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A Study on the Correlation between UtA-PI, Serum 25-(OH) D, and PLGF in Early Pregnancy and Preeclampsia

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Abstract: To study the correlation between uterine artery pulsatility index (UtA PI), serum 25 hydroxyvitamin D (25 - (OH) D) and angiogenesis factor (PLGF) in early pregnancy and preeclampsia. One hundred and fourteen pregnant women who delivered in our hospital from January 2022 to December 2022 were included in the study, of which 100 normal pregnant women were set as the control group; 7 cases of mild and 7 cases of severe preeclampsia were included. -(OH)D and PLGF in predicting preeclampsia. The blood pressure of pregnant women in the early-onset PE group group (107.45±11.45 mmHg and 156.56±15.45 mmHg) was higher than that of pregnant women in the late-onset PE group (105.45±11.23 mmHg and 153.56±11.21 mmHg) and the control group (82.76±6.12 mmHg and 131.01±11.45 mmHg) ($P < 0.05$), and the blood pressure level was higher in the late-stage PE group than in the control group ($P < 0.05$). The levels of 25-(OH)D (10.55±1.12ng/mL and 12.23±1.32ng/mL, respectively) and PLGF (34.43±6.23pg/mL and 38.56±7.45pg/mL, respectively) were lower in the early and late PE groups than in the control group (18.34±2.12pg/mL and 56.89±15.32pg/mL, respectively). Pearson analysis showed a negative correlation between UtA-PI and 25-(OH)D and PLGF ($P < 0.05$). Logistic regression equation results showed that all preeclamptic births were independently associated with UtA-PI, 25-(OH)D, and PLGF levels ($P < 0.05$). The equation was set: Logit (P) = 1.723*(age) + 1.589*(BMI) + 1.764*(blood pressure) + 1.634*(UtA-PI) + 1.231*(25-(OH)D) + 1.467*(PLGF) - 1.693. ROC was used to analyze the predictive models UtA-PI, 25-(OH)D, PLGF on the predictive value of preeclampsia, the results showed that the three combined had an AUC of (0.858) for preeclampsia, with a sensitivity of 88.75% and specificity of 82.20%, $P < 0.05$. The combined screening of UtA PI, serum 25 - (OH) D and PLGF in early pregnancy is of great significance in the prediction of preeclampsia. It can timely assess the risk of preeclampsia and provide basis for clinical diagnosis and intervention.

1. Introduction

Pre eclampsia (PE) is a pregnancy specific syndrome characterized by newly developed hypertension with multiple system involvement and damage that occurs after 20 weeks of pregnancy [1-2]. Preeclampsia seriously affects the short-term and long-term health of mothers and infants, but so far, the pathogenesis of preeclampsia is not fully understood, and there is a lack of effective prevention and treatment methods in clinical practice. With in-depth research on the pathogenesis, Staff A C proposed a revised two-stage model for preeclampsia: the first stage is maternal risk factors and placental hypoxia and stress caused by insufficient placental perfusion, releasing various inflammatory factors; The second stage is the occurrence of excessive systemic vascular inflammatory response, ultimately leading to diverse clinical manifestations of preeclampsia (signs of new onset hypertension, proteinuria, or other end-organ dysfunction). According to the existing pathogenesis, early prediction of preeclampsia, early intervention, and improvement of adverse pregnancy outcomes for mothers and infants have become a hot and difficult research topic in the international obstetrics field in recent years [2-3]. Multiple studies both domestically and internationally have shown a correlation between UtA-PI and PE, making it an internationally recognized and valuable predictor of preeclampsia [4]. Multiple research results have shown that average arterial pressure has a higher predictive value for preeclampsia than simple systolic and diastolic blood pressure [5]. PLGF is synthesized by vascular endothelial cells and placental syncytiotrophoblast cells, and has a high affinity for VEGF receptor 1 (VEGFR1). It can induce the proliferation, migration, and infiltration of trophoblasts and endothelial cells, playing a crucial role in placental angiogenesis and development in early pregnancy [6]. Numerous studies have shown a good correlation between the decrease of serum PLGF in early pregnancy and the onset of preeclampsia [7]. The best biomarker of vitamin D status is serum 25 hydroxyvitamin D [25 hydroxyvitamin D, 25 - (OH) D], which represents the metabolic status of calcium and bone, and is negatively related to body fat, blood glucose control, lipid metabolism and blood pressure. A survey shows that 80% of pregnant women in China suffer from vitamin D deficiency, especially in northern regions. More and more evidence shows that vitamin D deficiency is related to the occurrence of adverse pregnancy outcomes such as diabetes in pregnancy, abortion, premature delivery, hypertensive disorder in pregnancy [8]. Therefore, this study aims to analyze the predictive value of UtA-PI, serum 25- (OH) D, and PLGF in early pregnancy for PE, in order to provide reference for the early prediction of this disease.

2. Object and Method

2.1 Research Subjects

114 pregnant women who underwent regular prenatal examination and delivery in our hospital from January 2022 to December 2022 were included as the study subjects, with 100 normal pregnant women as the control group; There were 7 pregnant women with mild PE, 7 pregnant women with severe PE, and 14 pregnant women with PE were included in the study group. The age range is 20-36 years old. The study has been approved by the ethics committee, with the informed consent of pregnant women and their families. Inclusion criteria: ① Meets the diagnostic criteria for PE in Obstetrics and Gynecology; ② Symptoms such as headache and discomfort in the upper abdomen; ③ Random urine protein (+) or urine protein test ⩾ 0.3g/24h; ④ After 20 weeks of pregnancy, blood pressure ⩾ 140/90mmHg; ⑤ Severe preeclampsia has symptoms such as cerebral nervous system symptoms, persistent headache, visual impairment, etc. Blood pressure ⩾ 160/110mmHg, and elevated levels of lactate dehydrogenase, aspartate aminotransferase, and

alanine aminotransferase in the blood. Exclusion criteria: ① Prepregnancy patients with hypertension, chronic heart disease, or immune system disease; ② Prior to pregnancy, there was a history of chronic diseases such as hyperthyroidism, hematological disorders, and connective tissue diseases; ③ Pre pregnancy with diabetes, kidney disease.

2.2 Method

2.2.1 Variable Setting Dependent Variable

with or without PE as the dependent variable. Independent variables: General data of pregnant women were collected through an epidemiological survey questionnaire, including average age, BMI, gestational week, number of pregnancies, pregnancy outcome, parity, blood pressure, etc. A dedicated person will search for medical records to ensure data consistency and keep personal information of pregnant women confidential throughout the entire process.

2.2.2 Determination of UtA PI

During NT ultrasound examination, the sagittal plane of the uterus is scanned by transabdominal Doppler to determine the cervical canal and the internal orifice of the cervix. In the internal orifice plane of the cervix, color Doppler blood flow imaging is used to detect bilateral uterine arteries respectively. The angle between the sound beam and the blood flow is less than 30 °. Three characteristic uterine artery blood flow spectrums with consistent shape are continuously obtained, and the PI value of bilateral uterine arteries is recorded.

2.2.3 Detection Method

25- (OH) D is detected using enzyme-linked immunosorbent assay. Dilute 50mmol/L carbonate solution with 25- (OH) D antigen, then add the antigen to the reaction plate well of phosphate buffer solution at a temperature of 4 ℃, let it stand for 24 hours, wash 3 times the next day, and discard dry. Dilute 0.1mL of the sample to be tested with diluent, and add positive and negative control samples. Leave at 42 °C for 1 hour, wash three times, and discard until the liquid is removed. Add 0.1mL of enzyme labeled antibody to each well and place at 43 ℃ for 1 hour. Wash 3 times after pipetting and discard dry. Add Na2HPO4 according to the standard of 0.1mol/L, mix well with citric acid drops according to the standard of 0.05mol/L, then add 0.1mL of o-phenylenediamine, shade for 20 minutes, add H2SO4, and terminate the reaction. Detect and record the level of 25- (OH) D using an enzyme-linked immunosorbent assay. PLGF detection: 5 mL venous blood was collected from each group of pregnant women on an empty stomach the next morning after admission and placed in the blood collection vessel. Coagulation was performed at 20-25 ℃ for 200 minutes at 3000 r/min, with a radius of 10 cm. Centrifuge took 5 minutes, and the serum was separated and stored at -80 ℃. After the pregnancy outcome is confirmed, the serum is placed in a 4 ℃ refrigerator and taken out the next day. After equilibrium at room temperature for at least half an hour, the PLGF levels in the serum of two groups of pregnant women are measured using time-resolved fluorescence immunoassay (using PerkinElmer's DELFIA Xpress PLGF kit). All operations during the testing process are strictly carried out in accordance with the instructions of the reagent kit.

2.3 Data Analysis and Processing

SPSS 25.0 analysis was used, with count data subjected to x^2 test and grade data subjected to Ridit test. Multiple logistic regression analysis was used to screen for factors related to preeclampsia, and ROC analysis was used to assess the predictive value of various indicators for PE. $P<0.05$ was considered statistically significant.

3. Results

3.1 Comparison of 3 Sets of Baseline Data

The age, BMI, actual gestational age, pregnancy status (frequency and outcome), and birth frequency of the three groups of pregnant women were comparable ($P>0.05$); The blood pressure of pregnant women with PE was higher than that of the healthy control group ($P<0.05$); The blood pressure in the early onset PE group was higher than that in the late onset and control groups, and the blood pressure level in the late onset PE group was higher than that in the control group ($P<0.05$) is shown in Table1.

Table 1. Comparison of baseline data among three groups

target		Control group (n=100)	Early onset PE group (n=7)	Late onset PE group (n=7)	F/x^2	P
Average age (years)		29.34±6.34	30.23±6.87	29.37±6.45	0.536	>0.05
BMI(kg/m^2)		27.85±3.13	27.88±3.45	27.78±2.89	0.037	>0.05
Pregnancy week (week)		11.67±3.12	11.59±2.45	11.65±2.89	0.099	>0.05
Number of pregnancies (times)		1.76±0.56	1.85±0.66	1.77±0.58	0.610	>0.05
pregnancy outcome	Successful pregnancy	98	3	4	39.892	<0.05
	Adverse pregnancy	2	4	3		
Parity	unigravida	64	6	4	20.222	<0.05
	Pregnant women	36	1	3		
blood pressure	systolic pressure	82.76±6.12	107.45±11.45	105.45±11.23	14.478	>0.05
	diastolic pressure	131.01±11.45	156.56±15.45	153.56±11.21	8.367	>0.05

3.2 Comparison of UtA-PI, 25- (OH) D, and PLGFMOM Levels among Three Groups of Pregnant Women

The detection of UtA-PI in each group showed no difference ($P>0.05$), and pregnant women with early-onset PE and late-onset PE were slightly higher than healthy pregnant women; The levels of 25- (OH) D and PLGF in early and late onset PE pregnant women were significantly lower than those in the control group ($P<0.05$); The UtA-PI of late onset PE pregnant women was slightly higher than that of early onset PE pregnant women, but there was no significant difference ($P>0.05$); Pregnant women with PE were found to have lower levels of 25- (OH) D and PLGF in the early onset PE group (P<0.05) is shown in Table 2 and Figure 1.

Table 2. Comparison of UtA-PI, 25- (OH) D, and PLGFMOM values among three groups of pregnant women ()

group	Number of cases	UtA-PI	25-(OH)D(ng/mL)	PLGF(pg/mL)
control group	100	1.06±0.12	18.34±2.12	56.89±15.32
Early onset PE group	7	1.09±0.12	10.55±1.12	34.43±6.23
Late onset PE group	7	1.07±0.11	12.23±1.32	38.56±7.45
F	——	0.321	11.256	4.694
P	——	>0.05	<0.05	<0.05

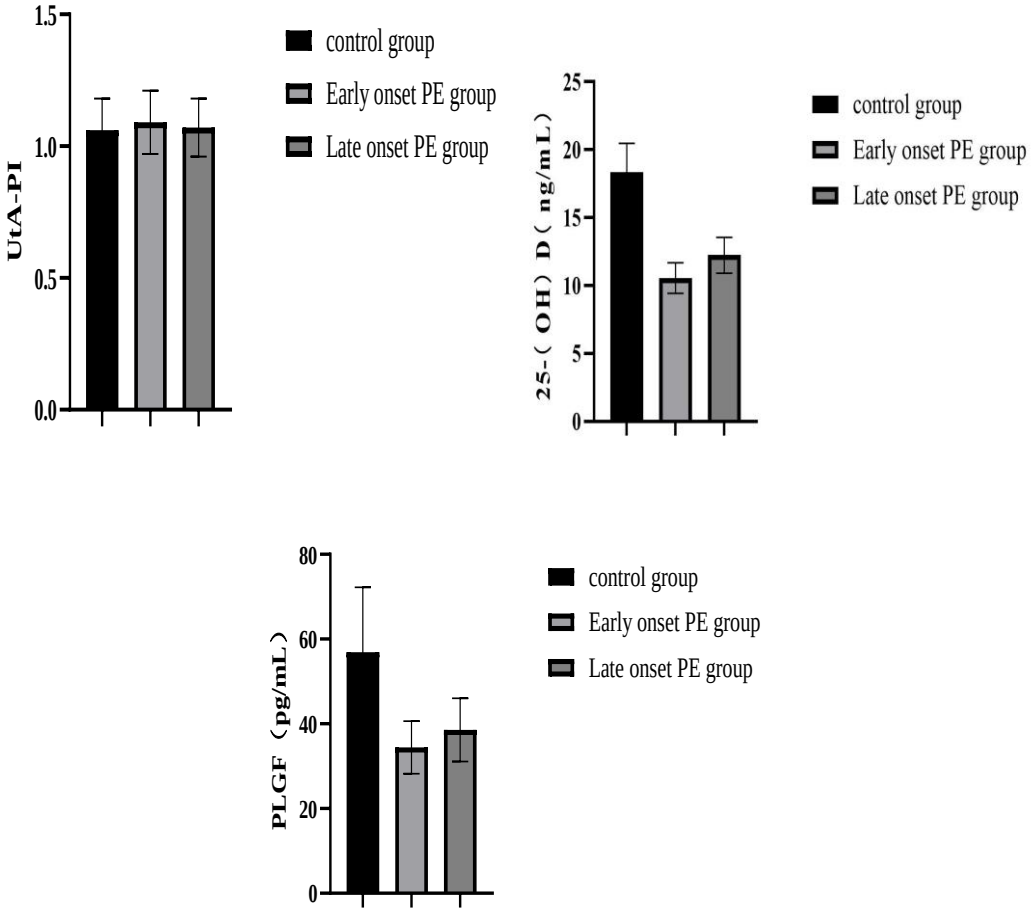

Figure 1. Comparison of UtA-PI, 25- (OH) D, and PLGFMOM values among three groups of pregnant women

3.3 Correlation Analysis of UtA-PI, 25- (OH) D, PLGF

Pearson analysis results showed that UtA-PI was negatively correlated with 25- (OH) D and PLGF (r=-0.881, -0.903, P<0.01), while 25- (OH) D was positively correlated with PLGF levels (P<0.01) is shown in Figure 2.

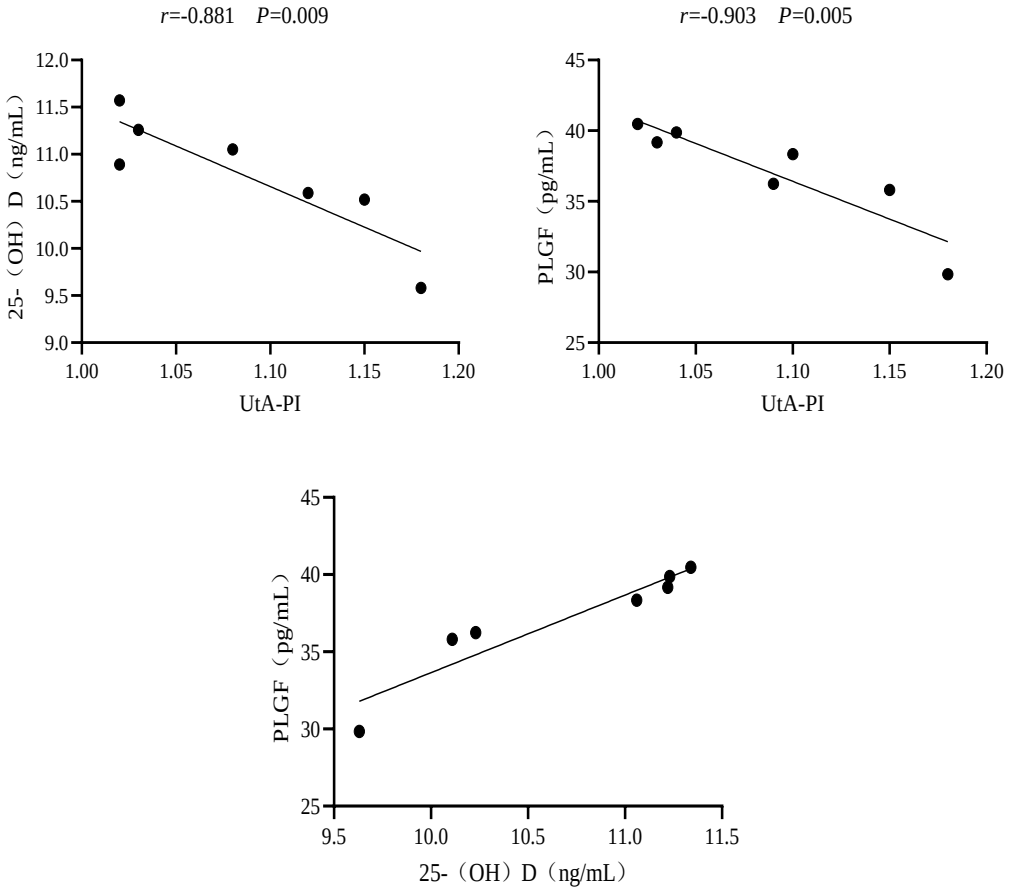

Figure 2. Correlation Analysis of UtA-PI, 25- (OH) D, PLGF

3.4 Logistic Regression Analysis of Factors Related to PE Occurrence

Using the occurrence of PE as the dependent variable (yes=0, no=1) and comparing the differences between the two groups of pregnant women as the independent variable, the regression equation was included, and the original values were entered. The results showed that pre eclampsia was associated with UtA-PI, 25- (OH) D, and PLGF levels, which were independent factors (P<0.05) is shown in Table 3.

Table 3. Logistic Multivariate Regression Analysis on the Causes of Preeclampsia

influence factor	β value	SE	Wald x^2	P-value	OR	95%CI
age	0.436	0.418	1.420	0.435	1.243	0.661-1.785
BMI	0.423	0.452	1.429	0.523	1.265	0.527-1.534
BP	0.423	0.432	1.243	0.447	1.523	0.784-1.954
UtA-PI	2.845	0.534	20.167	0.027	9.123	0.558-0.917
25-(OH)D	4.123	0.578	33.112	0.009	10.221	0.605-0.951
PLGF	3.154	0.511	21.216	0.002	9.156	0.655-0.998

Assignments: Age, BMI, blood pressure, UtA-PI, 25- (OH) D, PLGF all original values entered

The predictive value of 2.5 ROC analysis prediction models UtA-PI, 25- (OH) D, PLGF for preeclampsia

Re incorporate UtA-PI, 25- (OH) D, and PLGF into logistic regression analysis and establish the model using the formula: Logit (P)=1.723 * (age)+1.589 * (BMI)+1.764 * (blood pressure)+1.634 * (UtA-PI)+1.231 * (25- (OH) D)+1.467 * (PLGF) -1.693. The ROC analysis was used to predict the predictive value of UtA-PI, 25- (OH) D, and PLGF models for preeclampsia. The results showed that the combination of the three factors had a (0.858) AUC for preeclampsia, a sensitivity of 88.75%, a specificity of 82.20%, and a P<0.05 is shown in Figure 3.

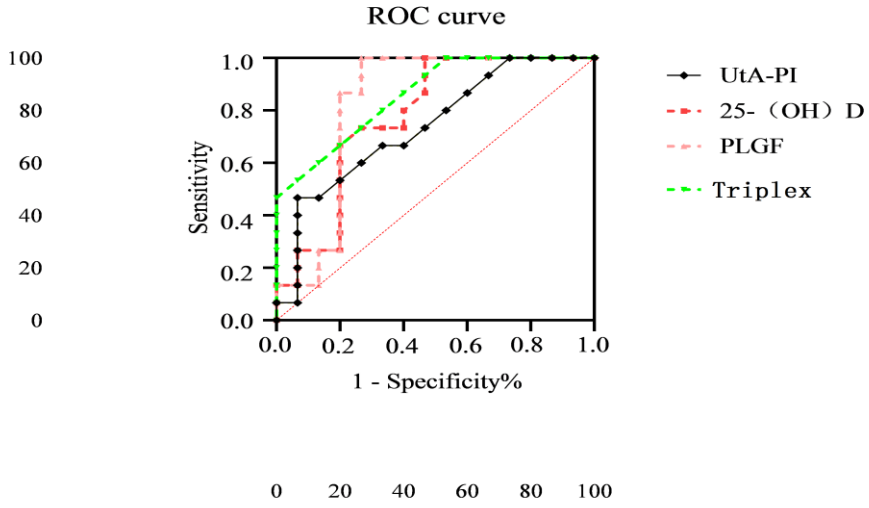

Figure 3. ROC analysis and prediction models UtA-PI, 25- (OH) D, and PLGF for the predictive value of preeclampsia

4. Discussion

PE is a common pregnancy syndrome, in which pregnant women may experience elevated blood pressure after 20 weeks of pregnancy, as well as multiple important organ and placental fetal or systemic involvement. PE can harm the physical and mental health of pregnant women, and in severe cases, it can endanger the lives of pregnant women and perinatal infants [9-10]. Research has shown that[11] pregnant women with preeclampsia have a four fold increased risk of heart failure compared to normal individuals, and a two to three fold increased risk of coronary heart disease, angina pectoris, stroke, and cerebral thrombosis. Preeclampsia seriously affects the health of mothers and infants, but so far, there is a lack of effective clinical prevention and treatment methods, and termination of pregnancy is still the only treatment method. Therefore, early prediction of preeclampsia is particularly important for improving the adverse pregnancy outcomes of mothers and infants. The pathogenesis of preeclampsia is still not fully elucidated, and its multifactorial induction, multi-channel pathogenesis, and individual heterogeneity characteristics determine that a single indicator cannot predict preeclampsia well. More and more research tends to combine multiple indicators in early pregnancy to predict preeclampsia [12-13].

4.1 The Predictive Value of UtA-PI for Preeclampsia

When pregnant women are in a normal pregnancy cycle, the invasion of trophoblastic cells into the spiral arteries of the uterus often occurs during the period of 14-16 weeks of pregnancy. However, due to various factors, the infiltration ability of trophoblastic cells in pregnant women

significantly decreases, leading to insufficient recasting of the aforementioned small arteries. In addition, due to the influence of "shallow implantation of the fetal disc," the vascular resistance increases significantly, and placental perfusion decreases accordingly. At this time, placental circulation is in a high resistance state, Final induction of preeclampsia [14]. Therefore, it can be concluded that there is no significant difference in uterine artery blood flow between pre eclampsia pregnant women and normal pregnant women in early pregnancy. The results of this study also confirmed that the UtA-PI levels of pregnant women in the preeclampsia group were higher than those in the control group, and the increase was more significant in the early-onset preeclampsia group. However, there was no statistically significant difference between the three groups of pregnant women (P>0.05). However, the sensitivity and specificity of UtA-PI alone in predicting preeclampsia were 79.40% and 70.70%, while the combination of 25- (OH) D and PLGF significantly improved the sensitivity and specificity of predicting preeclampsia, with 88.75% and 82.20%, respectively. Therefore, it is still believed that UtA-PI has certain predictive value in predicting preeclampsia in early pregnancy.

4.2 The Predictive Value of PLGF in Preeclampsia

PLGF is an important member of the VEGF family, mainly synthesized by vascular endothelial cells and maternal placental syncytiotrophoblast cells. It has a high affinity for VEGFR1, and endothelial cells and cytotrophoblasts can proliferate, migrate, and even infiltrate under its influence, greatly affecting placental angiogenesis and even placental development in early pregnancy [15-16]. If the expression level of PLGF decreases, it will weaken the proliferation and invasion ability of trophoblasts, hinder the formation of placental capillary network, and therefore, the decrease in PLGF level is related to the onset of preeclampsia. Numerous studies have found a good correlation between the decrease of serum PLGF in early pregnancy and the onset of preeclampsia [17]. In recent years, scholars have conducted a meta-analysis of 432621 pregnant women in 103 studies and found that the best predictor of preeclampsia is PLGF, and its predictive value for early-onset preeclampsia is higher than that for late-onset preeclampsia [18]. The results of this experiment showed that the PLGF levels in the early onset PE group and late onset PE group were lower than those in the control group, and the PLGF levels in the early onset PE group were lower than those in the late onset PE group (P<0.05). The ROC of early pregnancy maternal serum PLGF in predicting preeclampsia is 0.827, with a sensitivity of 67.1% and a specificity of 75.5%, indicating that early pregnancy maternal serum PLGF has certain diagnostic value for preeclampsia. There are also studies indicating that PLGF needs to be combined with other indicators to have predictive value for preeclampsia. The results of this experiment indicate that the combination of PLGF and other indicators has greater predictive value for preeclampsia.

4.3 The Predictive Value of 25- (OH) D for Preeclampsia

Vitamin D is an important and common fat soluble vitamin, with its main forms including vitamins D2, D3, etc. Among them, vitamin D2 is more common in plants, while vitamin D3 is more common in advanced animals [19-20]. Vitamin D3 itself is inactive and can produce 25 (OH) D after secondary hydroxylation. Multiple studies have confirmed that 25 (OH) D plays an important role in regulating calcium and phosphorus metabolism and bone mineralization. In addition, 25 (OH) D is also involved in immune regulation, cell proliferation, and other processes [21-22]. This study found that the levels of 25- (OH) D and PLGF in pregnant women with early and late onset PE decreased significantly compared to the control group (P<0.05); Pregnant women with late onset PE had lower levels of 25- (OH) D and PLGF compared to those with early onset PE (P<0.05). The cutoff value of maternal serum PLGF for predicting preeclampsia in early pregnancy

is 24.03 μ G/L, with a sensitivity of 88%, specificity of 82%, AUC of 0.864 (indicating high predictive value), and a 95% CI of 0.811-0.916 (P<0.05), indicating a high sensitivity and specificity in predicting PE at 25 (OH) D levels in early pregnancy.

4.4 The Predictive Value of Combined Testing for Preeclampsia

In theory, selecting a combination of multiple indicators for prediction can improve the sensitivity and specificity of screening. AUC between 0.7 and 0.9 indicates moderate diagnostic accuracy, while closer to 0.9 or even 1.0 indicates higher diagnostic accuracy. The results of this study showed that the AUC of the combined detection of UtA-PI, 25- (OH) D, and PLGF reached 0.857, which is higher than the accuracy of all individual indicator predictions. Moreover, the prediction method of combined multi indicator detection has the highest specificity, reaching 89.10%, sensitivity, 86.47%, and prediction efficiency.

In summary, the combined screening of UtA-PI, serum 25- (OH) D, and PLGF in early pregnancy is of great significance in predicting preeclampsia and has important value in early assessment of the risk of preeclampsia.

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Data Availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Conflict of Interest

The author states that this article has no conflict of interest.

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