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ORIGINAL RESEARCH

Investigating Serum and Placental Levels of IGF-1 and IGF-1R in Preeclampsia Patients and Their Clinical Implications

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Objective: To investigate the levels of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-1 receptor (IGF-1R) in the serum and placenta of patients with preeclampsia (PE), establish their correlations, and evaluate their diagnostic potential.

Methods: 22 PE patients and 22 normal pregnant women who underwent cesarean section deliveries at the First Affiliated Hospital of Guangxi Medical University between December 2021 and December 2022 were included in the observation group and the control group. Enzyme-linked immunosorbent assay (ELISA) was utilized to measure the levels of IGF-1 and IGF-1R in serum samples, and immunohistochemical techniques (IHC) were employed to evaluate the levels of IGF-1 and IGF-1R in placental samples. The association between IGF-1, IGF-1R, and PE was analyzed, and the diagnostic accuracy of serum IGF-1 and IGF-1R for PE was assessed by ROC curve analysis.

Results: The levels of IGF-1 and IGF-1R in the serum and average optical density (AOD) value of IGF-1 and IGF-1R in placental tissue of the observation group were significantly lower. In the group with PE, there was a reduction in the number of positive cells for IGF-1 and IGF-1R in placental tissue. Positive correlations were noted between IGF-1 and IGF-1R levels in both serum and placental tissue and neonatal birth weight. The ROC curve analysis revealed that serum IGF-1 exhibited an AUC of 0.944 for diagnosing PE, with a sensitivity of 86.00% and specificity of 100.00%. Serum IGF-1R showed an AUC of 0.820 for diagnosing PE, with a sensitivity of 77.00% and specificity of 77.00%.

Conclusion: The expression of IGF-1 and IGF-1R in the serum and placental tissues of preeclamptic pregnant women was significantly reduced. This reduction implies that IGF-1 and IGF-1R may potentially be used as biomarkers in the clinical prediction, diagnosis, and prognosis evaluation of PE.

Keywords: hypertensive disorders of pregnancy, preeclampsia, IGF-1, IGF-1R, pregnancy

Introduction

Preeclampsia (PE) is a pregnancy-related hypertensive disorder that typically manifests after 20 weeks of gestation, posing significant risks to both maternal and fetal health.[1] PE affects 3–5% of pregnant women worldwide and is a leading cause of maternal and perinatal morbidity and mortality.[2] Early identification and targeted intervention for high-risk pregnancies are crucial for reducing adverse pregnancy outcomes. Current guidelines in multiple countries recommend assessing biomarkers such as soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), and soluble endoglin (sEng) for predicting early-onset PE.[3–5] However, the multifactorial, multi-mechanism and multi-pathway nature of PE has hindered the development of highly specific and effective predictive methods.

Insufficient remodeling of uterine spiral arterioles, excessive activation of inflammatory immunity, and endothelial cell damage are significant pathological changes associated with the development of PE. Shallow invasion of trophoblast cells, resulting in insufficient remodeling of spiral arteries, is an important cause of PE.[6] Insulin-like growth factor-1

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(IGF-1) is a monomeric polypeptide with metabolic functions like insulin. IGF specifically binds to the insulin-like growth factor-1 receptor (IGF-1R), modulating crucial cellular processes such as proliferation, differentiation, and apoptosis.[7] Existing evidence indicates the involvement of IGF-1 and IGF-1R in trophoblast proliferation and invasion.[8] Studies have documented decreased level of IGF-1 in the placenta and trophoblasts of patients with PE, which is associated with adverse pregnancy outcomes.[9] Additionally, IGF-1R has been linked to PE due to its role in trophoblast syncytialization.[10] Despite these insights, the precise mechanisms underlying the contributions of IGF-1 and IGF-1R to the initiation and progression of PE remain unclear.

This study examined the levels and correlation between IGF-1 and IGF-1R in the serum and placental tissues of patients with PE. The research sought to enhance our comprehension of PE pathogenesis and facilitate the creation of predictive biomarkers characterized by high sensitivity and specificity.

Materials and Methods

Materials

A total of 22 patients diagnosed with PE who underwent cesarean section deliveries at the First Affiliated Hospital of Guangxi Medical University between December 2021 and December 2022 comprised the observation group. Meanwhile, 22 pregnant women with uncomplicated pregnancies who also underwent cesarean section deliveries at the same hospital during the specified period were randomly assigned to the control group based on predetermined matching criteria. The diagnostic criteria for PE included:[1] the development of new-onset hypertension after 20 weeks of gestation, accompanied by one or more of the following indicators: proteinuria (eg, 24-hour urine protein ≥0.3 g/d or urine dipstick test ≥++), maternal organ dysfunction such as neurological complications (eg, eclampsia, altered mental status, blindness, stroke, convulsions, severe headaches, or persistent visual disturbances), pulmonary edema, hematological complications [eg, platelet count <150,000/μL, disseminated intravascular coagulation (DIC), hemolysis], acute kidney injury (eg, creatinine levels ≥90 μmol/L or 1 mg/dL), liver involvement (eg, elevated transaminases such as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >40 U/L) with or without right upper quadrant or epigastric pain, and uteroplacental dysfunction (eg, placental abruption, imbalanced vascular growth, fetal growth restriction (FGR), abnormal umbilical artery Doppler waveforms, or fetal demise).

Inclusion criteria for the observation group were as follows: (1) meeting the diagnostic criteria for PE, (2) singleton pregnancies, (3) absence of other medical or obstetric complications, (4) delivery by cesarean section, and (5) complete clinical data. Exclusion criteria were: (1) not meeting the diagnostic criteria for PE, (2) the presence of cardiovascular, hematological, neurological, diabetes, liver, or kidney complications, or obstetric complications such as gestational diabetes, acute fatty liver of pregnancy, or intrahepatic cholestasis of pregnancy, (3) multiple pregnancies, (4) neonatal congenital anomalies, premature rupture of membranes, intrauterine infections, and (5) vaginal delivery. All participants in this study provided informed consent by signing the consent form, and the selected samples were approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (2024-E0831).

Methods

Clinical Data and Samples

Clinical data, including patient age, body mass index (BMI), gravidity, parity, newborn birth weight, gestational weeks at delivery, hemoglobin levels, platelet count, serum creatinine, and levels of AST and ALT, was collected.

On the day of delivery, 3–5mL fasting venous blood samples were collected from all participants. The samples were transported at 4°C and centrifuged at 2500 r/min for 10 minutes to obtain serum, which was then promptly frozen and stored at −80°C within 15 minutes for subsequent analysis of IGF-1 and IGF-1R levels. Within 15 minutes of cesarean delivery, 1cm3 placental tissue samples were collected from 2cm from the placental edge, with the maternal side facing the umbilical cord to avoid fetal penetration and major placental vessels. The tissues were washed with sterile PBS or saline, divided into 4 portions, fixed in 10% neutral formalin for 24–48 hours, embedded in paraffin, and sectioned into 4μm slices for further examination.

Enzyme-Linked Immunosorbent Assay (ELISA)

Enzyme-linked immunosorbent assay was performed to quantify the levels of IGF-1 and IGF-1R in serum samples. ELISA (SEA050Bo) kits were procured from Wuhan Yun Clone Technology Co., Ltd. Purified IGF-1 and IGF-1R capture antibodies were immobilized onto microplate wells to establish solid-phase antibodies. Subsequently, the respective IGF was introduced to the immobilized wells, followed by interaction with Horseradish Peroxidase-labeled (HRP-labeled) detection antibodies to generate an antibody-antigen-enzyme-antibody complex. This complex was visualized using Tetramethylbenzidine (TMB), which changes color from blue to yellow upon HRP enzyme catalysis and acid treatment. The results demonstrated a notable correlation between the colorimetric intensity and the levels of IGF-1/IGF-1R. The absorbance at 450 nm was gauged using an enzyme immunoassay reader, and the concentrations of IGF-1 and IGF-1R in the samples were determined by comparison against a standard curve.

Immunohistochemistry (IHC)

Immunohistochemistry was utilized to evaluate the levels of IGF-1 and IGF-1R in placental samples. Reagents for immunohistochemical staining (SPN-9001) were sourced from Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd., while the IGF-1 and IGF-1R antibodies (32070 and 43735) were acquired from Signalway Antibody (SAB) in the United States. Tissue sections underwent a series of procedures, including slicing, fixation, antigen retrieval, peroxidase removal, blocking, primary antibody incubation, PBS washing, secondary antibody application, PBS washing, chromogenic staining, counterstaining, blue counterstaining reversal, dehydration, and mounting. Known IGF-1 and IGF-1R positive breast cancer sections served as controls, with PBS substituting the primary antibody as a negative control. Imaging analysis was carried out using a tissue section imaging system to capture images of the immunohistochemically stained sections. Image analysis was conducted using ImageJ software, which automatically outlined and measured tissue areas, calculated the integrated optical density (IOD) values of positive staining, and determined the positive area. The average optical density (AOD) of the staining area (calculated as the positive integrated optical density IOD value divided by the positive area) was utilized to indicate the strength of IGF-1 and IGF-1R positive expression.

Statistical Analysis

The statistical analysis was conducted using SPSS 27.0 software for data processing and GraphPad Prism 8 software for correlation visualization. Descriptive statistics were expressed as mean ± standard deviation (mean ± s). Group comparisons were executed using independent samples t-tests, and non-normally distributed data were assessed through non-parametric tests. Correlation analyses encompassed Pearson, Spearman, and linear regression analyses, with statistical significance set at $P < 0.05$. Receiver operating characteristic (ROC) curve was used to analyze the diagnostic value of serum IGF-1 and IGF-1R levels on PE, and DeLong test was used to compare the area under the curve (AUC).

Results

Analysis of Clinical Data

As shown in Table 1, the observation group exhibited significantly higher systolic and diastolic blood pressure compared to the control group ($P<0.001$, $P<0.001$), along with a shorter gestation period resulting in pregnancy termination ($P=0.002$), lower newborn birth weight ($P=0.002$), and increased creatinine levels ($P=0.004$) relative to the control group. The groups had no statistically significant differences in age, BMI, gravidity, parity, hemoglobin, platelet count, AST, ALT, and other parameters ($P>0.05$)(Table 1).

Comparison of Serum Levels of IGF-1 and IGF-1R

As illustrated in Table 2, In the observation group, the levels of IGF-1 and IGF-1R in serum were significantly lower compared to the control group, with statistical significance (both $P<0.001$)(Table 2).

Table 1 Comparisons of Clinical Data Between Two Groups

Clinical Data	Observation (n=22)	Control (n=22)	*t/F*	*P*
Age (years)	33.40±6.15	31.55±4.07	1.121	0.270
BMI (kg/m²)	26.85±4.89	22.71±2.88	1.317	0.258
SBP (mmHg)	157.10±14.54	113.7±9.12	11.307	<0.001
DBP (mmHg)	100.05±11.17	73.80±7.55	8.707	<0.001
Gravidity (times)	1.70±1.41	1.50±1.43	0.444	0.660
Parity (times)	0.60±0.59	0.70±0.57	−0.541	0.592
NBW (g)	2228.50±1081.89	3166.40±647.40	−3.327	0.002
Gestational week of delivery (weeks)	34.88±4.99	39.06±2.55	−3.326	0.002
Hb (g/L)	117.79±13.60	117.00±10.74	0.205	0.839
PLT (10□/L)	235.53±93.97	234.42±52.77	0.046	0.963
CR (μmol/L)	60.45±19.37	45.7±9.68	3.045	0.004
AST (U/L)	20.15±6.58	16.8±5.40	1.758	0.087
ALT (U/L)	23.45±32.93	9.50±7.93	1.842	0.073

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; NBW, neonatal birth weight; Hb, hemoglobin; PLT, platelet; CR, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 2 Comparison of Serum Levels of IGF-1 and IGF-1R

Group	n	IGF-1 (ng/mL)	IGF-1R (ng/mL)
Observation	22	87.729±17.486	60.893±34.352
Control	22	113.459±16.572	148.622±91.983
F		28.993	17.563
P		<0.001	<0.001

Comparison of AOD Values of IGF-1 and IGF-1R in Placental Tissue

In the observation group, the AOD values of IGF-1 and IGF-1R in placental tissues were significantly lower compared to those in the control group, demonstrating statistical significance (both $P < 0.001$)(Table 3).

Distribution and Localization of IGF-1 and IGF-1R in Placental Tissue

Immunohistochemical analysis of normal placental tissue demonstrates the presence of positively stained cells, primarily localized in the cytotrophoblasts and syncytiotrophoblasts of the chorionic villi. IGF-I granules are diffusely distributed within these cells, predominantly in the cytoplasm and matrix, presenting as a distinct brown-yellow color against the background (Figure 1A). Similarly, IGF-IR granules show a diffuse distribution within the cells, notably in the cytoplasm and cell membrane, exhibiting a significantly higher intensity of brown-yellow staining than the background (Figure 1C). Conversely, in the PE group, there is a notable decrease in the number of IGF-1-positive cells in placental tissue compared to normal pregnancies, with a corresponding reduction in staining intensity (Figure 1B). Likewise, the PE group displays a diminished number of IGF-1R-positive cells in placental tissue compared to normal pregnancies, accompanied by decreased staining intensity (Figure 1D).

Table 3 Comparison of AOD Values of IGF-1 and IGF-1R in Placental Tissue

Group	n	IGF-1	IGF-1R
Observation	22	0.173±0.438	0.153±0.039
Control	22	0.251±0.792	0.242±0.075
F		16.616	24.390
P		<0.001	<0.001

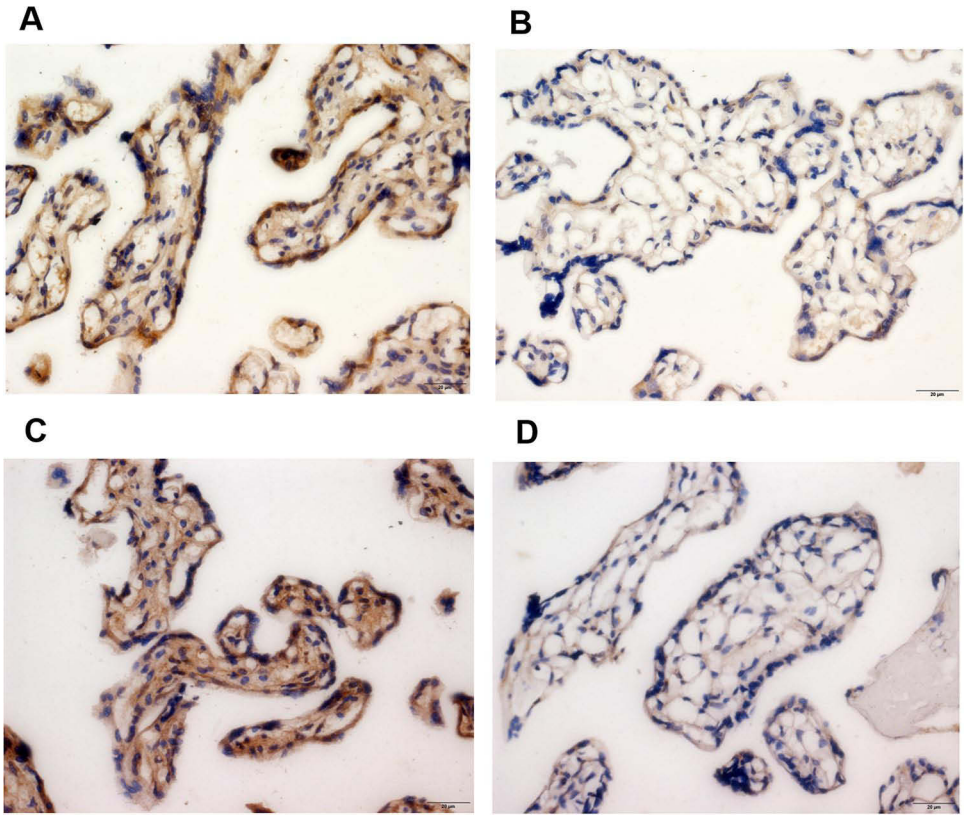

Figure 1 Distribution and localization of IGF-1 and IGF-1R in placental tissue. **(A)** The expression and distribution of IGF-1 in normal placental tissue. **(B)** The expression and distribution of IGF-1 in placental tissue of patients with PE. **(C)** The expression and distribution of IGF-1R in normal placental tissue. **(D)** The expression and distribution of IGF-1R in placental tissue of patients with PE. (Hematoxylin & Eosin staining, 40x magnification).

Correlation Between IGF-1, IGF-1R in Serum and Placental Tissue, and Neonatal Birth Weight

Correlation analyses were performed using Pearson or Spearman methods, demonstrating a significant positive correlation between serum IGF-1 and IGF-1R levels in both the control and experimental groups (r=0.8125, P<0.0001) (Figure 2A). Within placental tissue, a positive correlation was identified between IGF-1 and IGF-1R levels (r=0.5851, P<0.0001) (Figure 2B). Additionally, a positive correlation was observed between IGF-1 levels in placental tissue and serum IGF-1 levels (r=0.5979, P<0.0001) (Figure 2C). Furthermore, IGF-1R levels in placental tissue exhibited a positive correlation with maternal serum IGF-1R levels (r=0.7492, P<0.0001) (Figure 2D). Notably, serum IGF-1 levels were positively correlated with neonatal weight (r=0.8061, P<0.0001) (Figure 2E), while serum IGF-1R levels showed a similar positive correlation with neonatal weight (r=0.6614, P<0.0001) (Figure 2F). Moreover, a positive correlation was found between IGF-1 levels in placental tissue and neonatal weight (r=0.5701, P<0.0001) (Figure 2G), as well as between IGF-1R levels in placental tissue and neonatal weight (r=0.7024, P<0.0001) (Figure 2H).

Diagnostic Efficacy of Serum IGF-1 and IGF-1R in PE

As shown in Table 4 and Figure 3, the ROC curve analysis demonstrated that serum IGF-1 exhibited an AUC of 0.944, with a sensitivity of 86.00% and specificity of 100.00% in diagnosing PE. In contrast, serum IGF-1R had an AUC of 0.820, with a sensitivity and specificity of 77.00% (Table 4).

Discussion

PE is a pregnancy-specific syndrome characterized by new-onset hypertension and predominant proteinuria occurring mainly after 20 weeks of gestation. Severe PE can result in dysfunction of various organs such as the kidneys, heart,

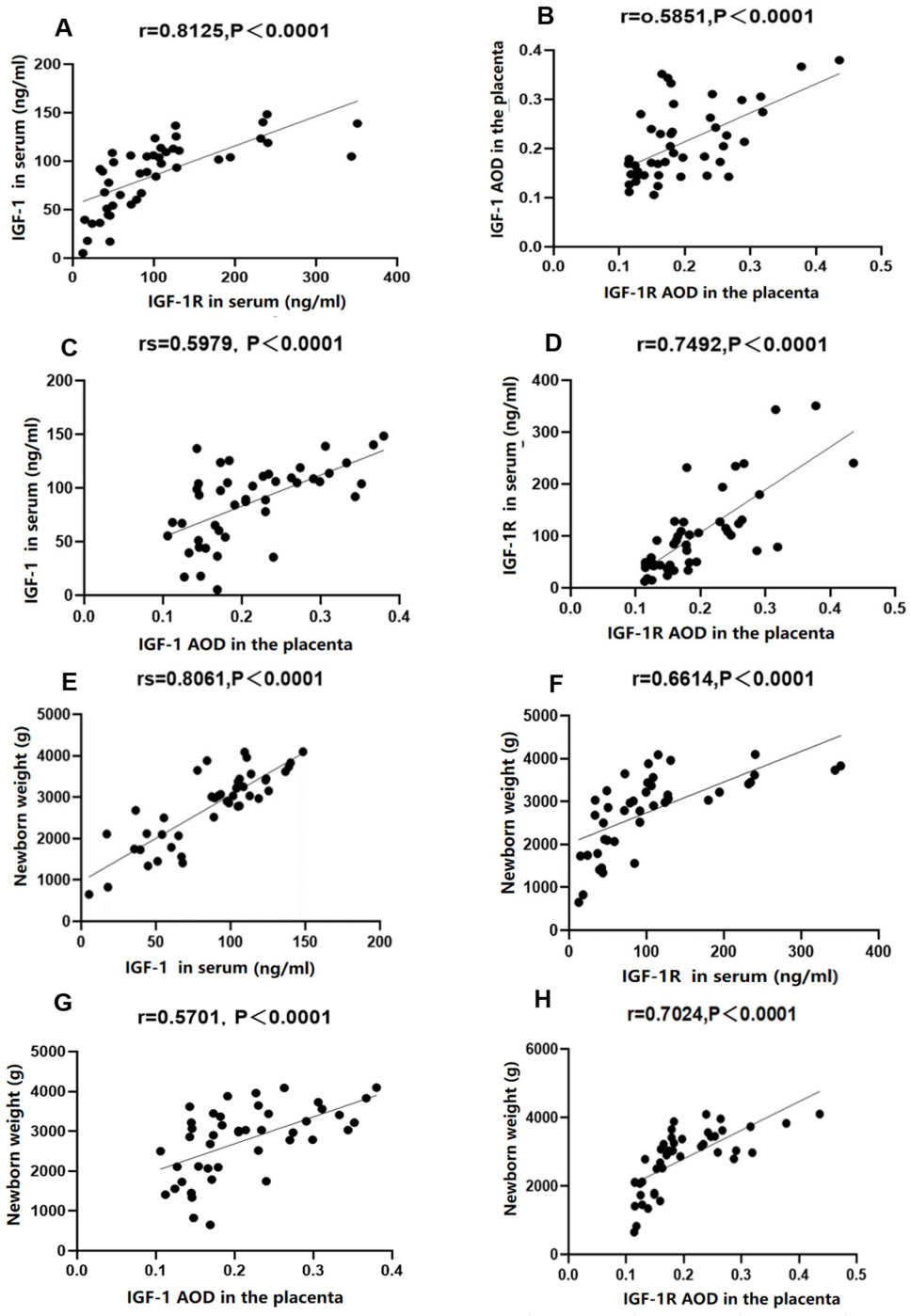

Figure 2 The correlation between IGF-1, IGF-1R in serum and placental tissue, and neonatal birth weight. **(A)** The correlation analysis between IGF-1 and IGF-1R in serum. **(B)** The correlation analysis between IGF-1 and IGF-1R in placental tissue. **(C)** The correlation analysis of IGF-1 in serum and placental tissue. **(D)** The correlation analysis of IGF-1R in serum and placental tissue. **(E)** The correlation analysis of IGF-1 in serum and neonatal birth weight. **(F)** The correlation analysis of IGF-1R in serum and neonatal birth weight. **(G)** The correlation analysis of IGF-1 in placental tissue and neonatal birth weight. **(H)** The correlation analysis of IGF-1R in placental tissue and neonatal birth weight.

lungs, liver, and nervous system, as well as hematological abnormalities, FGR, stillbirth, and maternal mortality.[11] In this study, adverse pregnancy outcomes observed in individuals with PE include elevated creatinine levels, shortened gestational age at delivery, and low birth weight in newborns. PE affects 5–7% of pregnancies globally, contributing to an estimated 70,000 maternal deaths and 500,000 fetal deaths annually.[2] The primary pathological features of PE involve compromised invasion of trophoblast cells due to placental ischemia and oxidative stress, coupled with

Table 4 ROC Curve Analysis of Serum IGF-1 and IGF-1R for Diagnosing PE

	AUC	95% CI	*P*	Cut-Off	Sensitivity (%)	Specificity (%)
IGF-1	0.944	0.873~1.000	*P*<0.001	89.18	86.00%	100.00%
IGF-1R	0.820	0.696~0.945	*P*<0.001	87.95	77.00%	77.00%

inadequate remodeling of uterine spiral arteries.[9] Despite advancements, the precise pathogenic mechanisms of PE remain incompletely elucidated. Current clinical diagnosis relies predominantly on symptomatology and blood pressure monitoring, lacking early predictive and preventive strategies for PE. Consequently, research focusing on identifying effective predictive factors for PE represents a critical and ongoing challenge in the field.

IGF-1, a monomeric peptide with insulin-like metabolic functions, is predominantly secreted by the liver in an endocrine manner into the bloodstream. Various tissues, including cardiac muscle, vascular endothelial cells, vascular smooth muscle cells, and the kidneys, produce limited amounts of IGF-1 through autocrine or paracrine mechanisms in response to growth hormone-releasing hormone and growth hormone stimulation.[12] Additionally, syncytiotrophoblasts, cytotrophoblasts, and smooth chorionic villus cells in placental tissue can synthesize IGF-1, thereby influencing cellular differentiation and proliferation.[13] Studies by Kabir have illustrated that IGF-1 can activate cytotrophoblast adhesion molecules, promote villous formation, and enhance cytotrophoblast adhesion to the extracellular matrix in a dose-dependent manner.[14] IGF-1R, a tyrosine kinase membrane receptor, specifically binds to IGF-1 to regulate cellular activities such as proliferation, differentiation, and apoptosis.[15] Current research indicates that IGF-1 is downregulated in individuals with PE and is closely associated with adverse pregnancy outcomes in this condition.[9,16] However, the precise mechanisms of IGF-1 in the pathogenesis of PE remain incompletely understood.

This study employed ELISA and immunohistochemistry to evaluate the levels of IGF-1 and IGF-1R in the serum and placenta of pregnant women. The research revealed a significant decrease in the levels of IGF-1 and IGF-1R in the serum and placenta of women with PE compared to those with normal pregnancies. Histological analysis indicated a notable reduction in the number of IGF-1 and IGF-1R positive cells in the placental tissues of the PE group in contrast to the control pregnancy group. Correlation analysis further demonstrated a positive relationship between IGF-1 and IGF-1R in the serum and placental tissues of both control and PE groups. These results suggest a strong link between the reduced levels of IGF-1 and IGF-1R and the development of PE. One

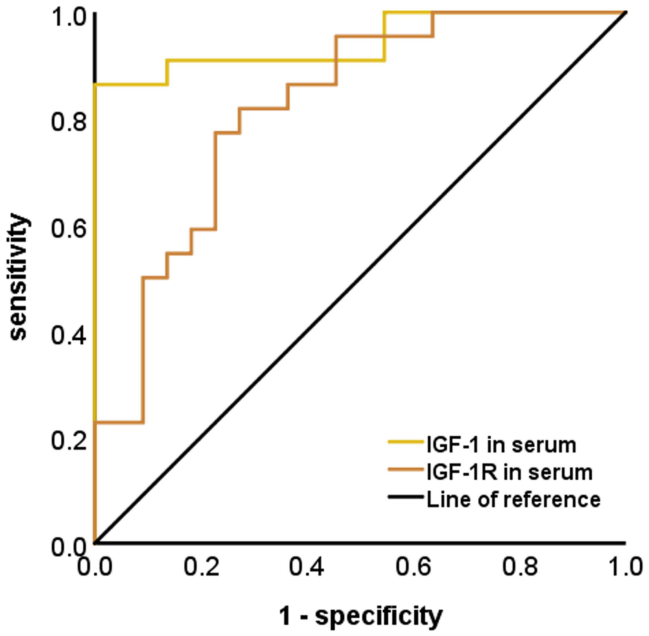

Figure 3 ROC Curve for Diagnosing PE with Serum IGF-1 and IGF-1R.

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potential explanation is that during pregnancy, placental growth hormone regulates the secretion of IGF-1, PE can induce placental ischemia, hypoxia, and functional impairment, leading to decreased growth hormone secretion and subsequently reduced levels of IGF-1. The diminished levels of IGF-1 and IGF-1R result in decreased receptor binding, excessive apoptosis of trophoblast cells, and disruptions in differentiation and replacement, ultimately causing reduced trophoblast invasiveness, impaired vascular remodeling, and potentially exacerbating PE.

IGF-1 plays a pivotal role in embryonic development, enhancing placental blood flow and stimulating the growth of fetal organs and endocrine glands to regulate fetal metabolism. IGF-1R is crucial for mediating IGF-1 effects by binding specifically to promote migration, invasion, proliferation, and differentiation of placental trophoblast cells, thus governing placental implantation and growth. Inadequate levels of IGF-1 and IGF-1R may lead to FGR.[17,18] This study identified a positive association between maternal serum and placental tissue levels of IGF-1 and IGF-1R and newborn weight. These findings suggest that reduced levels of IGF-1 could impair fetal nutrient intake, impacting fetal development and potentially contributing to FGR in preeclamptic patients. The observed positive correlation among IGF-1, IGF-1R, and newborn weight implies that diminished levels of IGF-1 and IGF-1R could serve as predictive indicators for adverse outcomes like low birth weight in pregnancies complicated by PE.

Moreover, the ROC curve analysis demonstrated that the area under the curve (AUC) for serum IGF-1 in diagnosing PE was 0.944, showing a sensitivity of 86.00% and specificity of 100.00%. In the case of serum IGF-1R, the AUC stood at 0.820, with a sensitivity of 77.00% and specificity of 77.00%. A meta-analysis found that the sensitivity and specificity of the sFlt-1/PlGF ratio in predicting PE were 86% and 96% respectively.[19] In this study, the sensitivity of serum IGF-1 in diagnosing PE was the same as that of the sFlt-1/PlGF ratio, but the specificity was higher. This indicates that serum IGF-1 may have more potential in diagnosing PE. These findings underscore the significant predictive ability of both serum IGF-1 and IGF-1R in anticipating PE.

Conclusion

In conclusion, a significant decrease in the levels of IGF-1 and IGF-1R was observed in the serum and placental tissue of pregnant women with PE. Additionally, a notable reduction in positive cells for IGF-1 and IGF-1R in placental tissue was noted, showing a positive correlation with newborn weight. These findings suggest that IGF-1 and IGF-1R may have crucial clinical implications in predicting, diagnosing, and assessing the prognosis of PE. However, due to the limited sample size and the single-center nature of this study, there may be limitations and regional biases. Moreover, given the complexity of the pathogenesis of PE, further research with large datasets and multicenter studies is needed to elucidate the mechanisms of action of IGF-1 and IGF-1R in the progression of PE, as well as their roles in clinical prediction and diagnosis.

Ethics Approval and Informed Consent/Consent for Publication

The study received approval from the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (2024-E0831), adhering to the principles of the Declaration of Helsinki. All participants provided informed consent by signing the consent form.

Data Sharing Statement

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

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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 report no conflicts of interest in this work.

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