. According to the diagnostic criteria of the Expert Consensus on Fetal Growth Restriction (2019 Edition) by the Chinese Medical Association,[12] the cases were categorized into the FGR group (n = 94) and the normal control group (n = 1508).

This study will comply with relevant laws and regulations, including the Declaration of Helsinki. The researchers collectively assume responsibility for maintaining confidentiality, ensuring the security and privacy of participant information throughout the study.

Diagnostic Criteria

FGR was defined by the "Expert Consensus on Fetal Growth Restriction (2019 Edition)" published by the Perinatal Medicine Branch of the Chinese Medical Association. This is typically indicated by estimated fetal weight (EFW) or abdominal circumference measurements falling below the 10th percentile for the corresponding gestational age.[12] By analyzing maternal pregnancy medical records, Doppler ultrasound examination report during pregnancy, gestational week at delivery and birth weight of the fetus, and comparing them with Percentile Charts for Neonatal Growth Indicators.[13] Newborns with birth weights below the 10th percentile for their gestational age are classified as having (FGR).

Inclusion Criteria

(1) Singleton live births;
(2) Routine antenatal examinations and delivery at our hospital;
(3) Assessment of serum PLGF and PAPP-A during early pregnancy.

Exclusion Criteria

(1) Twins or higher-order multiples;
(2) Abortion or intrauterine fetal;
(3) Voluntary pregnancy termination for personal reasons.

Research Methods

Serum biomarkers PLGF and PAPP-A were assessed through the collection of fasting pregnant women's blood samples (minimum 2 mL) from the antecubital vein between 11 and 13+6 weeks of gestation. Following centrifugation, the supernatant underwent analysis using the enzyme-linked immunosorbent assay (ELISA) on the Wallac AutoDELFIA® 1235 Automatic Immunoassay System (Manufacturer: Wallac Oy).

Observational Indicators

Data collected included maternal characteristics (age, height, pre-pregnancy and antepartum weight, parity), biomarkers (PLGF and PAPP-A levels), and various hematological parameters. Gestational age at termination, method of termination, and neonatal birth weight were also recorded. PLGF and PAPP-A levels were normalized to multiples of the median (MoM). Statistical analysis revealed significant differences between the FGR and control groups, denoted by $p < 0.05$.

Statistical Methods

The statistical analyses were conducted using IBM SPSS version 26.0 and R version 4.0.5. Continuous data were reported as the mean ± standard deviation ($\overline{x} \pm s$). Group comparisons were performed through one-way ANOVA, and correlation evaluations were based on Pearson correlation analysis. The predictive ability of PLGF and PAPP-A for FGR was appraised using receiver operating characteristic (ROC) curves, with statistical significance set at $p < 0.05$.

Results

Analysis of Factors Influencing FGR

During early pregnancy, the FGR group exhibited significantly lower serum levels of PLGF and PAPP-A compared to the control group, with statistically significant differences observed ($p < 0.05$). Conversely, variables such as pre-pregnancy BMI, hemoglobin levels during pregnancy, serum albumin, fibrinogen, and platelet counts did not show a significant association with FGR occurrence ($p > 0.05$), as presented in Table 1.

Correlation Analysis of Early Pregnancy PLGF and PAPP-A with FGR and Maternal Factors

The Pearson correlation analysis revealed a negative correlation between the incidence of FGR and the levels of early pregnancy serum PLGF and PAPP-A ($p < 0.05$). Moreover, PAPP-A exhibited negative correlations with maternal age, pre-pregnancy BMI, hemoglobin levels during pregnancy, platelet counts, and fibrinogen levels ($p < 0.05$) (Table 2).

Predictive Values of Early Pregnancy PLGF, PAPP-A, and Their Combination for FGR

Logistic regression analysis demonstrated the significant predictive value of PLGF, PAPP-A, and their combination for FGR ($p < 0.05$) (Table 3).

Table 1 Analysis of Factors Influencing FGR

Indicators	FGR (n=94 5.86%)	Control (n=1508)	*F* Statistic	*p* value
Age (years)	28.97 ± 5.14	29.57 ± 4.61	1.31	0.25
Pre-pregnancy BMI (kg/m²)	20.69 ± 2.85	21.21 ± 2.82	2.76	0.09
Hemoglobin (g/L)	119.04 ± 13.13	117.49 ± 13.68	1.04	0.308
Platelets (10^9/L)	239 ± 59.49	242 ± 61.13	0.195	0.659
Fibrinogen (g/L)	4.57 ± 0.67	4.65 ± 0.67	1.306	0.254
Albumin (g/L)	35.64 ± 3.06	35.88 ± 2.36	0.718	0.397
PAPP-A MoM	0.92 ± 0.45	1.06 ± 0.54	5.772	0.017
PLGF MoM	0.94 ± 0.52	1.14 ± 0.57	9.991	0.002

Table 2 Correlation Analysis of Early Pregnancy PLGF and PAPP-A with FGR and Maternal Factors

Variables	PLGF Correlation Coefficient	*p* value	PAPP-A Correlation Coefficient	*p* value
FGR	−0.121	0.002	−0.092	0.017
Age	0.032	0.415	−0.128	0.001
Pre-pregnancy BMI	0.030	0.441	−0.193	0.001
Hemoglobin	0.010	0.800	−0.027	0.492
Platelets	0.038	0.329	−0.089	0.022
Fibrinogen	0.038	0.331	−0.092	0.017
Albumin	0.020	0.611	0.034	0.382

Table 3 Predictive Value of Early Pregnancy Serum Biomarkers for FGR

Indicators	AUC	95% CI	Sensitivity	Specificity	*p* value
PLGF	0.734	0.677–0.790	62.1%	77.4%	$p < 0.001$
PAPP-A	0.729	0.676–0.781	50.5%	84.9%	$p < 0.001$
Combined Prediction	0.742	0.688–0.796	60.2%	79.6%	$p < 0.001$

The AUC for the model predicting FGR using early pregnancy PLGF combined with PAPP-A was 0.742 (95% CI: 0.688–0.796), with a cutoff value of p = −1.866, sensitivity of 60.2%, and specificity of 79.6%. This indicates that both early pregnancy PLGF and PAPP-A hold predictive value for FGR, and their combined utilization offers a slightly improved predictive capacity (Figure 1).

Discussion

FGR is a prevalent complication in pregnancy, with an incidence rate of 5.86% in this study, aligning with existing literature. A retrospective analysis demonstrated that pregnant women in the FGR group exhibited significantly diminished levels of serum PlGF and PAPP-A in early pregnancy compared to the normal control group. PlGF displayed an AUC of 0.734 (95% CI: 0.677–0.790) in FGR prediction, while PAPP-A showed an AUC of 0.729 (95% CI: 0.676–0.781). The joint assessment of both markers yielded an AUC of 0.742 (95% CI: 0.688–0.796), marginally exceeding the performance of the individual markers, providing innovative serological evidence for the early screening of FGR.

PLGF is a glycoprotein within the human vascular endothelial growth factor (VEGF) family. It plays a vital role in regulating placental vascular development, maintaining vascular integrity and permeability in the fetus, and is crucial for normal placental growth.[14] Reduced PLGF levels indicate impaired placental vascular development, leading to insufficient perfusion and reduced fetal nutrient delivery, which is the primary pathological process in FGR.[15] This study found a significant decrease in serum PLGF levels during early pregnancy in the FGR group ($P < 0.05$), consistent with previous research.[16,17] PAPP-A, synthesized and secreted by syncytiotrophoblasts and decidual cells in the placenta, is a zinc-binding metalloproteinase linked to insulin-like growth factor (IGF). It is intricately connected to insulin-like growth factor binding proteins (IGFBP) and IGF levels.[18] IGF governs autocrine and paracrine actions during trophoblast infiltration, regulating glucose and amino acid absorption. IGFBP inhibits IGF activity, serving as a negative regulator. PAPP-A degrades IGFBP, thereby reducing its levels, diminishing its negative impact, and enhancing the biological activity of IGF. This heightened

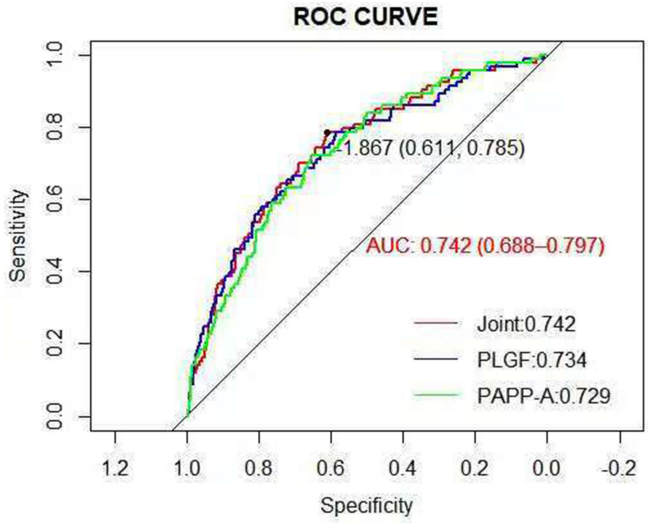

Figure 1 ROC Curves for Predicting FGR with Various Indicators.

biological activity of degraded IGF enhances insulin sensitivity and accelerates glucose and amino acid metabolism, ensuring the fetus receives sufficient nutrients for normal growth.[19] A decline in PAPP-A levels indicates impaired placental trophoblast cell function, reinforcing PAPP-A as an early indicator of placental function.[20]

The age, pre-pregnancy weight, pre-pregnancy body mass index, hemoglobin, platelet count, albumin, and fibrinogen levels of pregnant women showed no statistically significant differences between the two groups ($P > 0.05$), consistent with findings from prior studies.[21,22] Pearson correlation analysis revealed a negative correlation between PAPP-A in early pregnancy and maternal age, pre-pregnancy body mass index, platelet count, and fibrinogen ($P<0.05$). Further investigation is required to elucidate the underlying mechanisms. Therefore, monitoring PAPP-A levels may be advisable for pregnant women of advanced age, those with obesity, or those with an elevated platelet count and fibrinogen level in early pregnancy.

Both PLGF and PAPP-A showed an AUC greater than 0.7 in predicting FGR, indicating strong predictive ability. Their combined use resulted in an AUC of 0.742 (95% CI: 0.688–0.796), slightly higher than when used alone. The synergy between PLGF and PAPP-A likely stems from their complementary physiological functions, with PLGF reflecting placental vascular development and PAPP-A indicating trophoblast function. The risk of FGR increases with compromised placental perfusion (low PLGF) and abnormal trophoblast development (low PAPP-A). In a study by Mei et al[23] involving 125 FGR patients, the AUC for predicting FGR using mid-pregnancy serum PlGF levels was 0.807, higher than in our study. This difference may be due to impaired trophoblast function at the maternal-fetal interface as gestational age progresses, affecting the synthesis of PlGF.[24] While mid-pregnancy PlGF shows improved sensitivity and specificity in predicting FGR, our study's strength lies in its earlier predictive capability. PlGF is commonly used in early pregnancy to predict preeclampsia,[25] while PAPP-A is a standard screening marker for Down syndrome in early pregnancy. Thus, the combined use of PlGF and PAPP-A for predicting FGR does not impose additional medical or economic burdens and is feasible for clinical application.

In summary, the application of PLGF and PAPP-A during early pregnancy should be considered for evaluating fetal growth and development. Nevertheless, the joint predictive capacity of PLGF and PAPP-A for FGR, yielding an AUC of 0.742, indicates restricted clinical usefulness. Additional investigation is imperative to identify supplementary markers for enhanced predictive accuracy.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

This medical research study is a retrospective case study. Ethics review and approval in this study is required according to the Declaration of Helsinki (World Medical Association Inc, 2009), and Ethics approval for the study was obtained from the Ethics Committee of the Second Nanning People's Hospital guidelines and national regulations. Ethics approval for the study was obtained from the Ethics Committee of the Second Nanning People's Hospital [Y2023054].

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare for this work.

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