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The Association and diagnostic value between Maternal Serum Placental Markers and Placenta Previa

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ABSTRACT

Objective: This study aims to evaluate the correlation and diagnostic value of maternal serum placental markers: pregnancy-associated plasma protein-A (PAPP-A), free beta human chorionic gonadotropin (free β-hCG), and alpha fetoprotein (AFP) in relation to placenta previa.

Methods: A retrospective case-control study was conducted to gather data on 137 pregnant women who were hospitalized for delivery at Hangzhou Women's Hospital. These women participated in the late stage of early and mid-term maternal serum prenatal screening between January 2018 and December 2020. Of the 137 women, 45 were diagnosed with placenta previa, while 92 were selected at random as the control group, in a ratio of 1: 2. Independent samples t-test or Mann-Whitney U test were utilized to compare the quantitative data of the two groups, and the Receiver operating characteristic curve (ROC) was used to evaluate the diagnostic value of maternal serum placental marker levels for placenta previa.

Results: The levels of first trimester and second trimester free beta subunit of human chorionic gonadotropin (FT-Free β-hCG; ST-Free β-hCG) in the placenta previa group were higher than those in the normal group [1.38 (0.55–6.03) MoM vs.1.08 (0.32–4.00) MoM, 1.38 (0.39–4.10) MoM vs.1.01 (0.29–4.12) MoM], and the differences between the groups were statistically significant ($Z = 2.830$, $Z = 2.846$, both $P < 0.05$). The AFP level was higher than the normal group [1.13 (0.65–2.15) MoM vs. 0.94 (0.51–2.02) MoM], and the difference was statistically significant ($Z = 2.551$, $P < 0.05$). There was no significant difference in PAPP-A between the placenta previa group and the normal group ($Z = 1.396$, $P > 0.05$). The ROC curve analysis results showed that the AUCs of FT-Free β-hCG and ST-Free β-hCG for placenta previa were 0.649 (95 % CI: 0.551–0.747, $P = 0.005$), 0.634 (95 % CI: 0.539–0.730, $P = 0.011$), and 0.650 (95 % CI: 0.554–0.746, P = 0.004). Using PPV, NPV, FPR, FNR, +LR, and -LR as evaluation indicators for the 5 models, the results showed that FT-Free β-hCG was the best performer in terms of PPV, FPR, and +LR, with values of 0.725, 0.600, and 2.632, respectively. The three-indicator combined detection model (AFP + ST-Free β-hCG + FT-Free β-hCG) had the best performance in terms of NPV and -LR, with values of 0.770 and 0.298, respectively.

Conclusion: The elevated maternal serum levels of Free β-hCG and AFP may be associated with placenta previa. The combined detection of maternal serum markers in the early and mid-trimesters has better diagnostic value for predicting placenta previa than individual detection.

Introduction

The placenta, an essential fetal appendage, typically attaches to the anterior, posterior, lateral, and fundus of the uterus. After 28 weeks of pregnancy, if the placenta is attached to the lower segment of the uterus, or even if the lower edge of the placenta reaches or covers the cervical opening, its position is lower than the fetal presenting part, which is called placenta previa [1]. When the decidua is incomplete or traumatic

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endometrial defects, such as a scarred uterus, uterine anomalies, adenomyosis, or pregnancy in the uterine horns, the placental villi infiltrate the muscularis propria resulting in placental implantation [2–5]. The placenta normally detaches from the uterine wall following fetal delivery. However, in cases of placenta implantation, the placenta becomes firmly attached to the myometrium, leading to hemorrhaging and endangering the patient's life during manual stripping [6–8]. The prevalence of placenta previa ranges from roughly 0.24 % to 1.57 %, with the possibility of morbidity and mortality rates up to 10 % [9–11]. Therefore, it is important to clarify the incidence of placenta previa implantation to guide early intervention.

Ultrasound is a commonly used method for examining placenta previa due to its simple operation and repeatability, and can locate the surface position of the placenta [12,13]. However, the examination is susceptible to factors such as scanning thickness and obesity, which can lead to misdiagnosis or failure to diagnose [14]. Ultrasound transmission is significantly influenced by tissue and spatial resolution, leading to limitations in image field of view and application [15,16]. As a consequence, there remains a requirement to identify effective serologic indicators of placenta praevia for assessment purposes.

Human chorionic gonadotrophin (hCG), and pregnancy-associated plasma protein-A (PAPP-A) are produced by the syncytiotrophoblast and decidua of the placenta, which are mainly involved in placental formation, embryonic development, and maintenance of pregnancy. They are commonly used indicators for assessing placental function. Abnormal placental function is closely related to the occurrence of placental implantation [17]. Alpha-fetoprotein (AFP) is a serum glycoprotein synthesized by fetal hepatocytes and the yolk sac. Its concentration gradually increases from 6 weeks of gestation, peaking between 16 and 20 weeks. An abnormally elevated AFP level can be observed in conditions such as fetal neural tube defects, spina bifida, and anencephaly. Conversely, an abnormally low AFP level indicates a risk of Down syndrome in the fetus. Studies have indicated [18] that serum biochemical markers used in gestational aneuploidy screening could also be used for placental implantation screening, leading to potential advancements in early prenatal diagnosis of placenta previa with combined placental implantation.

This study used a case-control retrospective study design, based on prenatal screening in early and mid-pregnancy, to select pregnant women in the control group and those diagnosed with placenta previa as study subjects. We explored the correlation and diagnostic value of PAPP-A, free β-hCG, and AFP in predicting placenta previa.

Materials and methods

Participants

The data of pregnant women who participated in the joint prenatal screening for early and mid pregnancy and were hospitalized for delivery at Hangzhou Women's Hospital from January 2018 to December 2020 were selected as the research objects. Based on the principle of unique matching, Excel data were exported from the hospital information system (HIS) and prenatal screening system. After eliminating duplicate test results, a case-control method was used to select 137 pregnant women who met the matching criteria. Among them, 45 cases of placenta previa were selected, and 92 normal pregnant women were randomly selected in the same period as the control group. All subjects were single pregnancy, and they all signed the informed consent before the examination. This study was approved by the medical ethics committee of the Linhai First People's Hospital [2024] Medical Ethics Review (011).

Inclusion and exclusion criteria

Inclusion criteria

Inclusion criteria: Placenta praevia implantation meets the relevant diagnostic and treatment standards in the "Guidelines for the Diagnosis and Treatment of Placenta Implantation (2015) [19], and is confirmed by the surgical results; delivery gestational age is 28 weeks; single pregnancy; undergoing cesarean section.

Exclusion criteria:twin or multiple pregnancies; in vitro fertilization pregnancies; coexistence of significant organ diseases such as congenital heart disease or renal failure; coexistence of diseases such as infectious pneumonia or myocarditis; coexistence of malignant tumors; incomplete information or data.

Detection methods

Reagents and instruments

Automatic time-resolved fluorescence immunoassay analyzer (PerkinElmer, Shelton, USA). The ultrasound instrument was a VolusonE8 ultrasound system (GE, Boston, USA).

Materials and test indicators

Fasting venous blood of 2 mL to 3 mL was taken in Hangzhou hospitals qualified for prenatal screening blood collection in early pregnancy (9 to 13^{+6} weeks of gestation) and in mid-pregnancy (16 to 18^{+6} weeks of gestation), and the serum specimens were separated and stored in a refrigerator at 2 ℃ to 8 ℃ for 30 min and were sent to be examined within one week. Screening indexes and protocols: early pregnancy maternal serum PAPP-A and free β-hCG levels, middle pregnancy maternal serum AFP and free β-hCG levels.

The measurement method and screening criteria for nuchal translucency (NT) are based on the standards of the British Fetal Foundation [20]: specially trained physicians conduct ultrasound examinations according to standardized protocols to assess the translucency of the neck, using the fetal mid-sagittal plane view and measuring while the fetus is in its natural position; the image is enlarged so that only the fetal head and upper chest are displayed; the measurement is taken at the widest translucent area between the skin and soft tissue on the cervical spine. The reference range for fetal NT is NT thickness < 3.5 mm for the normal screening group, and ≥ 3.5 mm for the abnormal screening group.

Quality control

Indoor quality control products (PerkinElmer, USA) consist of two different levels of fixed value quality control serum, low and high, are used within their expiration dates. External quality assessment is conducted twice a year by the Clinical Laboratory Center of the Ministry of Health, and a certificate of qualification is obtained. Both testing and follow-up personnel receive unified pre-job training and obtain qualification certificates from the health authority.

MoM calculation

Measured levels of PAPP-A, free β-hCG, NT, and AFP are calibrated by replacing the original concentration values with multiple of median (MoM) values and calibrating the MoM values using body weight and gestational age. The definition and calculation formula of MoM value are as follows [21]: MoM= Original Conj/Median, Original Conj. refers to the original concentration values of PAPP-A, free β-hCG, NT, and AFP; Median represents the median of the corresponding indicator's original concentration values.

Establishment of prediction models

Five risk prediction models were constructed based on maternal serum placental markers (FT-free β-hCG MoM, AFP MoM and ST-free β-hCG MoM) as follows: Model 1: FT-free β-hCG MoM value; Model 2: ST-free β-hCG MoM value; Model 3: AFP MoM; Model 4: ST-free β-hCG + AFP combination; Model 5: FT-free β-hCG + ST-free β-hCG + AFP combination.

Data analysis

IBM-SPSS 25.0 software was used for data processing. The Shapiro-Wilk test was used for normality testing, and the normal distribution was represented by mean ± standard deviation ($\overline{X} + s$). The independent sample t-test was used for comparison between the two groups. The skewed distribution was represented by the median and percentile [M ($P_{2.5}$, $P_{97.5}$)], and the quantitative data was analyzed using the Mann-Whitney U test for independent samples. The receiver operator characteristic (ROC) curve was plotted, and the area under the curve (AUC) was calculated to evaluate the diagnostic value of serum hCG, AFP, and PAPP-A detection for placenta previa diagnosis. The optimal cut-off, AUC, and Youden index were calculated. We used sensitivity (Se), specificity (Sp), false negative rate (FNR), false positive rate (FPR), positive likelihood ratio (+LR), and negative likelihood ratio (-LR) values to evaluate the performance of the model. When $P < 0.05$, the difference was considered statistically significant.

Results

Comparison of patient characteristics

The amount of bleeding in the placenta previa group was higher than that in the control group (400.00 mL vs. 300.00 mL), and the difference was statistically significant ($Z = 3.444$, $P = 0.001$). The gestational age at delivery in the placenta previa group was lower than that in the control group (260 days vs. 274 days), and the difference was statistically significant ($Z = 7.810$, $P < 0.001$). There were no statistically significant differences in other factors, including maternal age, body weight, height, BMI, systolic blood pressure on admission, diastolic blood pressure on admission, AMP, expected delivery age, and early pregnancy weight, between the two groups (all $P > 0.05$) (Table 1).

Comparison of newborn Characteristics

The birth weight and length of the newborns in the placenta previa group were lower than those in the control group (2947 g vs. 3251 g, 48.89 cm vs. 49.96 cm), and the differences between the groups were statistically significant ($Z = 3.785$, $Z = 4.328$, both $P < 0.001$). There was no significant difference in fetal scores between the groups ($P > 0.05$) (Table 2).

Comparison of the levels of prenatal screening markers between the two groups

The free β-hCG MoM level in the first trimester and the free β-hCG MoM level in the second trimester in the placenta previa group were both higher than those in the control group [1.38 (0.55–6.03) MoM vs. 1.08 (0.32–4.00) MoM; 1.38 (0.39–4.10) MoM vs. 1.01 (0.29–4.12) MoM], with statistical differences between the groups ($Z = 2.830$, $Z = 2.846$, both $P < 0.05$). The AFP MoM level in the placenta previa group was higher than that in the control group [1.13 (0.65–2.15) MoM vs. 0.94 (0.51–2.02) MoM], with statistical differences between the groups ($Z = 2.551$, $P = 0.011$). There was no significant difference in the PAPP-A index between the placenta previa group and the control group in the first trimester ($Z = 1.396$, $P = 0.163$) (Table 3).

Diagnostic value of FT-free β-hCG, ST-free β-hCG and AFP levels for predicting placenta previa

ROC curve analysis was performed for FT-free β-hCG, ST-free β-hCG, and AFP in predicting placenta previa. The AUC values were 0.649 (95 % CI: 0.551–0.747, $P = 0.005$), 0.634 (95 % CI: 0.539–0.730, $P = 0.011$), and 0.650 (95 % CI: 0.554–0.746, $P = 0.004$), respectively. When the cut-off values were set at 1.860, 0.925, and 0.985, the corresponding specificities were 0.848, 0.489, and 0.489, and the sensitivities were 0.400, 0.800, and 0.778, respectively. Among them, the AUC value of the combined detection of AFP + ST-free β-hCG + FT-free β-hCG was the highest, reaching 0.687 (Fig. 1). Six indicators including PPV, NPV, FPR, FNR, +LR, and -LR were used to evaluate the five models. The results showed that PPV, FPR, and +LR were best for FT-free β-hCG, with values of 0.725, 0.60, and 2.632, respectively. NPV and -LR were best for the combined detection of the three indicators (AFP + ST-free β-hCG + FT-free β-hCG), with values of 0.770 and 0.298, respectively (Table 4).

Table 1
Univariate demographic analysis of control group and placenta previa group.

Indicators	Groups		*Z / t*	*P value*
	Control (n = 92)	Placenta Previa (n = 45)		
Amount of bleeding (mL)	300.00 (300.00-)	400.00 (212.50 −1425.00)	3.444	0.001**
Maternal Age (years)	28.34 ± 2.68	28.93 ± 2.50	1.248	0.214
Maternal Weight (kg)	67.00 (56.00 −85.00)	65.00 (51.30 −98.15)	1.076	0.282
Body Height (cm)	160.97 ± 4.79	160.98 ± 4.69	0.012	0.990
BMI (kg/m^2)	26.19 ± 2.64	25.78 ± 3.28	0.787	0.433
SBP (mmHg)	121.79 ± 12.74	117.13 ± 11.74	1.704	0.092
DBP (mmHg)	76.88 ± 9.36	74.09 ± 10.40	1.293	0.199
MAP (mmHg)	91.84 ± 9.84	88.44 ± 10.06	1.556	0.123
Gestational age (days)	273.72 ± 8.44	260.16 ± 11.47	7.810	< 0.001*
Expected age (years)	28.88 ± 2.64	29.52 ± 2.50	1.330	0.186
FT-Maternal Weight (kg)	52.00 (44.00 −72.35)	52.30 (43.17 −86.60)	0.348	0.727
FT-BMI	20.96 ± 2.62	20.82 ± 2.74	0.308	0.759
FT-Gestational age (days)	89.76 ± 4.66	88.36 ± 4.51	1.673	0.097
FT-CRL (mm)	61.86 ± 7.58	59.88 ± 7.76	1.402	0.163
ST-Maternal Weight (kg)	53.90 (44.83 −72.90)	53.20 (44.83 −87.34)	0.399	0.690
ST-BMI	21.52 ± 2.66	21.38 ± 2.71	0.295	0.769
ST-Gestational age (days)	118.42 ± 4.62	118.84 ± 5.76	0.460	0.646
ST-CRL (mm)	61.64 ± 7.48	60.50 ± 7.68	0.813	0.418
BPD (mm)	35.04 ± 5.39	36.38 ± 2.97	1.372	0.173

BMI: body Mass Index; SBP: systolic blood pressure; DBP: Diastolic blood pressure; MAP: mean arterial pressure; FT: First trimester; ST: Second trimester; CRL: crown-rump length; BPD: biparietal diameter; Data the normal distribution was represented by the $\overline{X} + s$, The skewed distribution was represented by the [M ($P_{2.5}$, $P_{97.5}$)]; *$P < 0.001$; **$P < 0.05$.

Table 2
Univariate demographic analysis of newborns in control group and placenta previa group.

Indicators	Groups		*Z / t*	*P value*
	Control (n = 92)	Placenta Previa (n = 45)		
Infant Apgar scores	10.00 (8.10 −10.00)	10.00 (7.02 −10.00)	0.433	0.665
Infant length (cm)	49.96 ± 0.55	48.89 ± 2.24	4.328	< 0.001*
Infant weight (g)	3251 ± 401	2947 ± 516	3.785	< 0.001*

Data the normal distribution was represented by the $\overline{X} + s$, The skewed distribution was represented by the [M ($P_{2.5}$, $P_{97.5}$)]; *$P < 0.001$.

Table 3
Comparison of screening indicators in pregnant women in control group and placenta previa group.

Indicators	Groups		*Z/t*	*P value*
	Control (n = 92)	Placenta Previa (n = 45)		
PAPP-A (mU/L)	4115 (1258 −14270)	4450 (1266 −20095)	0.619	0.536
PAPP-A (MoM)	1.03 (0.33 −2.77)	1.26 (0.33 −4.33)	1.396	0.163
FT-free β-hCG (ng/mL)	51.15 (14.54 −188.65)	69.50 (27.96 −303.95)	3.430	0.001**
FT-free β-hCG (MoM)	1.08 (0.32 −4.00)	1.38 (0.55 −6.03)	2.830	0.005**
NT (cm)	1.44 ± 0.36	1.42 ± 0.38	0.191	0.849
NT (MoM)	0.98 ± 0.24	1.00 ± 0.22	0.358	0.721
AFP (U/mL)	35.60 (17.46 −80.86)	43.40 (22.00 −85.06)	2.415	0.016**
AFP (MoM)	0.94 (0.51 −2.02)	1.13 (0.65 −2.15)	2.551	0.011**
ST-free β-hCG (ng/mL)	15.75 (4.12 −61.09)	21.10 (5.22 −61.79)	2.674	0.007**
ST-free β-hCG (MoM)	1.01 (0.29 −4.12)	1.38 (0.39 −4.10)	2.846	0.004**

FT-free β-hCG: first trimester free β subunit of human chorionic gonadotropin; PAPP-A: pregnancy associated plasma protein A; MoM: multiple of median;; NT: nuchal translucency; AFP: alpha-Fetoproteins; ST-free β-hCG: second trimester free beta subunit of human chorionic gonadotropin; Data the normal distribution was represented by the$\overline{X} + s$, The skewed distribution was represented by the [M ($P_{2.5}$, $P_{97.5}$)]; *$P < 0.001$; **$P < 0.05$.

Discussion

If the endometrium at the implantation site of the placenta is defective or underdeveloped, resulting in direct implantation of the chorionic villi into the myometrium or even deep into the myometrium, it becomes a pathological phenomenon. When the placenta separates from the uterine wall, due to the close adhesion of the placenta to the myometrium, the separation may cause massive bleeding, which threatens the patient's life safety [22]. In recent years, biochemical indicators related to prenatal diagnosis of placental implantation have gradually become a research hotspot, opening up new ideas for prenatal diagnosis of placenta implantation.

The main findings of this study revealed that the placenta previa group had significantly higher levels of serum FT-free β-hCG, ST-free β-hCG and AFP than the control group (all $P < 0.05$). The increase in maternal serum free β-hCG and AFP levels can predict placenta previa, and the combined detection of maternal serum markers in the first and second trimesters has better diagnostic value than individual detection for predicting placenta previa.

HCG is a glycoprotein secreted by placental trophoblast cells, which is mostly used for the diagnosis of early pregnancy. The level reaches its peak at 8–10 weeks of pregnancy and then steadily decreases to maintain a certain level after 20 weeks of pregnancy, and drops sharply two weeks after delivery [23]. The results of this study suggest that the levels of serum FT-free β-hCG and ST-free β-hCG in the placenta previa group are higher than those in the control group. This is consistent with the results obtained by Lijuan Cheng [24], who reported significantly greater serum hCG levels in individuals with placenta previa implantation than in the control group. These results suggest that hCG could be diagnostically useful for placenta previa implantation. Due to the similar effect of hCG to luteinizing hormone, it can maintain luteal activity, reduce maternal lymphocyte activity, and is related to pregnancy, trophoblastic tumors, etc [25]. When the placenta is implanted in the uterine scar or the placenta is poorly formed due to other reasons, the placental trophoblast cells are in an oxygen-deficient environment, and the trophoblast cells reactively proliferate to seize nutrients, which will cause a significant increase in the production of hCG, and the maternal serum β-hCG level will also increase accordingly [26,27]. In the case of free β-hCG value ≥ 2.2 MoM, the risk of pregnancy-induced hypertension, intrauterine fetal growth restriction, and miscarriage will increase. The symptoms of placental dysfunction caused by changes in hCG indicators will also increase the incidence of intrauterine fetal growth restriction [28].

The results of this study also suggest that the serum AFP level in the

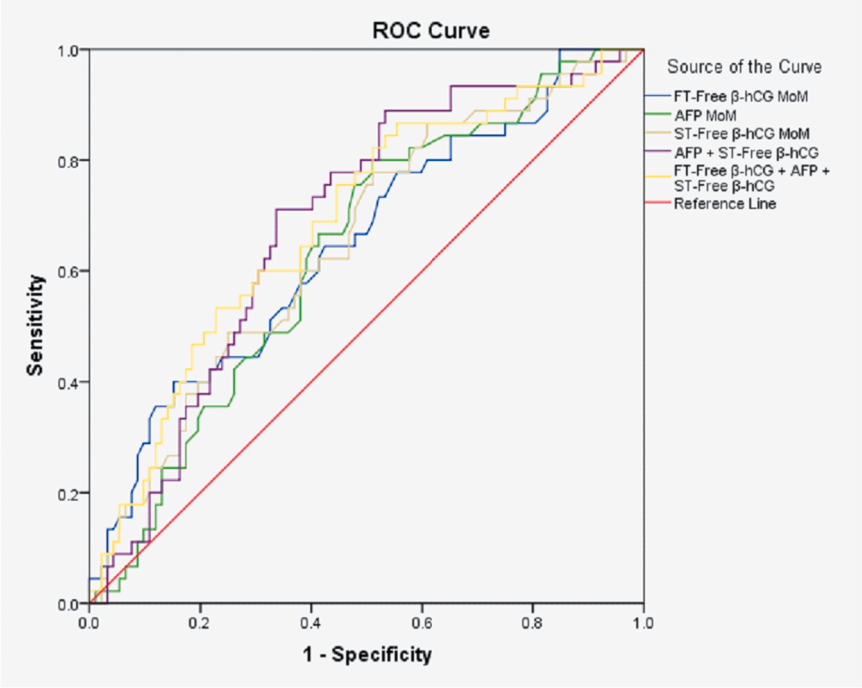

Fig. 1. ROC curve for the diagnosis of FT-free β-hCG MoM, ST-free β-hCG MoM, AFP MoM and combined above index screening for the placenta previa. FT-free β-hCG: first trimester free beta subunit of human chorionic gonadotropin; AFP: alpha-Fetoproteins; ST-free β-hCG:second trimester free beta subunit of human chorionic gonadotropin; MoM: multipleof median; ROC, receiver operating characteristic curve.

Table 4
The value of Free β-hCG, AFP MoM, and combined above index screening for the placenta previa.

Index	Youden	Sensitivity	Specificity	Cut-off	AUC	95 %CI	*P-value*
FT-Free β-hCG MoM	0.248	0.400	0.848	1.860	0.649	0.551−0.747	0.005**
AFP MoM	0.289	0.800	0.489	0.925	0.634	0.539−0.730	0.011**
ST-Free β-hCG MoM	0.267	0.778	0.489	0.985	0.650	0.554−0.746	0.004**
AFP + ST-Free β-hCG	0.374	0.711	0.663	0.004	0.686	0.594−0.777	< 0.001*
AFP + ST-Free β-hCG + FT-Free β-hCG	0.312	0.867	0.446	0.004	0.687	0.593−0.781	< 0.001*
Index	PPV	NPV	FPR	FNR	+LR	-LR	
FT-Free β-hCG MoM	0.725	0.586	0.152	0.600	2.632	0.708	
AFP MoM	0.610	0.710	0.511	0.200	1.566	0.409	
ST-Free β-hCG MoM	0.604	0.688	0.511	0.222	1.523	0.454	
AFP + ST-Free β-hCG	0.678	0.696	0.337	0.289	2.110	0.436	
AFP + ST-Free β-hCG + FT-Free β-hCG	0.610	0.770	0.554	0.133	1.565	0.298	

FT-Free β-hCG: first trimester free beta subunit of human chorionic gonadotropin; MoM: multiple of median; AFP: alpha-Fetoproteins; ST-Free β-hCG: second trimester free beta subunit of human chorionic gonadotropin; PPV: Positive predictive value; NPV: Negative predictive value; FNR: False negative rate; FPR: False positive rate; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio; $^{*}P < 0.001$; $^{**}P < 0.05$.

placenta previa group is higher than that in the control group. Serum AFP is an embryo-related glycoprotein that is produced by the yolk sac before 6 weeks of pregnancy and synthesized by the fetal liver after 6 weeks of pregnancy [29]. High concentrations of AFP exist in the fetal blood circulation and actively diffuse into the maternal blood circulation through the concentration difference on both sides of the placenta or fetal membranes [30]. When the placenta is implanted, the placental barrier can be damaged, which can damage the uterine muscle layer. AFP enters the placental barrier with the fetal blood circulation and reaches the maternal body, resulting in a significant increase in AFP level in the implantation group [31,32]. Recent studies have also shown that the increase in maternal serum AFP level is associated with intrauterine fetal death, intrauterine growth retardation, maternal-fetal transfusion syndrome, and pre-eclampsia [33–35].

PAPP-A is a syncytiotrophoblast-derived metalloproteinase produced by the placental syncytiotrophoblast and decidua. It cleaves the complex formed between insulin-like growth factor and insulin-like growth factor binding protein [36]. PAPP-A is an essential growth regulatory factor in the body, mainly involved in important processes such as placental formation, embryonic development, and maintenance of pregnancy. Studies have confirmed that PAPP-A increases exponentially in early pregnancy and continues to rise throughout pregnancy until delivery [37,38]. The level of PAPP-A in maternal serum is associated with various diseases, such as stillbirth, premature delivery and certain chromosomal diseases [39,40]. Combining previous studies, the author believes that placenta previa implantation may be related to the above indicators [41]. However, the results of this study suggest that the level of PAPP-A in the placenta previa group is higher than that in the control group, but there is no significant difference between the two groups ($P > 0.05$), which is inconsistent with the above literature reports. The reason may be related to our small sample size, and further research is needed to increase the sample size.

The ROC curve in Fig. 1 of this study shows that the AUCs of the five different models for predicting placenta previa are: AFP + ST-free β-hCG + FT-free β-hCG (0.687) > AFP + ST-free β-hCG (0.686) > ST-free β-hCG (0.650) > FT-free β-hCG (0.649) > AFP (0.634). The combined prediction value is better than individual prediction, but the prediction performance after mid-pregnancy screening + early pregnancy free β-hCG is not improved. From an economic perspective, it is only necessary to achieve the best prediction effect for placenta previa in mid-pregnancy. In clinical practice, individualized medical needs can be considered for the choice of pregnancy testing during pregnancy.

This study is a cross-sectional survey with a limited sample size and a single center. The relationship between study factors and conclusions is exploratory, and its causal relationship requires further validation with large sample size, prospective, and multi-center studies. These tests are all routine items and do not require additional payment for obtaining these results, which represents a considerable advantage. However, the false positive and false negative rates of these results are relatively high, so it is necessary to consider other data and clinical manifestations when making evaluations.

Conclusion

The levels of serum free β-hCG and AFP in the placenta previa group were higher than those in the control group during the first and second trimesters. By constructing a risk model, maternal serum high levels of free β-hCG and AFP can predict placenta previa. The diagnostic value of combined detection of various markers for predicting placenta previa is superior to that of individual detection.

Ethics approval

This study has been conducted under the approval of the Human Research Ethics Committee of the Linhai First People's Hospital, [2024] Medical Ethics Review (011), and the procedures have been performed by the Declaration of Helsinki. This research has obtained informed consent from the patients.

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CRediT authorship contribution statement

Yiming Chen: Writing – review & editing, Data curation. **Tingting Hu:** Funding acquisition. **Panpan Ma:** Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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