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First-trimester maternal serum aneuploidy markers as predictors of placenta accreta spectrum and placenta previa; a retrospective case–control study

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Abstract

Introduction: Placenta previa and placenta accreta spectrum (PAS) are major causes of obstetric hemorrhage and peripartum hysterectomy, yet reliable tools for early risk stratification remain limited. First-trimester serum aneuploidy screening, including measurement of pregnancy-associated plasma protein-A (PAPP-A) and free beta-human chorionic gonadotropin (β-hCG), is routinely performed in many settings and may reflect underlying placental dysfunction.

Objectives: This study aimed to evaluate whether these widely available first-trimester markers are associated with subsequent placenta previa and PAS and to assess their potential diagnostic performance for early identification of women at increased risk.

Patients and Methods: This retrospective case–control study included singleton pregnancies undergoing routine first-trimester aneuploidy screening at Alzahra Hospital, Rasht (2021–2022), comparing women with placenta previa or PAS to uncomplicated controls. Demographic characteristics, obstetric data, and first-trimester serum PAPP-A and free β-hCG values were extracted from medical and laboratory records and compared between three groups.

Results: Our results indicate that increased first-trimester PAPP-A levels were independently associated with both placenta previa and PAS, with adjusted odds ratios (ORs) of 7.46 and 6.26, respectively. At a cut-off of 1.41 multiples of the median (MoM), PAPP-A achieved area under the curves (AUCs) of 0.768 and 0.785, with sensitivities of 80 and 75 and specificities of 65 and 65 for placenta previa and PAS, respectively. Free β-hCG was likewise independently associated with placenta previa and PAS (OR 3.52 and 4.31, respectively) and, at a cut-off of 1.45 MoM, yielded AUCs of 0.696 and 0.770, with sensitivities of 70 and 80 and specificities of 70 and 70 for placenta previa and PAS, respectively.

Conclusion: First-trimester maternal serum aneuploidy markers such as PAPP-A and free β-hCG levels are independently associated with both placenta previa and PAS and show acceptable diagnostic performance, supporting their potential use in early risk stratification for these placental disorders.

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Introduction

Placenta accreta spectrum (PAS) encompasses a heterogeneous group of disorders characterized by abnormal adhesion or invasion of placental villi into the myometrium, ranging from superficial adherence (placenta accreta) to deep myometrial invasion (increta) and full-thickness penetration of the uterine serosa (percreta) (1-3). According to the International Federation of Gynecology and Obstetrics (FIGO) 2019 clinical classification, PAS is graded into three categories based on the depth of placental invasion, with Grade 3 subdivided according to involvement of adjacent organs, including the urinary bladder and pelvic structures (4). The worldwide incidence of PAS has risen substantially over the past century, closely paralleling the global increase in cesarean delivery (CD) rates (5). Prior CD constitutes the major predisposing significant risk factor (6-8). PAS is associated with severe maternal morbidity and mortality principally due to massive obstetric hemorrhage, with perioperative hysterectomy required in the majority of cases (9). Placenta previa, defined as implantation of the placenta overlying or adjacent to the internal cervical os (10,11), shares overlapping risk factors with PAS (12,13). The prevalence of placenta previa ranges from approximately 1.01% to 2.01% across different regions of China, with a pooled incidence equal to

Key point

In this retrospective case–control study, our findings suggest that first-trimester pregnancy-associated plasma protein-A (PAPP-A) and free beta-human chorionic gonadotropin (β-hCG) levels carry clinically relevant information for the early identification of pregnancies at increased risk of placenta previa and placenta accreta spectrum (PAS), over and above established maternal and obstetric risk factors. In practice, abnormal elevations in these routinely measured aneuploidy markers could prompt closer sonographic surveillance of placental location and adherence, earlier referral to centers with expertise in PAS, and more proactive multidisciplinary birth planning, particularly in women with additional risk factors such as prior cesarean delivery. However, given the only moderate discriminative performance observed, these markers should currently be viewed as adjuncts rather than stand-alone screening tools, and their integration into robust multivariable prediction models, ideally validated in large prospective cohorts, will be essential before they can be recommended for routine clinical decision-making.

1.24%, and its occurrence is strongly linked to scarred uterine tissue and deficient decidualization (14). Most women diagnosed with PAS also have a concurrent placenta previa, a combination that substantially amplifies the risk of life-threatening hemorrhage and necessitates multidisciplinary management in specialist centers (15).

Pregnancy-associated plasma protein-A (PAPP-A) and free beta-human chorionic gonadotropin (free β-hCG) are well-established first-trimester biochemical markers used routinely in combined screening programs for fetal aneuploidies, including trisomy 21, 18, and 13, at 11–13+6 weeks of gestation (16,17). PAPP-A is a metalloproteinase produced by the syncytiotrophoblast and decidua, playing an essential role in placental formation, trophoblast invasion, and the regulation of insulin-like growth factor bioavailability; its serum concentration normally increases exponentially throughout pregnancy (18-20). Free β-hCG, the beta subunit of human chorionic gonadotropin secreted by placental trophoblast cells, reaches its peak serum concentration at 8–10 weeks of gestation before declining progressively; it is a sensitive indicator of trophoblast function and placental integrity (21).

Several studies have investigated whether first-trimester aneuploidy screening analytes may carry secondary diagnostic information relevant to abnormal placentation beyond their established role in chromosomal risk assessment. Previously, Büke et al reported that first-trimester free β-hCG and PAPP-A levels differed significantly between women who subsequently developed PAS and controls, establishing an early association between routine serum screening profiles and abnormal trophoblast behavior (22). In a retrospective analysis of routine first-trimester screening data by Penzhoyan and Makukhina, PAPP-A was elevated in women with abnormal placental location, including placenta previa and PAS, compared with controls with a normal placental position and a uterine scar, with higher blood loss correlating with higher serum marker values (23). A retrospective case-control study by Ma et al demonstrated that first-trimester free β-hCG was significantly elevated in women with placenta previa compared with healthy controls (24). The emerging body of evidence, while not yet definitive, supports the hypothesis that first-trimester aneuploidy markers may carry latent predictive value for both PAS and placenta previa, particularly in women with predisposing risk factors (22-24). Given the limitations of ultrasound-based detection at the population level and the potential for biochemical screening to be incorporated into existing first-trimester protocols without additional cost burden, formal evaluation of PAPP-A and free β-hCG as adjunctive predictors of these high-risk placental conditions is warranted. The present study therefore aimed to evaluate the diagnostic value of first-trimester maternal serum aneuploidy markers, PAPP-A and free β-hCG, as predictors of PAS and placenta previa.

Objectives

The objective of this study was to investigate whether first-trimester maternal serum aneuploidy markers, specifically PAPP-A and free β-hCG, are associated with subsequent placenta previa and PAS and to evaluate their diagnostic performance for early identification of these conditions.

Patients and Methods

Study design and participants

This retrospective case–control investigation included pregnant women who underwent routine first-trimester aneuploidy screening and subsequently delivered at Alzahra hospital in Rasht, Iran, between 2021 and 2022. Women with a final diagnosis of placenta previa or PAS, based on antenatal imaging and intraoperative and/or histopathological findings, were identified as cases, while women with uncomplicated singleton pregnancies and normal placental location served as controls. Eligible participants were required to have complete clinical records and available first-trimester serum PAPP-A and free β-hCG measurements.

Inclusion and exclusion criteria

Inclusion criteria were; pregnant women who underwent routine first-trimester aneuploidy screening at Alzahra hospital; availability of maternal serum PAPP-A and free β-hCG values expressed as multiples of the median (MoM); singleton gestation; and delivery at the same center with a clearly documented placental outcome (normal placental location, placenta previa, or PAS). Women were excluded if they had multiple gestations, major fetal structural or chromosomal anomalies, incomplete medical records, or missing data on key exposure (aneuploidy markers) or outcome variables. Additional exclusion criteria included pregnancies with uncertain or indeterminate diagnosis of placenta previa or PAS, or those delivered elsewhere so that final placental status could not be reliably verified.

Group classification

Group classification was based on pregnancy outcome and final placental diagnosis. Women with a confirmed diagnosis of placenta previa, defined as a placenta partially or completely covering the internal cervical os on second- or third-trimester ultrasound and/or intraoperative findings, were allocated to the placenta previa group. Women with PAS were identified by characteristic imaging features and intraoperative evidence of abnormal placental adherence or invasion, with or without histopathological confirmation, and were assigned to the PAS group. Pregnancies without placenta previa or PAS and with a normal placental location and uneventful obstetric course served as the healthy control group.

Data collection

In this retrospective case–control study, data were obtained from medical records of pregnant women who underwent routine first-trimester aneuploidy screening and subsequently delivered at the study center. Cases comprised women with a final diagnosis of placenta previa or PAS, confirmed by antenatal imaging and/or intraoperative and histopathological findings, while controls were women with uncomplicated singleton pregnancies and normal placental implantation. For all eligible participants, demographic and obstetric characteristics (including maternal age, body mass index [BMI], gravidity, parity, number of prior cesarean deliveries, and medical comorbidities such as diabetes, hypertension, and smoking status) were extracted using a standardized data abstraction form. First-trimester serum concentrations of PAPP-A and free β-hCG, originally measured for aneuploidy screening, were retrieved as MoM from the laboratory information system and linked to pregnancy outcomes.

Outcome measurement

The primary outcome was assessing the association between first-trimester maternal serum aneuploidy markers (PAPP-A and free β-hCG) and the subsequent occurrence of placenta previa and PAS. The secondary outcome was evaluating the diagnostic performance of these markers for identifying placenta previa and PAS, as assessed by receiver operating characteristic (ROC) curve analysis.

Statistical analysis

Statistical analyses were performed using SPSS version 27 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed with the Kolmogorov–Smirnov test. Group comparisons for normally distributed quantitative variables (e.g., maternal age, BMI, gravidity, parity, number of prior cesarean deliveries, and serum marker levels) were conducted using one-way analysis of variance (ANOVA) with post hoc least significant difference (LSD) tests. Categorical variables were compared across groups using the chi-square test or Fisher's exact test, as appropriate. Binary logistic regression models were fitted to estimate unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between first-trimester PAPP-A and free β-hCG levels and the presence of placenta previa or PAS, adjusting for maternal age, body mass index, gravidity, parity, number of previous cesarean sections, and history of hypertension, diabetes, and smoking. The ROC curve analysis was used to evaluate the diagnostic performance of PAPP-A and free β-hCG for placenta previa and PAS, and to derive optimal cut-off values along with corresponding sensitivity and specificity. Meanwhile, a two-sided P value <0.05 was considered statistically significant.

Results

The results indicated that across the three study groups, maternal age and parity were broadly comparable, with no meaningful differences in gravidity or previous cesarean deliveries between healthy controls, women with placenta previa, and those with PAS. The BMI showed a modest tendency to be greater in the placenta previa group, whereas women with PAS had values more similar to the healthy controls, although these patterns did not reach statistical significance. The prevalence of pre-existing diabetes appeared higher among women with placenta previa compared with the other two groups, without reaching statistical significance, while hypertension and smoking were relatively infrequent and similarly distributed, with smoking absent in the PAS group. Educational attainment showed a broadly similar and non-significant distribution across groups, with most participants having completed at least a diploma or associate degree, and a small subset in each group holding a bachelor's or higher degree (Table 1).

Serum PAPP-A levels were lowest in the healthy control group and progressively higher in women with placenta previa and PAS, with a statistically significant elevation in both pathological groups compared with controls, while the difference between placenta previa and PAS did not reach significance. Similarly, free β-hCG concentrations were lowest in healthy controls, intermediate in the placenta previa group, and highest in women with PAS, with significant pairwise differences across all three groups (Table 2).

Binary logistic regression showed that higher maternal serum PAPP-A levels were strongly associated with the presence of placenta previa compared with healthy pregnancies, and this association remained robust after adjustment for key maternal and obstetric covariates. Elevated free β-hCG concentrations were also significantly related to placenta previa, with only minimal attenuation after multivariable adjustment (adjusted for maternal age, body mass index, gravidity, parity, number of prior cesarean deliveries, and history of hypertension, diabetes, and smoking). Similarly, both increased PAPP-A and free β-hCG levels were independently associated with PAS when

Table 1. Demographic and baseline characteristics of studied individuals

Variable		Group			*P* value*
		Healthy control (n=40)	Placenta previa (n=40)	PAS (n=40)	
Quantitative variables (Mean ± SD)					
Maternal age (year)		33.55 ± 4.09	35.15 ± 4.20	35.07 ± 4.60	0.177
BMI (kg/m²)		31.30 ± 3.95	32.57 ± 3.29	30.80 ± 3.16	0.070
Gravidity		2.65 ± 0.73	2.75 ± 0.83	2.97 ± 1.18	0.290
Parity (N)		1.52 ± 0.71	1.30 ± 0.64	1.50 ± 0.93	0.367
Cesarean (N)		1.47 ± 0.71	1.20 ± 0.72	1.32 ± 0.79	0.260
Qualitative variables, N (%),					
Diabetes	Yes	11 (27.5)	21 (52.5)	12 (30)	0.124**
	No	29 (72.5)	19 (47.5)	18 (70)	
Hypertension	Yes	9 (22.5)	10 (25)	5 (12.5)	0.179**
	No	31 (77.5)	30 (75)	35 (87.5)	
Smoking	Yes	1 (2.5)	3 (7.5)	0 (0.0)	0.164**
	No	39 (97.5)	37 (91.5)	40 (100)	
Education level	High school	8 (20)	5 (12.5)	10 (25)	0.392***
	Diploma	18 (45)	18 (45)	11 (27.5)	
	Associate's degree	10 (25)	11 (27.5)	10 (25)	
	Bachelor's degree	4 (10)	5 (12.5)	5 (12.5)	
	Master's degree	0 (0)	1 (2.5)	4 (10)	

PAS: Placenta accreta spectrum; BMI: Body mass index; SD: Standard deviation. *One-way ANVA, **Chi-square, ***Fisher's exact test.

Table 2. The frequency distribution of serum aneuploidy markers among the studied groups

Serum aneuploidy markers	Group			*P* value
	Healthy control (n=40)	Placenta previa (n=40)	PAS (n=40)	
PAPP-A (MoM)#	1.24 ± 0.58	1.71 ± 0.39	1.94 ± 0.69	<0.001*
	Group		**Mean difference**	***P* value****
	Healthy control	Previa	0.47	<0.001
		PAS	0.70	<0.001
	Previa	PAS	0.23	0.074
Free β-hCG (MoM)#	1.34 ± 0.64	1.64 ± 0.36	2.01 ± 0.70	<0.001
	Group		**Mean difference**	***P* value****
	Healthy control	Previa	0.30	0.024
		PAS	0.67	<0.001
	Previa	PAS	0.37	0.005

PAS: Placenta accreta spectrum; PAPP-A: Pregnancy-associated plasma protein-A; β-hCG: Beta-human chorionic gonadotropin; SD: Standard deviation; MoM: Multiples of the median.
#Data reported as mean ± SD; *One-way ANOVA, **Post hoc LSD.

compared with healthy women, and these relationships persisted with comparable strength in adjusted models controlling for maternal age, body mass index, gravidity, parity, number of prior cesarean deliveries, and history of hypertension, diabetes, and smoking (Table 3).

ROC curve analysis demonstrated that both free β-hCG and PAPP-A provided statistically significant discrimination between placenta previa and healthy pregnancies, with PAPP-A showing a somewhat stronger overall performance than free β-hCG at their respective cut-off values. In the diagnosis of PAS, both markers again showed good discriminatory capacity, with PAPP-A and free β-hCG yielding broadly comparable areas under the curve and acceptable sensitivity–specificity trade-offs at the selected thresholds (Table 4 and Figures 1 and 2).

Discussion

The central finding of this study is that elevated first-trimester PAPP-A levels were independently associated with both placenta previa and PAS, with adjusted ORs of 7.46 and 6.26, respectively. These observations add to a growing body of literature that has consistently implicated elevated first-trimester PAPP-A as a marker of excessive or abnormal trophoblastic activity. Desai et al published one of the earliest reports in this regard, demonstrating that among pregnancies with placenta previa, those complicated by histologically confirmed placenta accreta had significantly higher median PAPP-A MoM values compared to non-accreta counterparts (1.68 vs. 0.98 MoM), and concluded that first-trimester PAPP-A may be useful for identifying pregnancies at heightened risk (25). A

Table 3. The association between serum aneuploidy markers with placenta previa and PAS using binary logistic regression

Serum aneuploidy markers		Placenta status		
		OR	95% CI	*P* value
Placenta previa compared to healthy women				
PAPP-A (MoM)	Unadjusted	6.72	2.37–18.93	<0.001
	Adjusted*	7.46	2.25–24.80	0.001
β-hCG (MoM)	Unadjusted	3.03	1.23–7.46	0.016
	Adjusted*	3.52	1.24–9.95	0.017
PAS compared to healthy women				
PAPP-A (MoM)	Unadjusted	5.94	2.33–12.93	<0.001
	Adjusted*	6.26	2.42–16.15	<0.001
β-hCG (MoM)	Unadjusted	4.12	1.96–8.65	<0.001
	Adjusted*	4.31	1.89–9.84	<0.001

PAS: Placenta accreta spectrum; PAPP-A: Pregnancy-associated plasma protein-A; β-hCG: Beta-human chorionic gonadotropin; OR: Odds ratio; CI: Confidence interval; MoM: Multiples of the median.
*Adjusted for maternal age, BMI, gravidity, parity, number of cesareans, and history of hypertension, diabetes, and smoking

Table 4. Diagnostic value of serum aneuploidy markers in the diagnosis of placenta previa and PAS using ROC curve analysis

Serum aneuploidy markers	Placenta status						
	Cut off (MoM)	AUC (0-1)	95% CI		*P* Value	Sensitivity (%)	Specificity (%)
			Lower	Upper			
Placenta previa							
PAPP-A	1.41	0.768	0.660	0.875	<0.001	80	65
Free β-hCG	1.45	0.696	0.572	0.821	0.003	70	70
PAS							
PAPP-A	1.41	0.785	0.685	0.785	<0.001	75	65
Free β-hCG	1.45	0.770	0.662	0.877	<0.001	80	70

PAS: Placenta accreta spectrum; PAPP-A: Pregnancy-associated plasma protein-A; β-hCG: Beta-human chorionic gonadotropin; CI: Confidence interval; MoM: Multiples of the median; AUC; Area under curve.

subsequent retrospective study by Wang et al corroborated these findings, reporting that elevated first-trimester serum PAPP-A was significantly and independently associated with placenta accreta after controlling for gestational age, BMI, maternal age, smoking, and prior cesarean section history (OR: 3.51) (26). The present study's adjusted ORs are numerically larger, which may reflect differences in study populations, covariate adjustment strategies, or the inclusion of both placenta previa and PAS as separate outcome groups. In a more recent case–control study by Belousova et al involving 100 patients, PAPP-A levels in absolute units were paradoxically lower in the PAS and placenta previa groups compared to healthy controls, a discrepancy that was also noted by the authors, who attributed it to differences in reporting units (IU/L versus MoM), population heterogeneity, and PAS subtype composition (27). This highlights the importance of harmonizing measurement units and accounting for

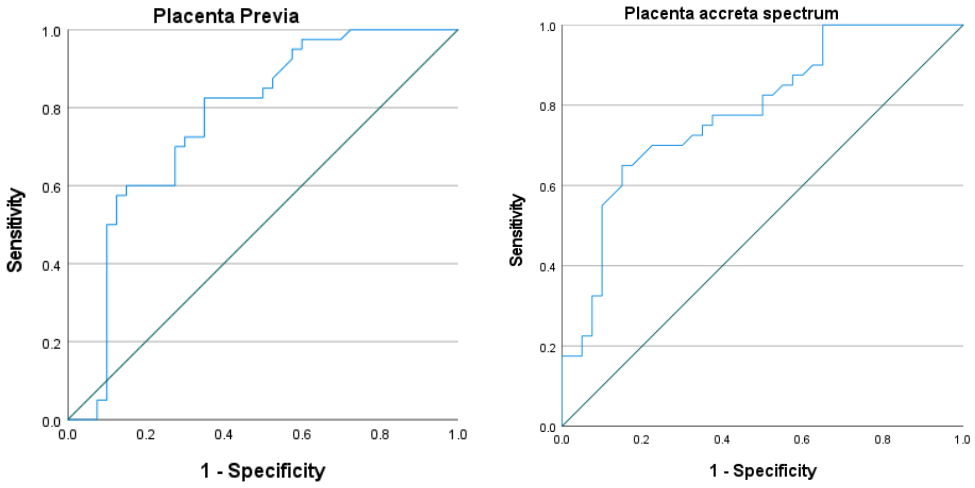

Figure 1. PAPP-A as a predictor of placenta previa and PAS using ROC curve analysis

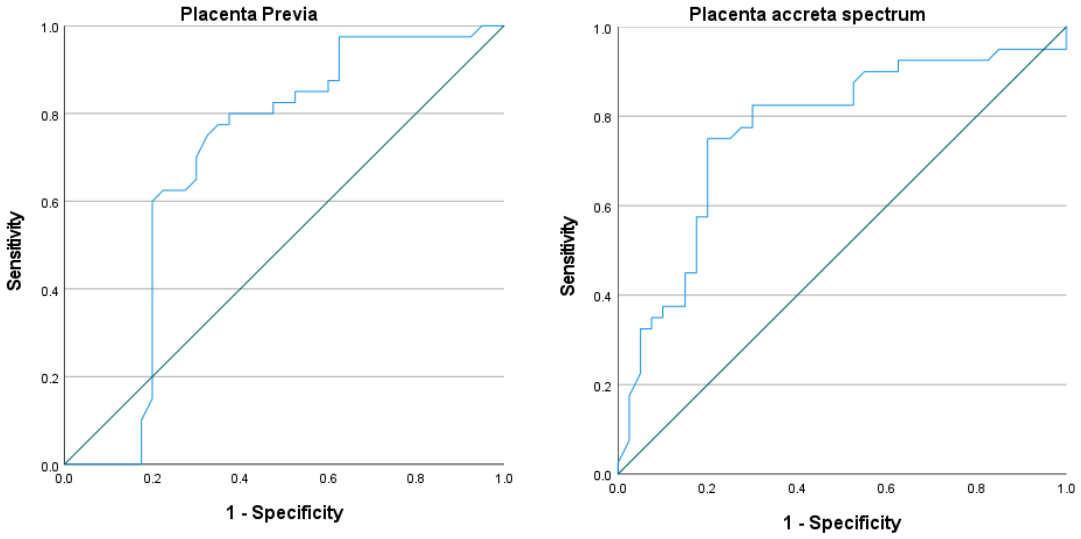

Figure 2. Free β-hCG as a predictor of placenta previa and PAS using ROC curve analysis.

gestational-age adjustment when comparing serum marker levels across studies.

The finding that elevated PAPP-A was associated with both placenta previa and PAS independently aligns with the biological role attributed to this protein. PAPP-A is a zinc-dependent metalloproteinase secreted by the syncytiotrophoblast that facilitates trophoblast invasion by cleaving IGFBP-4 (insulin-like growth factor–binding protein 4), thereby increasing the local bioavailability of insulin-like growth factors (IGFs) critical for implantation and placental growth; it has been proposed that an overexpression of PAPP-A in early pregnancy may drive excessive trophoblast invasion, potentially predisposing to the deepened placental adherence characteristic of PAS (28,29). A 2023 meta-analysis by Li et al analyzing eight observational studies encompassing 243 women with PAS and 1,599 controls found that women who developed PAS had significantly higher first-trimester serum PAPP-A levels compared to those who did not, and that high first-trimester PAPP-A was associated with a nearly threefold increase in the odds of PAS (OR: 2.89) (30). The adjusted ORs reported in the current study considerably exceed this pooled estimate, which warrants careful interpretation but does not detract from the general direction of the association

A further validation of the present PAPP-A findings comes from a 2023 retrospective study by Balkaş and Çaglar, which similarly demonstrated that elevated first-trimester PAPP-A MoM was significantly higher in a group of patients with placenta previa complicated by PAS compared to non-adherent placenta previa and controls (median PAPP-A MoM 1.96 in PAS-complicated previa vs. 0.88 in non-adherent previa), and further showed that PAPP-A elevation correlated with severity of intraoperative blood loss and the need for peripartum hysterectomy (31). Penzhoyan and Makukhina, in a 2019 retrospective study of 48 women with abnormal placentation, also reported higher PAPP-A MoM values in the group with placenta previa compared to controls, and found that PAPP-A assessed in the first trimester was potentially useful for early prognostication of pathological blood loss at delivery (23). Similarly, Büke et al found that both PAPP-A and free β-hCG MoM values were significantly higher in women with placenta accreta compared to those with non-adherent placenta previa (22), a finding that further contextualizes the present study's independent associations for both markers.

In terms of diagnostic performance, PAPP-A at a cut-off of 1.41 MoM achieved AUCs of 0.768 and 0.785 for placenta previa and PAS, respectively, with sensitivities of 80% and 75% and specificities of 65% and 65%. These figures are broadly consistent with the moderate-to-good diagnostic accuracy reported by others. The 2024 systematic review and meta-analysis by Mortaki et al, which analyzed eight retrospective studies involving 1,886 participants across five major databases, found that first-trimester PAPP-A levels were significantly higher in the PAS group relative to the placenta previa group (mean difference [MD]: 0.48 MoM), and that first-trimester β-hCG was elevated in the placenta previa group compared to those with normal attachment (MD: 0.27) (32). These meta-analytic findings are consistent with the statistically independent associations for both markers demonstrated in the present study across two distinct outcome groups. The combined approach explored by Belousova et al, integrating PAPP-A and free β-hCG into a logistic regression model, yielded improved AUCs of 0.85 for PAS and 0.88 for placenta previa (27), surpassing single-marker analyses, a strategy worth pursuing in future iterations of this research domain to determine whether a multi-marker model would further improve the AUCs reported here.

Regarding free β-hCG, the present study found that

elevated first-trimester free β-hCG was also independently associated with placenta previa and PAS (ORs of 3.52 and 4.31, respectively). At a cut-off of 1.45 MoM, free β-hCG achieved AUCs of 0.696 and 0.770, with sensitivities of 70% and 80% and specificities of 70% and 70% for the two conditions. Free β-hCG is produced by the syncytiotrophoblast and plays a fundamental role in progesterone production, trophoblast differentiation, angiogenesis, and immunomodulation at the maternal–fetal interface; elevated levels may reflect increased trophoblastic mass or heightened proliferative activity, both of which are consistent with the exaggerated invasion characteristic of PAS (27). The findings by Büke et al lend support to the association between free β-hCG and placenta accreta, as these investigators likewise observed significantly higher free β-hCG MoM values in the accreta group (22). By contrast, Penzhoyan and Makukhina reported that comparison of free β-hCG between groups with abnormal placentation and controls did not reach statistical significance in their cohort (23), and Thompson et al similarly found no significant difference in free β-hCG MoM values between pregnancies complicated by abnormally invasive placentation and controls (33). These discrepancies may be attributable to differences in sample sizes, patient selection criteria, gestational age at sampling, and the degree of heterogeneity in PAS subtype composition. The relatively modest AUC values for free β-hCG observed in the current study, particularly for placenta previa (AUC 0.696), are consistent with the limited standalone specificity of this marker acknowledged in the wider literature.

Several considerations are relevant to the interpretation of this study's diagnostic performance data. The AUC values of 0.768–0.785 for PAPP-A and 0.696–0.770 for free β-hCG, while statistically significant, indicate moderate but not definitive discrimination. This is not unexpected for a single biomarker in a complex, multifactorial clinical entity. Importantly, as highlighted in a comprehensive scoping review by Givens et al encompassing the maternal serum biomarker literature for PAS, important evidence gaps remain regarding suitable cut-off values, variability of gestational age at sampling, and potential overlap with other placenta-related complications (34). The lack of a universally validated MoM cut-off for clinical decision-making has been a consistent limitation across the literature, and the cut-off values of 1.41 MoM for PAPP-A and 1.45 MoM for free β-hCG reported in the current study should be regarded as population-specific thresholds requiring external validation. In a review of potential serum biomarkers in the prenatal diagnosis of PAS, Zhang and Wang noted that no single circulating biomarker has yet demonstrated sufficient accuracy for routine clinical PAS screening, partly because the precise molecular mechanisms of PAS remain incompletely characterized, and partly because most markers are not specific to PAS but shared with other adverse pregnancy outcomes such as preeclampsia and fetal growth restriction (35). This underscores the need for integrating biochemical markers with ultrasonographic findings and clinical risk stratification within a multimodal framework.

In summary, the findings of this study demonstrate that elevated first-trimester maternal serum PAPP-A and free β-hCG levels are independently and significantly associated with both placenta previa and PAS, with PAPP-A showing particularly strong adjusted odds ratios and moderate-to-acceptable diagnostic performance on ROC analysis. These associations are biologically plausible, consistent with the broader body of literature, and clinically meaningful in that both markers are already routinely collected during standard first-trimester aneuploidy screening, imposing no additional procedural burden on patients or healthcare systems. The diagnostic accuracy of each marker individually, while acceptable, is unlikely to be sufficient for standalone clinical screening, but the integration of these biomarkers, especially in high-risk women with prior uterine surgery or placenta previa, into a composite first-trimester risk algorithm holds genuine promise. Future prospective, multicentre studies with standardized measurement protocols and histopathological outcome verification are warranted to validate the cut-off values identified here, to explore combined biomarker and sonographic prediction models, and to assess whether early identification through biochemical risk stratification can translate into improved peripartum planning and reduced maternal morbidity.

Conclusion

This case–control study demonstrates that first-trimester maternal serum aneuploidy markers, specifically PAPP-A and free β-hCG, are significantly elevated in pregnancies complicated by placenta previa and PAS compared with uncomplicated pregnancies, independent of major maternal and obstetric confounders. Both markers showed meaningful associations with these placental disorders in adjusted logistic regression models and provided acceptable diagnostic performance on ROC analysis, with PAPP-A generally exhibiting slightly stronger discriminative ability. Collectively, these findings suggest that routinely measured first-trimester aneuploidy markers may have a role in early risk stratification for placenta previa and PAS, and could be considered as components of multivariable prediction models to guide targeted surveillance and peripartum planning.

Limitations of the study

First, its retrospective, single-center design and relatively small sample size limit the generalizability of the findings and increase the risk of selection bias. Second, reliance on medical records may have introduced information bias due to variability in documentation quality and incomplete capture of potential confounders, including other placental or maternal factors that could influence PAPP-A

and β-hCG levels. Third, assay-specific characteristics and laboratory calibration may restrict the applicability of the proposed MoM cut-offs to other settings using different platforms. Finally, we did not externally validate our models in an independent cohort, and the diagnostic performance estimates should therefore be interpreted as exploratory and hypothesis-generating rather than definitive for clinical implementation.

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Authors' contribution

Conceptualization: Soudabeh Kazemi Aski and Zahra Hamidi Madani.
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Formal analysis: Habib Eslami-Kenarsari.
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Methodology: Habib Eslami-Kenarsari and Misa Naghdipour.
Project management: Zahra Hamidi Madani.
Resources: All authors.
Supervision: All authors.
Validation: Samaneh Kheirab and Misa Naghdipour.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

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

Declaration of generative artificial intelligence (AI) and AI-assisted technologies in the writing process

While preparing this work, the authors utilized AI (Grammarly and Perplexity) to refine grammar points and language style. Subsequently, they thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

The research was conducted in accordance with the principles of the Declaration of Helsinki. This study was conducted at Alzahra Hospital in Rasht, Iran, and was derived from a research project (No: 5090), approved by the ethics committee of Guilan University of Medical Sciences, Rasht, Iran, (ethical code number: IR.GUMS.REC.1402.067; https://ethics.research.ac.ir/form/q7z5tcrul3azs239.pdf) registered on May 3, 2023. Besides, the authors have ultimately observed ethical issues (including plagiarism, data fabrication, and double publication).

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