Original paper

Folia Neuropathologica

The early predictive value of maternal serum PAPP-A concentration at 11-14 weeks of pregnancy for preeclampsia

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Folia Neuropathol 2024; 62: 1-9 *DOI: https://doi.org/10.5114/fn.2024.140447*

Abstract

Introduction: *To determine the expression and clinical significance of maternal serum pregnancy-associated plasma protein A (PAPP-A) in pregnant women with different degrees of preeclampsia at 11-14 weeks of gestation.*

Material and methods: *The clinical data of 65 pregnant women with preeclampsia admitted to our hospital from January 2020 to October 2022 were retrospectively analysed. Another 45 normal pregnant women who came to our hospital for prenatal examination and delivery during the same period were selected as the healthy control group. The serum contents of PAPP-A, α-fetoprotein (AFP) and free estriol (uE3) in each group were compared. The correlation between PAPP-A and AFP as well as uE3 was analysed by Pearson analysis. The clinical value of serological indexes in diagnosing preeclampsia was analysed using ROC curve.*

Results: *The levels of PAPP-A and uE3 in pregnant women in the preeclampsia group were lower, while the contents of AFP were higher than these in the healthy control group ($p < 0.01$). The pregnant women with severe preeclampsia had lower levels of PAPP-A and uE3 with higher levels of AFP compared to these with mild preeclampsia ($p < 0.001$). Pearson correlation analysis showed that serum PAPP-A was negatively correlated with AFP ($r = –0.246$, $p < 0.05$) and positively correlated with uE3 ($r = 0.398$, $p < 0.01$) in preeclampsia patients. ROC curve analysis demonstrated that the area under the curve (AUC) of PAPP-A, AFP and uE3 to assist in the diagnosis of preeclampsia was 0.740, 0.738 and 0.806, respectively. The AUC of the combination of PAPP-A, AFP and uE3 to assist in the diagnosis was 0.912, with a sensitivity of 90.38% and a specificity of 80.33%. The clinical assisted diagnostic value of combined detection was high.*

Conclusions: *The serum level of PAPP-A in pregnant women with preeclampsia in the early pregnancy was significantly lower and related to the severity of the disease. The combination of routine detection for AFP and uE3 had a good predictive value for preeclampsia, which was helpful to take relevant interventions to reduce the incidence of preeclampsia as early as possible, and had a positive impact on protecting maternal and infant health.*

Key words: *11-14 weeks of gestation, pregnancy, serum pregnancy-associated plasma protein A, preeclampsia, predictive value.*

Introduction

Preeclampsia refers to a pregnancy-specific disease in which the blood pressure is normal before pregnancy. The main clinical manifestations are the rise of blood pressure and/or proteinuria after 20 weeks of pregnancy, which can affect multiple important organs and tissues of the whole body [13]. According to epidemiological statistics [24], the incidence of preeclampsia is about 5~10%, which means that 5~10 pregnant women may develop preeclampsia in every 100 pregnant women in China. It is reported that about 76,000 preg-

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Received: 04.05.2023, **Accepted:** 12.10.2023, **Online publication:** 2024

nant women and 500,000 foetuses die of preeclampsia and its complications every year, 19 pregnant women develop preeclampsia every minute, and up to 20% of premature babies are born due to preeclampsia [17]. Currently, preeclampsia is considered as a multi-factor, multi-mechanism and multi-pathway disease, which is caused by the joint action of the mother-foetus-placenta. It is mainly related to genetic factors, placental dysfunction, an imbalance in the immune system and a few other variables [16,21]. The primary clinical manifestations of preeclampsia are hypertension and proteinuria, which are also one of the leading causes of premature delivery, neonatal illness, or death [9]. Preeclampsia is a major form of gestational hypertension, and early warning, identification, and intervention are crucial for optimizing preeclampsia management and reducing the incidence of adverse perinatal outcomes in pregnant women [14].

Serum pregnancy-associated plasma protein A (PAPP-A) is a large-molecule glycoprotein complex derived from the placenta, which plays an important role in maintaining pregnancy, and promoting foetal and placental growth and development. During the early stages of pregnancy, the concentration of PAPP-A gradually rises with the duration of pregnancy until it reaches its peak at 12-14 weeks of pregnancy. Thereafter, it gradually decreases until the end of pregnancy [2]. *In vitro* experiments found that PAPP-A2 was highly expressed in placenta, foetal bones and reproductive organs, which promoted the release of insulin-like growth factor 1 (IGF-1), thereby activating the IGF signalling pathway, and promoting the proliferation of vascular smooth muscle cells and vascular intima cells. IGF-1 promotes the viscosity of the extracellular matrix and stimulates the invasion of trophoblasts into the uterine decidua. Placental implantation induced by abnormal invasion of trophoblasts is one of the possible pathophysiologies of preeclampsia [7]. The above studies suggest that PAPP-A may be used as a serological marker for predicting preeclampsia. Alpha-fetoprotein (AFP) is the most common and important serum protein in the foetal period. Normally, only a small amount of AFP passes through the placenta to the mother during pregnancy. However, in the setting of preeclampsia, foetal transport of AFP transplacentally to the mother is reduced due to spasm of arterioles throughout the mother's body [8]. Free estriol (uE3) is a steroidal hormone synthesized by the foetal adrenal glands and liver, and placenta. uE3 synthesized during pregnancy is not excreted by the pregnant woman's kidneys, including up to 90 percent from the adrenal glands of the embryo, so that serum uE3 levels reflect placental function [23]. Placental growth factor detection in the first trimester (11~14 weeks of pregnancy), combined with maternal risk factors, mean arterial pressure, and uterine artery pulse index for comprehensive assessment, as well as early intervention and management of high-risk groups of preeclampsia, is of great significance to improve pregnancy outcomes [22].

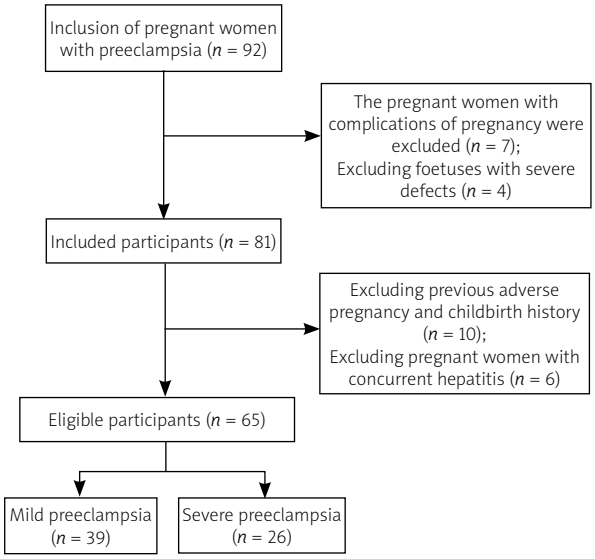

Fig. 1. Inclusion process of 65 pregnant women with preeclampsia.

In this study, pregnant women with preeclampsia were selected as the participants, aiming to investigate the expression and clinical significance of maternal serum PAPP-A in pregnant women with different degrees of preeclampsia from 11 to 14 weeks of pregnancy. Besides, the correlation between serum PAPP-A and serum levels of AFP and uE3 was further analysed.

Material and methods

General material

The clinical data of 65 pregnant women with preeclampsia admitted to our hospital from January 2020 to October 2022 were analysed in the study. The inclusion process was shown in Figure 1. Inclusion criteria: 1) All pregnant women met the clinical diagnostic criteria for preeclampsia [11]; 2) All pregnant women were single birth primiparous women; 3) Pregnant women whose first prenatal examinations were performed 14 weeks ago; 4) Patients without high-risk factors for preeclampsia, including chronic/persistent hypertension, chronic kidney disease, or diabetes; 5) The body mass index (BMI) of pregnant women was 18.5-25 kg/m^2; 6) This pregnancy was natural and not assisted by reproductive technology; 7) Pregnant women underwent serum PAPP-A testing; 8) First-time pregnant

woman with single pregnancy examined in our hospital and voluntarily gave birth or had labour induced in our hospital. Exclusion criteria: 1) Preeclampsia due to chronic hypertension, diabetes, nephritis and other medical diseases; 2) Pregnant women with other complications of pregnancy; 3) Pregnant women with severe foetal defects; 4) Pregnant women with a history of preeclampsia or other adverse pregnancies; 5) Pregnant women with a concomitant or previous history of malignant tumours; 6) Pregnant women with severe blood system diseases, hepatitis, etc. Another 45 normal pregnant women who came to our hospital for prenatal examination and delivery during the same period were selected as the healthy control group. Inclusion criteria: 1) Age ≥ 18 years; 2) Single pregnancy. Exclusion criteria: 1) Exclusion of preeclampsia in this pregnancy; 2) Hypertension, diabetes and other diseases in the past; 3) Bad habits such as drug use, smoking, or alcohol abuse. This study was approved by the Ethics Committee of the Jinan Maternity and Child Care Hospital.

Diagnostic criteria [20]

The diagnostic criteria for mild preeclampsia: 1) Systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg after 20 weeks of pregnancy; 2) With proteinuria ≥ 0.3 g/24 h or random urinary protein ≥ 1.

The diagnostic criteria for severe preeclampsia: Preeclampsia with any of the following manifestations was diagnosed as severe preeclampsia. 1) Systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg (bed rest with a minimum interval of 4 hours between measurements); 2) Thrombocytopenia (platelets < 100 × 10^9/l); 3) Liver function damage (serum transaminase level was more than twice the normal value), or severe and persistent right upper quadrant or upper quadrant pain, which could not be explained by other diseases, but both of these two symptoms could exist; 4) Renal function impairment (blood creatinine level greater than 1.1 mg/dl or creatinine concentration more than twice the normal value in the absence of other kidney diseases); 5) Pulmonary oedema; 6) Newly occurring central nervous system abnormalities or visual impairments.

Outcome measures

1) Clinical data: age, years of education, gestational age at initial prenatal examination, BMI, systolic blood pressure and diastolic blood pressure at initial prenatal examination for preeclampsia and normal pregnant women were collected.

2) Serological indicators: venous blood from all pregnant women during prenatal examination at 11-14 weeks of pregnancy was collected and placed in a refrigerator (Qingdao Haier Biomedical Co., Ltd., Hightech Zone, Qingdao City, Shandong Province, China, catalogue number: HXC-158) at 4°C for 1 h. The venous blood was centrifuged at a speed of 3000 r/min for 10 min. The supernatant was collected and refrigerated in a –80°C freezer (Senxi Saizhi Technology Co., Ltd., Tianhe District, Guangzhou, China, catalogue number: MUF 40). Serum PAPP-A, AFP and free estriol (uE3) levels were measured by ELISA. The ELISA kits for detecting the serum level of PAPP-A, AFP and uE3 were purchased from Shanghai Fuyu Biotechnology Co., Ltd. (Jiading District, Shanghai, China, catalogue number: FY-03440H1), CUSABIO® (Wuhan Huamei Bioengineering Co., Ltd., Wuhan, China, catalogue number: CSB-E04770h), and Nanjing Wanmuchun Biotechnology Co., Ltd. (Nanjing, Jiangsu Province, China, catalogue number: WM-YX10707), respectively. The specific steps were as follows: sample addition: 0.1 ml diluted sample to be tested was added into the coated reaction well and incubated at 37°C for 1 h. Then the reaction wells (with blank wells, negative control wells, and positive control wells set at the same time) were washed. Adding enzyme-linked antibodies: 0.1 ml of freshly diluted enzyme-linked antibodies (diluted after titration) (Shanghai Boulson Biotechnology Co., Ltd., Shanghai, China, catalogue number: BES-20733CBR) was added into each reaction well and incubated at 37°C for 0.5-1 h, and then the wells were washed. Colour development: 0.1 ml of temporarily prepared TMB substrate solution was added to each reaction well, and incubated at 37°C for 10 to 30 min. 0.05 ml of 2 M sulfuric acid was added to terminate the reaction; Result determination: the results could be directly observed with the naked eye on a white background. The darker the colour inside the reaction hole, the stronger the positivity. The negative reaction was colourless or extremely light. The results could also be detected through OD value detection on an ELISA detector (Shanghai Meigu Molecular Instruments (Shanghai) Co., Ltd., China, catalogue number: SpectraMax iD5) at 450 nm.

Statistical analysis

The enumeration data in this study were presented as examples (%), and compared using χ^2 test. The measurement data were tested for normality distribution with Levene analysis and were consistent with the normal distribution and variance homogeneity. The measurement data were shown in the form of ($x \pm s$). The measurement data between two groups were tested using independent sample *t*-tests. Multiple inter

group data were analysed using repeated measures of variance, and pairwise comparisons were conducted for further LSD-*t* testing. The correlation between serum PAPP-A with AFP and uE3 at 11-14 weeks of pregnancy was analysed using Pearson analysis. ROC analysis was used to analyse the clinical value of serological indicators in the diagnosis of preeclampsia. In this study, SPSS 23.0 software was used for statistical data analysis, and $p < 0.05$ was considered statistically significant.

Results

Comparison of general information between the preeclampsia group and the healthy control group

There was no significant difference in general information such as age and education years between two groups ($p > 0.05$, Table I).

Comparison of serological indicators between the preeclampsia group and the healthy control group

To investigate the expression of serum PAPP-A, AFP and uE3 in pregnant women with preeclampsia, the comparison was conducted between the preeclampsia group and the healthy control group. The results showed that the serum levels of PAPP-A and uE3 in pregnant women in the preeclampsia group were lower, while the serum contents of AFP were higher than these in the healthy control group ($p < 0.01$; Table II and Figs. 2 and 3).

Correlation analysis of serum indicators from 11 to 14 weeks of pregnancy

In order to analyse the correlation between serum PAPP-A and AFP as well as uE3 at 11~14 weeks of pregnancy, Pearson correlation analysis was conducted in this study. The results showed that serum PAPP-A was negatively correlated with AFP ($r = –0.246$, $p < 0.05$) and positively correlated with uE3 ($r = 0.398$, $p < 0.01$) in preeclampsia patients (Table III and Fig. 4).

ROC analysis for the clinical value of serum PAPP-A in the diagnosis of preeclampsia

ROC curve analysis demonstrated that the AUC of PAPP-A, AFP and uE3 to assist in the diagnosis of preeclampsia was 0.740, 0.738 and 0.806, respectively. The AUC of the combination of PAPP-A, AFP and uE3 to assist in the diagnosis was 0.912, with a sensitivity of 90.38% and a specificity of 80.33%. The clinical auxil-

Table I. Comparison of general information ($\bar{x} \pm s$)

General information	Preeclampsia group ($n = 65$)	Healthy control group ($n = 45$)	*t* value	*P* value
Age (year)	27.21 ±4.80	26.84 ±5.14	0.386	0.700
Education years (year)	14.25 ±2.51	14.55 ±2.50	0.617	0.538
Pregnancy week at initial prenatal examination (weeks)	11.20 ±0.81	11.35 ±0.52	1.095	0.276
BMI (kg/m^2)	22.68 ±1.25	22.15 ±1.69	1.891	0.061
Systolic blood pressure at initial prenatal examination (mm Hg)	112.82 ±15.71	113.52 ±14.47	0.237	0.813
Diastolic blood pressure at initial prenatal examination (mm Hg)	79.52 ±6.25	78.84 ±6.51	0.552	0.582

Table II. Comparison of serological indicators ($\bar{x} \pm s$)

Groups	Cases	PAPP-A (MoM)	AFP (U/ml)	uE3 (nmol/l)
Healthy control group	45	1.30 ±0.36	32.65 ±11.49	4.98 ±1.25
Preeclampsia group	65	0.35 ±0.18***	39.51 ±12.77***	3.11 ±1.04***
Mild preeclampsia group	39	0.59 ±0.12***	34.42 ±6.52*	3.88 ±0.96**
Severe preeclampsia	26	0.26 ±0.07***###	41.33 ±5.58***###	2.90 ±1.06***###
F value		195.15	6.13	32.34
P value		< 0.001	0.0014	< 0.001

**p < 0.05, **p < 0.01 and ***p < 0.001 vs. the healthy control group; ###p < 0.001 vs. the mild preeclampsia group.*

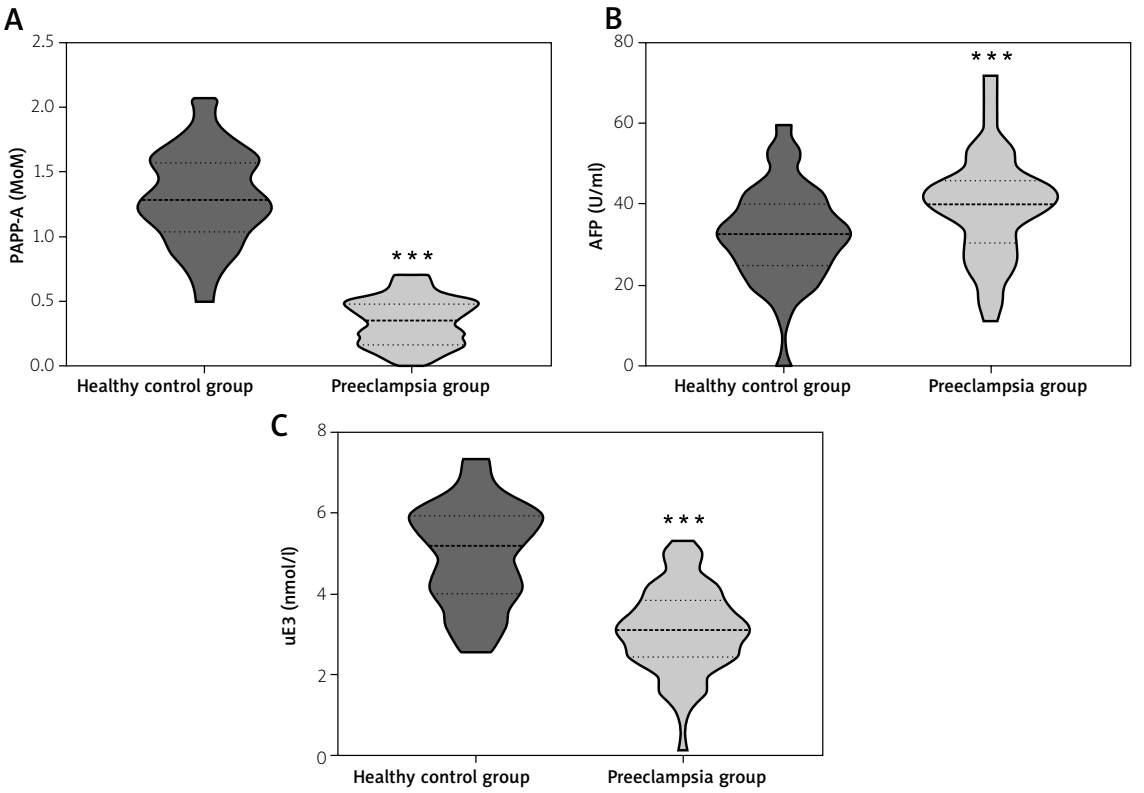

Fig. 2. Comparison of serological indicators. **A**) Comparison of PAPP-A levels; **B**) Comparison of AFP levels; **C**) Comparison of uE3 levels. $^{***}p < 0.001$ compared with the healthy control group.

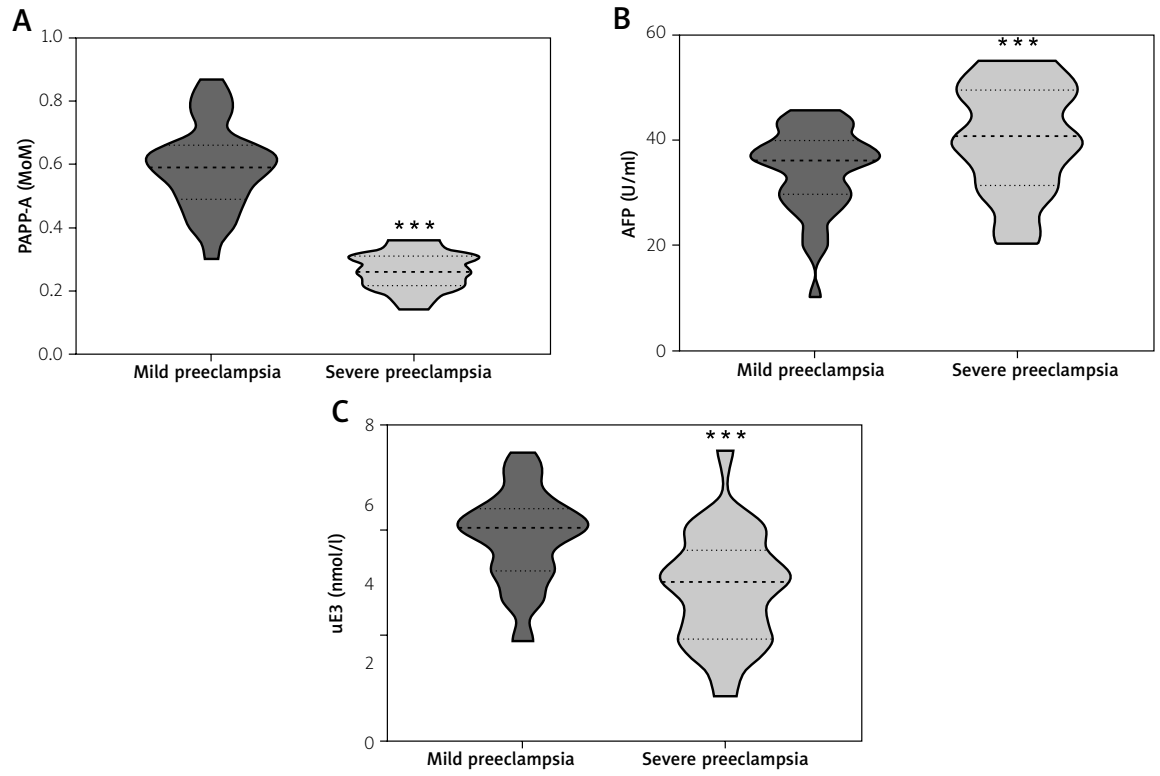

Fig. 3. Comparison of serological indicators in pregnant women with different degrees of preeclampsia. **A**) Comparison of PAPP-A levels; **B**) Comparison of AFP levels; **C**) Comparison of uE3 levels. $^{***}p < 0.001$ compared with the mild preeclampsia group.

iary diagnostic value of combined detection was high (Table IV and Fig. 5).

Discussion

Preeclampsia is a kind of disease with gestational hypertension and proteinuria as the main symptoms, which is the main cause of death for mothers and foetuses, accounting for about 3~8% of all premature birth cases [1]. The study has reported that preeclampsia increases the risk of long-term cardiovascular disease and other complications in mothers and infants, in which women with severe preeclampsia have a 4.74 times higher risk of postpartum maternal cardiovascular events than normal pregnant women, and children with neurodevelopmental disorders or psychiatric disorders have a 18% higher risk than normal children [15]. The pathogenesis of preeclampsia has not been fully elucidated and may involve both maternal and foetal/placental factors, including abnormal remodelling of spiral arteries, defects in trophoblast cell differentiation, placental hypoperfusion, hypoxia, ischemia, and immunological, genetic, and environmental factors [11]. Therefore, early prediction and accurate identification of the risk of preeclampsia in pregnant and postpartum women, combined with early drug intervention and symptomatic treatment, are important clinical measures for the diagnosis and treatment of preeclampsia. It can reduce the incidence and mortality rate of maternal and foetal complications during the perinatal period, and avoid the occurrence of adverse pregnancy outcomes. Measures, including early detection, early diagnosis, early treatment, advance of screening for foetal abnormalities, and early screening of abnormal foetuses make enough time to decide the fate of the foetus. Besides, these measures can reduce the psychological and physical trauma of pregnant women if labour is induced, as well as reduce unnecessary waste of resources. If the foetus is not found to be abnormalized during the first trimester screening, it can enhance the confidence of pregnant women, alleviate their worries and concerns, and promote humanistic care.

PAPP-A is a compound of macromolecular glycoproteins that gradually increases in maternal plasma during pregnancy, playing an important role in main-

Table III. Pearson analysis of the correlation between serum PAPP-A with AFP and uE3 at 11-14 weeks of pregnancy

Indicators	PAPP-A	
	R	*p*
AFP	–0.246	0.048
uE3	0.398	0.001

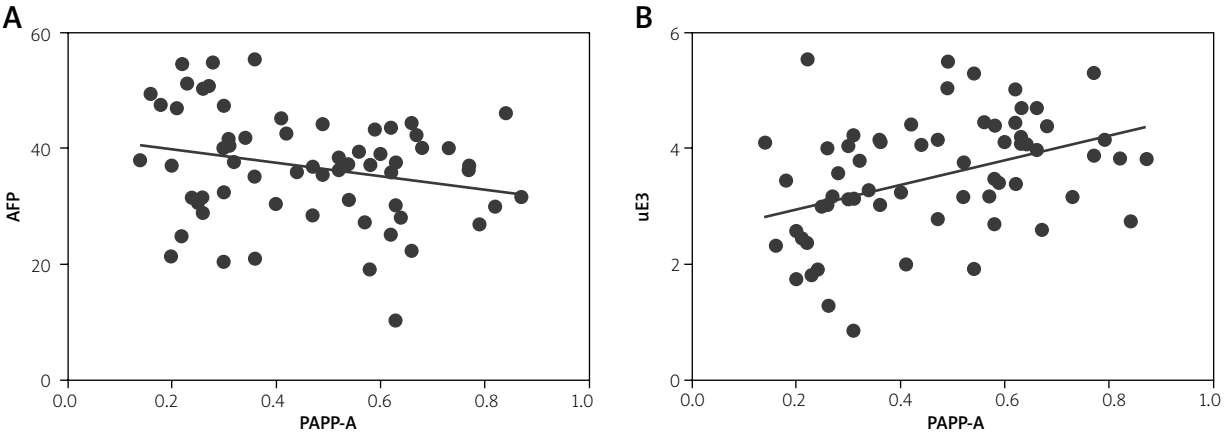

Fig. 4. Pearson correlation analysis of serological indicators correlation. **A**) The correlation between serum PAPP-A and AFP; **B**) The correlation between serum PAPP-A and uE3.

Table IV. ROC analysis of the clinical value of serum PAPP-A to assist in the diagnosis of preeclampsia

Indicators	AUC	95% CI	Sensitivity	Specificity	*P* value	Cut-off value	Youden index
PAPP-A	0.740	0.645~0.835	85.69	63.81	0.008	0.60	0.495
AFP	0.738	0.642~0.834	83.15	58.11	0.010	35.74	0.413
uE3	0.806	0.724~0.888	78.69	75.22	0.001	3.92	0.539
Combined diagnosis	0.912	0.852~0.972	90.38	80.33	0.001	–	0.707

taining pregnancy and promoting foetal and placental growth and development [5]. In the early stages of pregnancy, the concentration of PAPP-A gradually increases with the duration of pregnancy with a peak at 12-14 weeks of pregnancy, and then gradually decreases until the end of pregnancy [19]. Currently, PAPP-A is widely considered as an important indicator for maternal serological prenatal screening. PAPP-A early pregnancy detection, combined with B-ultrasound measurement of posterior cervical transparent zone thickness, is an effective method for prenatal screening of foetal chromosomal abnormalities, with a detection rate of up to 85% [27]. In prenatal screening of foetuses with trisomy 21 and trisomy 18 in women 74-97 days of early pregnancy, the accuracy of the combined diagnosis of PAPP-A and β-human chorionic gonadotropin (β-hCG) for Down syndrome is 85.2% [25]. In a study conducted in Hungary in 2019 on risk assessment of early pregnancy preeclampsia, the detection rate is 63.6% with only incorporating prior (maternal factors) and biophysical parameters for risk assessment, and 72.7% with incorporating PAPP-A indicators, with an increase of nearly 10% [18]. The results of this study showed that the levels of PAPP-A of pregnant women in the preeclampsia group were much lower than those in the healthy control group. Meanwhile, the levels of PAPP-A of pregnant women in the severe preeclampsia group were sharply lower than those in the mild preeclampsia group. The AUC of PAPP-A alone in diagnosing preeclampsia was 0.740. These results indicated that maternal serum PAPP-A in early pregnancy had a certain predictive value for preeclampsia. PAPP-A was easy to obtain in early Down's serum screening and was associated with preeclampsia, which suggested that it could be a predictor of the onset of preeclampsia in early pregnancy. It may be related to the fibrinolytic inhibition of PAPP-A and its impact on the insulin-like growth factor system. PAPP-A may be related to placental function and maturity at the molecular level, and measuring its serum concentration can directly monitor placental maturity and indirectly reflect foetal growth. The protein acts immunosuppressively, protecting the foetus from maternal rejection and maintaining the placental barrier [2].

Analysing the relationship between relevant indicators in pregnant women's serum and the occurrence of preeclampsia can better predict the occurrence of preeclampsia. However, the application value of individual PAPP-A detection for predicting preeclampsia is limited with low sensitivity and specificity. Under normal circumstances, the oestrogen in the serum of pregnant women gradually increases with the prolongation of pregnancy time. Therefore, free uE3 can better reflect the true condition of the body and is an

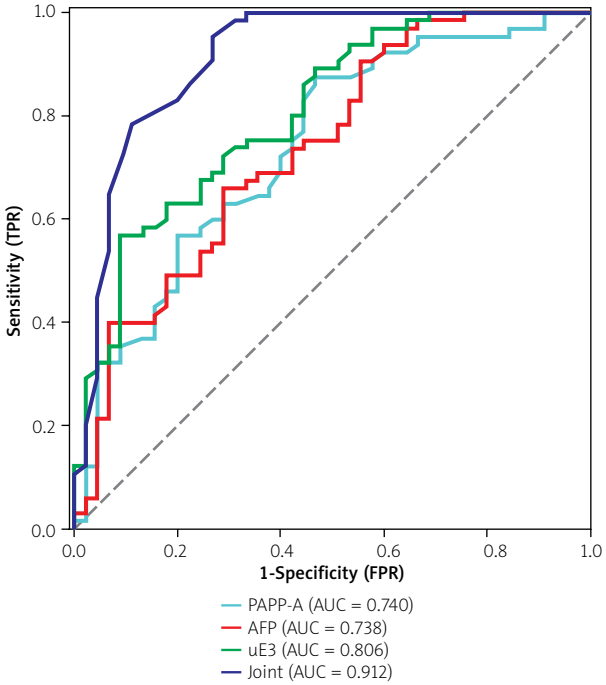

Fig. 5. ROC analysis of the clinical value of serum PAPP-A to assist in the diagnosis of preeclampsia.

important indicator for determining placental function, making it more valuable in clinical practice [23,26]. Alpha-fetoprotein, a common serum protein in foetal life, mainly derived from embryonic liver cells, protects the liver from maternal influences. During normal pregnancy, only a portion of AFP enters the mother's body through the placenta, whose level in the mother's serum is linked to changes in foetal membrane permeability and placental blood flow [3,10]. Pregnant women with preeclampsia may experience systemic arterial spasm, reducing placental blood flow and foetal AFP secretion, thereby reducing the level of AFP transmitted from the placenta to the mother [4]. Insufficient uterine placental blood perfusion, causing degenerative lesions in villi, and in severe cases, causing bleeding and necrosis, is leading to abnormal placental function, so the level of different markers secreted by the placenta is significantly reduced, and the level of uE3 in serum is significantly reduced [6]. The study has found that low uE3 is associated with gestational diabetes, oligohydramnios, threatened preterm birth, and small-for-gestational-age infants, and that one possible pathogenesis of preeclampsia is placental dysplasia due to placental hypoperfusion, which is speculated to be associated with preeclampsia [12]. The results of this study showed that compared with the healthy control group, the pregnant women in the preeclampsia group had much lower levels of uE3 and strongly higher

levels of AFP, indicating a certain correlation between serum AFP and uE3 levels in the onset of preeclampsia at 11-14 weeks of pregnancy. In addition, Pearson correlation analysis in this study showed a negative correlation between serum PAPP-A and AFP, and a positive correlation between serum PAPP-A and uE3 levels in patients with preeclampsia. The AUC of the combination of PAPP-A, AFP and uE3 to assist in the diagnosis for preeclampsia was 0.912, indicating that the combination of PAPP-A, AFP and uE3 to assist in the diagnosis for preeclampsia had a higher value and more effective complementary advantages, improving the sensitivity and specificity of the diagnosis of preeclampsia.

In general, the serum level of PAPP-A in pregnant women with preeclampsia in the early pregnancy was significantly lower and related to the severity of the disease. The combination of routine detection for AFP and uE3 had a good predictive value for preeclampsia, which was helpful to take relevant interventions to reduce the incidence of preeclampsia as early as possible, and had a positive impact on protecting maternal and infant health. Serological marker screening is rapid, non-invasive, low-cost and easy to perform in the first trimester, and has high sensitivity and specificity, making it the best method for preeclampsia screening. Dynamic assessment was carried out at 11~14 weeks of pregnancy, high-risk pregnant women were identified, and monitoring and active intervention were strengthened to detect preeclampsia early and reduce the risk of adverse pregnancy outcomes. There were still certain limitations in this study. Pregnant women with preeclampsia had not been followed up to observe the maternal and infant outcomes, and the relationship between serum PAPP-A with maternal and infant outcomes had not been analysed. In addition, this study did not address the maternal basal risk, the predictors of the study were few, and the results had certain limitations and geographical biases. Therefore, the specific mechanism of action of this indicator still needs further follow-up and confirmation by expanding the sample size.

Consent for publication

Informed consent was obtained from participants for the participation in the study and all methods were carried out in accordance with relevant guidelines and regulations.

Informed consent was obtained from all individual participants included in the study. The patients participating in the study all agreed to publish the research results.

Availability of data and material

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

Funding

This study was funded by the Science and Technology Plan of the Jinan Health Commission (No. 2022-1-38).

Disclosures

The study was approved by the Ethics Committee of the Jinan Maternity and Child Care Hospital (Approval No. 2020-1-019).

The authors declare no conflict of interest.

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