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ORIGINAL RESEARCH

Relationship Between PAPP-A Levels in the First Trimester of Pregnancy and Complication Risk

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Purpose: Pregnancy-associated plasma protein A (PAPP-A) is increasingly being recognized as a valuable biochemical marker for identifying pregnant women at risk of experiencing complications during pregnancy. We aimed to determine the association between first-trimester PAPP-A levels and the risk of pregnancy complications.

Patients and Methods: A prospective cohort study was conducted on 606 pregnant women who were screened for aneuploidy in the first trimester using the double test at the Hai Phong Obstetrics and Gynecology Hospital from February 2023 to February 2024. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated to assess the association between PAPP-A levels and various pregnancy complications, including hypertensive disorders, fetal growth restriction, preterm birth, miscarriage, and stillbirth. A multivariate binary regression model was used to analyze the relationship between PAPP-A levels and these complications, with p-values < 0.05 considered significant.

Results: Among the 606 participants, 86 (14.2%) presented with low PAPP-A levels (< 0.5 multiple of the median (MoM)), of whom 50 (58.1%) experienced pregnancy complications. A significant association was observed between low PAPP-A levels and hypertensive disorders, fetal growth restriction, spontaneous preterm birth, and miscarriage (OR: 5.1 [95% CI: 2.8–9.4]; 2.54 [1.38–4.68]; 7.48 [3.07–18.21]; and 4.5 [1.4–14.6], respectively). Multivariate regression analysis revealed a significant independent association between PAPP-A levels and these complications (OR: 5.05 [95% CI: 2.71–9.42], 2.52 [1.36–4.66], 7.76 [3.16–19.07], and 4.06 [1.17–14.11], respectively).

Conclusion: Our findings suggest that pregnant women with low PAPP-A levels during the first trimester are at an increased risk of developing pregnancy complications, including hypertensive disorders, fetal growth restriction, preterm birth, and miscarriage. Further studies that integrate PAPP-A with other parameters in the predictive model are necessary to reach definitive conclusions.

Keywords: pregnancy complication, pregnancy-associated plasma protein A, hypertensive disorders in pregnancy, fetal growth restriction, preterm birth, miscarriage

Introduction

Pregnancy-associated plasma protein A (PAPP-A) is a high-molecular-weight glycoprotein produced in the placenta by syncytiotrophoblasts, shortly after conception. PAPP-A plays a vital role in embryonic development by supporting placental growth and function, regulating fetal development, and protecting the fetus from the maternal immune system.[1] For over four decades, the combined measurement of PAPP-A and free beta-human chorionic gonadotropin (β-hCG) levels in maternal serum (double test), along with the evaluation of nuchal translucency via ultrasound (referred to as the combined test), has been used for screening of first-trimester aneuploidy, with detection and false-positive rates of approximately 85% and 5%, respectively.[2,3]

Besides its well-known role in first-trimester aneuploidy screening, low maternal serum PAPP-A levels have recently been recognized as an early indicator of placental dysfunction and a significant predictor of adverse obstetric outcomes such as preeclampsia, preterm birth, and stillbirth.[4,5] Additionally, low maternal serum PAPP-A levels may impact fetal growth by decreasing the activity of proteases on IGF-binding proteins (IGFBPs), which are essential regulators of fetal

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development.[5] A study by Movahedi et al found that mothers with low PAPP-A levels (<0.5 MoM) are more likely to experience adverse pregnancy outcomes such as miscarriage, preterm labor, and preeclampsia.[6] A prospective study (2023) that included 2150 pregnant women found that low PAPP-A levels (<0.4 MoM) were associated with a higher risk of requiring closer monitoring for serious pregnancy outcomes.[7] This evidence underscores the importance of PAPP-A in developing preventive strategies and refining monitoring protocols for high-risk pregnancies, thereby enhancing pregnancy outcomes.

However, the role of low PAPP-A levels as an independent biomarker for predicting adverse pregnancy outcomes, along with the variability in threshold values used across studies, remains debated.[8–10] In Vietnam, only a few studies have investigated the association between PAPP-A concentration and specific pregnancy complications such as preeclampsia or diabetes mellitus.[11,12] To the best of our knowledge, no study has evaluated the overall relationship between first-trimester PAPP-A levels and various pregnancy complications. Therefore, in this study, we aimed to determine the association between first-trimester PAPP-A concentrations and adverse pregnancy outcomes.

Materials and Methods

Study Population

A prospective cohort study was conducted among singleton pregnant women aged 18–40 years who were screened for aneuploidy in the first trimester (gestational age 11^{+0}–13^{+6} weeks) using the double test at Hai Phong Obstetrics and Gynecology Hospital from February 2023 to February 2024. Participants who provided written informed consent were included in the study. Gestational age was determined by the first day of the last menstrual period or by the expected date of birth determined using ultrasound in the first trimester (GE Voluson E6, GE Healthcare Korea).

The exclusion criteria were as follows: (1) a previous history of cardiovascular disease, diabetes, or hypertension; (2) a body mass index (BMI) > 30 or <18 kg/m^2; (3) medical indications for preterm birth; (4) a diagnosis of fetal anomalies or chromosomal disorders; and (5) lost to follow-up.

A total of 1500 pregnant women voluntarily participated in this study. Data were collected through interviews conducted during their first prenatal visit using self-designed research records that included maternal and fetal characteristics, double-test screening results, and PAPP-A levels. Each patient was closely monitored throughout pregnancy and until delivery. Pregnancy and neonatal outcomes were recorded from the patients' electronic medical records. After excluding 894 pregnant women who met the above exclusion criteria, the final analysis included 606 pregnant women (Figure 1).

Sample Size

$$n = \frac{Z^2_{(1-\alpha/2)} S^2}{(\bar{X}\delta)^2}$$

The sample size for this study was estimated using the following formula: Where,

$Z\ (1 - \alpha/2) = 1.96$, δ value = 0.04.

$\bar{X}$: Mean PAPP-A level; S: Standard deviation. According to Hatav Ghasemi-Tehrani et al, the mean PAPP-A level was 1.26 ± 0.58 MoM.[13]

Based on these values, the minimum sample size required was determined to be 509. The actual sample size obtained in the study was 606.

Outcome Definition

The primary outcome of interest was pregnancy complications, including hypertensive disorders of pregnancy, fetal growth restriction, spontaneous preterm birth, spontaneous miscarriage, and stillbirth.

Hypertensive disorders of pregnancy, defined as a blood pressure reading of ≥ 140/90 mmHg on two occasions, a few hours apart, were classified according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) classification.[14] Fetal growth restriction was defined as an ultrasonographically estimated fetal weight below the 10th percentile of the gestational age.[15] Preterm birth was defined as spontaneous delivery before the 37th week of gestation.[16]

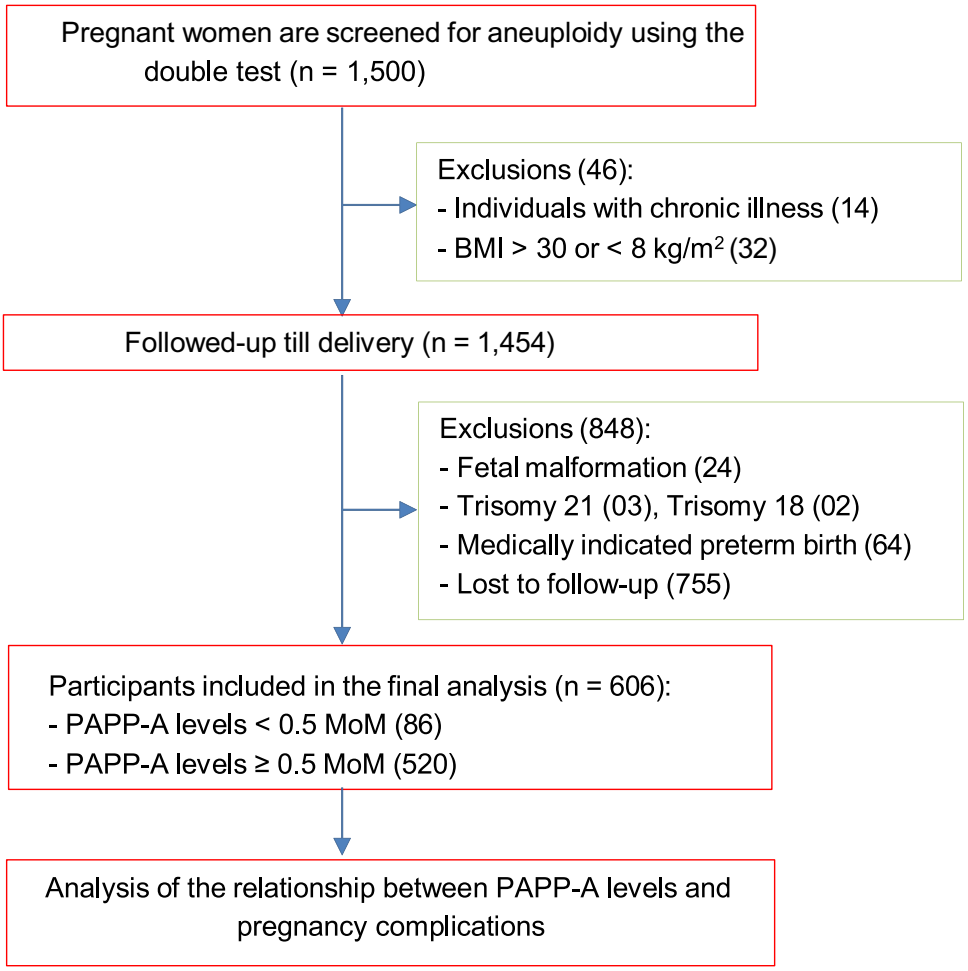

Figure 1 Study diagram.
Abbreviations: BMI, body mass index; PAPP-A, Pregnancy-associated plasma protein A; MoM, multiple of the median.

Stillbirth refers to fetal death that occurs before the 23rd week of gestation.[17] Second-trimester miscarriage refers to the loss of pregnancy from 13 weeks and 0 days to 19 weeks and 6 days of gestation.[18]

Assessment of PAPP-A

This study was conducted at the Department of Biochemistry of Hai Phong Obstetrics and Gynecology Hospital. Maternal blood samples were collected after obtaining informed consent. The serum was separated and stored at –20°C. The PAPP-A test was performed using a time-resolved immunoassay on the COBAS 6000 system (Roche, Switzerland). Our laboratory's inter-assay coefficients of variation were found to be 3.71% for level 1 and 4.62% for level 2, as illustrated in the Levey-Jennings chart "Supplementary Material 1". Similarly, the intra-assay coefficients of variation were 2.18% "Supplementary Material 2".

The final concentrations of β-hCG and PAPP-A (UI/L) were measured and converted into MoM values using the following formula:

$$\mathrm{PAPP-A(MoM)} = \frac{\mathrm{PAPP-A\ concentration\ in\ pregnant\ women(UI/L)}}{\mathrm{Expected\ median\ PAPP-A\ value}}$$

Low PAPP-A levels: Pregnant women with a PAPP-A level < 0.5 MoM were considered at risk for pregnancy complications, based on previous studies.[6,19]

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Statistical Analysis

All statistical analyses were performed using SPSS version 26.0 (SPSS, Armonk, NY, USA). Categorical variables are presented as frequencies (n) and percentages (%), and continuous variables are expressed as means and standard deviations. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to determine the association between outcomes and independent variables. A multivariate binary regression model was used to assess the relationship between PAPP-A levels and pregnancy-related complications. The participants were allocated into two groups based on PAPP-A levels < 0.5 MoM or ≥ 0.5 MoM for analysis. The significance level was set at $p < 0.05$.

Ethical Considerations

The research was approved by the Ethical Council in Biomedical Research at Haiphong University of Medicine and Pharmacy, Vietnam (Ethics Committee ID number 314/QĐ-YDHP), and the Scientific Council of Haiphong Hospital of Obstetrics and Gynecology, Vietnam (IEC, 1189/QĐ-BVPSHP). Our study strictly adhered to the ethical principles of the Declaration of Helsinki. All participants signed a written informed consent form after receiving a comprehensive explanation of the study's purpose and procedures.

Results

The mean PAPP-A level among participants was 1.12 ± 0.67 MoM (range 0.06–6.78 MoM). Among the 606 participants, 117 (19.3%) had pregnancy-related complications (Table 1).

Eighty-six participants (14.2%) had low PAPP-A levels (< 0.5 MoM) (Table 2).

Table 1 Participant Characteristics (n = 606)

Characteristics	n% or Median
Maternal age (years)	34.1 ± 4.9
BMI (kg/m^2)	26.6 ± 16.9
Obstetric history: Nulliparous Multiparous	 199 (32.8%) 407 (67.2%)
Screening time: 11–11^{+6} weeks 12–12^{+6} weeks 13–13^{+6} weeks	 41 (6.8%) 410 (67.7%) 154 (25.4%)
Mean PAPP-A level (MoM) (Min–Max)	1.12 ± 0.67 (0.06–6.78)
Pregnancy complications: Hypertensive disorders in pregnancy Fetal growth restriction Preterm birth Miscarriage Stillbirth	117 (19.3%) 52 63 21 12 06
Gestational age at birth (weeks)	37.9 ± 3.7
Birth weight (grams)	3028 ± 466.2

Abbreviations: BMI, body mass index; PAPP-A, Pregnancy-associated plasma protein A; MoM, multiple of the median.

Table 2 Distribution of Pregnancy Complications According to PAPP-A Levels

Pregnancy Complications		PAPP-A Levels			
		< 0.5 MoM (n = 86)		≥ 0.5 MoM (n = 520)	
Hypertensive disorders in pregnancy	Yes (n, %)	21	40.4%	31	59.6%
	No (n, %)	65	11.7%	489	88.3%
	OR (95% CI); p	5.1 (2.8–9.4); p < 0.001			
Fetal growth restriction	Yes (n, %)	17	27.0%	46	73.0%
	No (n, %)	69	12.7%	474	87.3%
	OR (95% CI); p	2.54 (1.38–4.68); p = 0.002			
Preterm birth	Yes (n, %)	11	52.4%	10	47.6%
	No (n, %)	75	12.8%	510	87.2%
	OR (95% CI); p	7.48 (3.07–18.21); p < 0.001			
Miscarriage	Yes (n, %)	5	41.7%	7	58.3%
	No (n, %)	81	13.6%	513	86.4%
	OR (95% CI); p	4.5 (1.4–14.6); p = 0.018			
Stillbirth	Yes (n, %)	1	16.7%	5	83.3%
	No (n, %)	85	14.2%	515	85.8%
	OR (95% CI); p	1.21 (0.14–10.5); p = 0.861			

Abbreviations: PAPP-A, Pregnancy-associated plasma protein A; OR, odds ratio; CI, confidence intervals.

There was a statistically significant relationship between low PAPP-A levels and hypertensive disorders in pregnancy, fetal growth restriction, spontaneous preterm birth, and miscarriage with ORs (95% CIs) of 5.1 (2.8–9.4), 2.54 (1.38–4.68), 7.48 (3.07–18.21), and 4.5 (1.4–14.6), respectively. No statistically significant relationship was found between low PAPP-A levels and stillbirth (p > 0.05) (Table 2).

In the multivariate regression model, after adjusting for several confounding factors, including age, BMI, and obstetric history, the relationship between low PAPP-A and pregnancy complications remained significant for hypertensive disorders in pregnancy, fetal growth restriction, spontaneous preterm birth, and miscarriage, with ORs (95% CIs) of 5.05 (2.71–9.42), 2.52 (1.36–4.66), 7.76 (3.16–19.07), and 4.06 (1.17–14.11), respectively. However, no statistically significant association was found between low PAPP-A levels and stillbirths (p > 0.05) (Table 3).

Table 3 Multivariable Binary Regression Model to Assess the Association Between PAPP-A Levels and Pregnancy Complications (n = 606)

Pregnancy Complications		Beta	OR	95% CI	p
Hypertensive disorders in pregnancy	Maternal age	–0.09	0.92	0.86–0.98	< 0.007
	BMI	0.001	1.01	0.99–1.02	0.91
	Obstetric history (Nulliparous vs multiparous)	–0.19	0.82	0.38–1.76	0.62
	PAPP-A (Low level vs normal level)	1.62	5.05	2.71–9.42	< 0.001

(*Continued*)

Table 3 (Continued).

Pregnancy Complications		Beta	OR	95% CI	p
Fetal growth restriction	Maternal age	0.003	1.01	0.95–1.06	0.917
	BMI	–0.007	0.99	0.98–1.01	0.168
	Obstetric history (Nulliparous vs multiparous)	–0.08	0.93	0.49–1.73	0.81
	PAPP-A (Low level vs normal level)	0.93	2.52	1.36–4.66	0.002
Preterm birth	Maternal age	–0.06	0.95	0.86–1.04	0.251
	BMI	0.001	0.94	0.98–1.03	0.937
	Obstetric history (Nulliparous vs multiparous)	0.65	1.91	0.69–5.31	0.21
	PAPP-A (Low level vs normal level)	2.05	7.76	3.16–19.07	< 0.001
Miscarriage	Maternal age	–0.17	0.85	0.75–0.95	0.005
	BMI	0.23	1.26	1.08–1.45	0.002
	Obstetric history (Nulliparous vs multiparous)	–0.07	0.93	0.18–4.93	0.935
	PAPP–A (Low level vs normal level)	1.4	4.06	1.17–14.11	0.027
Stillbirth	Maternal age	–0.17	0.85	0.71–1.01	0.062
	BMI	0.30	1.36	1.12–1.64	0.002
	Obstetric history (Nulliparous vs multiparous)	0.08	1.09	0.1–11.39	0.94
	PAPP-A (Low level vs normal level)	–0.07	0.94	0.09–9.67	0.96

Abbreviations: BMI, body mass index; PAPP-A, Pregnancy-associated plasma protein A; OR, odds ratio; CI, confidence intervals.

Discussion

Our results demonstrated that the mean PAPP-A level among participants was 1.12 ± 0.67 MoM (Table 1). This result is consistent with those of previous studies on first-trimester PAPP-A.[6,13] Eighty-six participants (14.2%) exhibited low PAPP-A levels (Table 2), a finding similar to that of Movahedi et al, who reported a 14.7% prevalence of low PAPP-A levels.[6] In contrast, Jindal et al observed a 9.8% rate of low PAPP-A levels in 2150 screened pregnancies.[7] This discrepancy could be explained by the varying thresholds for low PAPP-A concentrations used across studies. For instance, Jindal et al defined low PAPP-A as < 0.4 MoM, whereas our research and that of Movahedi et al set the low PAPP-A threshold at < 0.5 MoM.

PAPP-A plays a role in first-trimester aneuploidy screening, and its multiple of the median (MoM) value may serve as an early predictor of pregnancy complications. Specifically, in chromosomally normal pregnancies, low maternal serum PAPP-A levels measured between 11 and 13+6 weeks of gestation have been associated with an increased risk of adverse pregnancy outcomes, including fetal growth restriction, preterm birth, stillbirth, and especially, preeclampsia.[20–23] Notably, among the 86 women with low serum PAPP-A levels, 50 (58.1%) experienced one or more pregnancy complications, including five who presented with two or more complications simultaneously. A comprehensive analysis of the complications in the low PAPP-A group revealed that hypertensive disorders during pregnancy (HDP) occurred in 21 of the 86 patients (24.4%), representing the highest proportion of complications observed. Decreased serum PAPP-A levels in HDP have been reported previously.[20,24,25] Evidence confirms that PAPP-A enhances the mitogenic function of insulin-like growth factors (IGFs), which are crucial for trophoblast invasion into the uterine arteries. Therefore, low maternal PAPP-A levels may reflect impaired placental function and predispose women to HDP.[1] A recent meta-analysis by Ismini Tzanaki et al, which included 33,651 pregnant women, 2001 of whom were diagnosed with preeclampsia, reported that PAPP-A is a promising predictor for the early screening of preeclampsia. This finding enables women at

risk to be diagnosed early in their pregnancy and benefit from individualized preeclampsia treatment before it progresses.[26] In a cohort of 47,770 women, Spencer et al reported significantly lower PAPP-A levels in pregnancies with preeclampsia than in controls (0.772 vs 1.037 MoM, $p < 0.0001$). The 5th percentile threshold (0.415 MoM) was associated with an OR (95% CI) of 3.7 (2.3–4.8) for preeclampsia, with a 15% incidence at this cutoff.[24] Moreover, a large trial involving 34,271 women found that PAPP-A levels below the 10th percentile (0.52 MoM) increased the risk of preeclampsia.[20] Another study demonstrated that PAPP-A levels below the 10th percentile increased both early-onset preeclampsia and overall preeclampsia risk, with risk ratios (95% CIs) of 9.26 (2.33–36.87) and 3.27 (2.19–4.88), respectively.[25]

Additionally, low maternal serum PAPP-A levels may affect fetal growth by reducing the impact of proteases on IGF-binding proteins (IGFBPs), which are vital regulators of fetal development.[5,27] In our study, the incidence of fetal growth restriction (FGR) was 19.8%, which is higher than the 12.9% reported by Jindal et al and the 15.2% reported by Mithil et al, both of whom used a cutoff of <0.4 MoM.[7,28] Honarjoo et al demonstrated PAPP-A levels of < 0.4 MoM as an FGR indicator. In contrast, elevated β-hCG levels did not correlate with FGR.[29] Kaijomaa et al reported that PAPP-A levels < 0.3 and < 0.52 MoM were associated with FGR, with ORs of 4.9 (95% CI: 3.2–7.5) and 3.3 (95% CI: 2.8–5.7), respectively.[19] Ranganathan et al discovered that PAPP-A with< 0.4 MoM had a positive predictive value of 83.3% and a negative predictive value of 79.3% for FGR.[30]

In the current research, we evaluated the significance of low maternal serum PAPP-A concentration as an early indicator of placental dysfunction by examining the association between PAPP-A levels and pregnancy complications. Table 2 shows that, among the 606 women screened using the double test in the first trimester, the odds of developing HDP, FGR, preterm birth, and miscarriage were significantly higher in the low PAPP-A group compared to the normal PAPP-A group. After adjusting for maternal confounding factors, including maternal age, BMI, and obstetric history, in the multivariate regression model, the results presented in Table 3 demonstrated that PAPP-A concentration had a significant independent association with these complications. Hughes et al studied 4057 pregnant women and reported that low maternal PAPP-A levels were associated with an increased risk of severe preeclampsia, FGR, and stillbirth.[31] A systematic review by Morris et al, which included 32 studies with 175,240 women, found that maternal PAPP-A below the 5th percentile is moderately associated with FGR, preeclampsia, preterm birth, and other complications, with ORs (95% CIs) of 2.08 (1.89–2.29), 1.94 (1.63–2.30), 2.09 (1.87–2.33), and 3.31 (1.80–5.11), respectively; however, the predictive value was low. The authors recommended considering PAPP-A as a continuous variable and integrating it with other parameters in predictive models to enhance screening accuracy.[32] Mithil et al also highlighted that first-trimester PAPP-A is a significant indicator of potential pregnancy complications, noting that its predictive value is limited unless used in conjunction with other markers.[28]

Preeclampsia remains a leading cause of maternal mortality, while FGR and low birth weight significantly contribute to neonatal morbidity and mortality, presenting serious public health challenges. Studies have consistently demonstrated that low first-trimester PAPP-A is a critical biochemical marker that indicates an increased risk of preeclampsia and FGR. This strategy has the potential to reduce adverse maternal and neonatal outcomes as well as healthcare costs.

In our study, no significant association was found between PAPP-A levels and stillbirth ($p > 0.05$) (Table 3). Serum PAPP-A levels have been used for aneuploidy screening for over four decades, and are typically decreased in cases of aneuploidy. However, many pregnancies with chromosomal abnormalities can result in miscarriage or stillbirth.[33] Although we excluded cases of fetal aneuploidy, the limited number of stillbirths (six cases) in our cohort may have affected the reliability of our analysis regarding this complication. The selection of a control group and a low PAPP-A threshold is critical when interpreting these findings. Kaijomaa et al reported that very low levels of PAPP-A (< 0.3 MoM) are strong independent indicators of aneuploidy and are associated with an increased risk of spontaneous miscarriage. However, these low levels did not correlate with a higher risk of fetal structural anomalies. PAPP-A levels categorized in the "gray zone" (between 0.3 and 0.9 MoM) are associated with an elevated risk of preterm birth, preeclampsia, stillbirth, and low birth weight. In contrast, normal PAPP-A levels (ranging from 0.9 to 1.1 MoM) are associated with typical fetal development and positive outcomes.[19]

Low PAPP-A levels reflect suboptimal or impaired placental function and may lead to adverse pregnancy outcomes.[34] However, it remains unclear whether pregnancies with low PAPP-A levels should receive intensive management. Given

the heterogeneous data and low positive predictive value, PAPP-A levels alone are not currently recommended for routine screening for pregnancy complications in low-risk populations.[35–37] However, it is a strong indicator of potentially complicated pregnancies.

To evaluate the association between PAPP-A levels and pregnancy complications, we considered several confounding maternal factors, including age, BMI, and obstetric history, in the multivariate regression model (Table 3). However, data on other maternal and fetal factors that may be related to pregnancy outcomes, such as uterine artery Doppler, β-hCG, and Placental Growth Factor (PIGF), were unavailable. Previous studies have highlighted the critical role of low PAPP-A levels as indicators of the risk for pregnancy complications. Therefore, PAPP-A levels should be evaluated in conjunction with other parameters in the prediction model to enhance the effectiveness of screening. While low PAPP-A levels in the first trimester of pregnancy are consistently associated with adverse outcomes, a specific cutoff value for Vietnamese women has not yet been established. Therefore, well-designed multicenter prospective cohort studies with sufficiently large sample sizes are necessary to determine the appropriate cutoff for low PAPP-A in our population.

Conclusion

Pregnant women with low PAPP-A levels during the first trimester are at an increased risk of pregnancy-related complications such as hypertensive disorders, FGR, spontaneous preterm birth, and miscarriage. Further studies that utilize predictive models integrating PAPP-A levels with other parameters are necessary to draw definitive conclusions.

Data Sharing Statement

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

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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