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The Association Between Low Pregnancy-Associated Plasma Protein-A levels and Adverse Pregnancy Outcomes

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ABSTRACT

Objective: The primary objective was to evaluate the association between low pregnancy-associated plasma protein-A (PAPP-A) levels and preterm birth. The secondary objectives included assessing the relationship between low PAPP-A levels and other adverse pregnancy outcomes, as well as analyzing factors affecting PAPP-A levels.

Materials and Methods: Medical records of all women with singleton pregnancies undergoing the combined first trimester Down syndrome screening test between 11-14 weeks of gestation from January 2014 to December 2023 were reviewed. Baseline characteristics and pregnancy outcomes, including miscarriage, stillbirth, gestational diabetes mellitus, gestational hypertension, preeclampsia, preterm delivery, and fetal growth restriction were compared between women with normal and low PAPP-A levels (< 0.4 multiples of median (MoM)).

Results: A total number of 2,023 women were enrolled, of whom 120 (5.9%) had low PAPP-A levels. Higher body mass index, multiparity, diabetes mellitus and hypertension negatively influenced PAPP-A levels. Women with low PAPP-A levels had significantly higher rates of preterm birth (15.8% vs 7.2%), gestational hypertension (12.5% vs 5.3%), and fetal growth restriction (10.8% vs 3.7%). At the 0.4 MoM cutoff, the sensitivity, specificity, NPV, and PPV for predicting preterm birth were 12.18%, 94.64%, 92.72%, and 16.10%, respectively. The area under the receiver operative characteristic curve was 0.597 for preterm birth, 0.578 for gestational hypertension, and 0.585 for fetal growth, respectively.

Conclusion: Low PAPP-A levels were significantly associated with preterm birth, gestational hypertension, and fetal growth restriction. However, the overall predictive performance was limited so PAPP-A should not be used as the sole indicator for clinical decision-making.

Keywords: pregnancy-associated plasma protein-A, PAPP-A, adverse pregnancy outcomes, preterm delivery.

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ความสัมพันธ์ระหว่างระดับ pregnancy-associated plasma protein-A ที่ต่ำกับผลลัพธ์ที่ไม่พึงประสงค์ของการตั้งครรภ์

รัญชิดา แสงศิริวุฒิ , เพียงบุหลัน ยาปาน, ตวงสิทธ์ วัฒกนารา, สุพิชญา สุรเสรีวงษ์, ธนาภา เรขาวศิน พินนิงตัน

บทคัดย่อ

วัตถุประสงค์: *วัตถุประสงค์หลักของการศึกษานี้คือเพื่อประเมินความสัมพันธ์ระหว่างระดับ pregnancy-associated plasma protein-A (PAPP-A) ที่ต่ำกับการคลอดก่อนกำหนด ส่วนวัตถุประสงค์รอง ได้แก่ การศึกษาความสัมพันธ์ระหว่างระดับ PAPP-A ที่ต่ำกับภาวะแทรกซ้อนอื่น ๆ ในระหว่างตั้งครรภ์ และวิเคราะห์ปัจจัยที่มีผลต่อระดับ PAPP-A*
วัสดุและวิธีการ: *มีการทบทวนข้อมูลเวชระเบียนของหญิงตั้งครรภ์ที่มีครรภ์เดี่ยวซึ่งเข้ารับการตรวจคัดกรองดาวน์ซินโดรมไตรมาสแรกแบบรวม (combined first-trimester screening) ระหว่างอายุครรภ์ 11–14 สัปดาห์ ตั้งแต่เดือนมกราคม พ.ศ. 2557 ถึงธันวาคม พ.ศ. 2566 โดยเปรียบเทียบลักษณะพื้นฐานและผลลัพธ์ของการตั้งครรภ์ เช่น การแท้ง การเสียชีวิตของทารกในครรภ์ เบาหวานขณะตั้งครรภ์ ความดันโลหิตสูงขณะตั้งครรภ์ ภาวะครรภ์เป็นพิษ การคลอดก่อนกำหนด และการเจริญเติบโตช้าของทารกในครรภ์ ระหว่างกลุ่มที่มีระดับ PAPP-A ต่ำ (< 0.4 multiples of median (MoM)) และ ระดับปกติ*
ผลการศึกษา: *มีหญิงตั้งครรภ์จำนวนทั้งสิ้น 2,023 รายเข้าร่วมการศึกษา พบว่า ดัชนีมวลกายสูง การตั้งครรภ์หลายครั้ง เบาหวาน และความดันโลหิตสูง มีความสัมพันธ์กับระดับ PAPP-A ที่ลดลงอย่างมีนัยสำคัญ หญิงที่มีระดับ PAPP-A ต่ำมีอัตราการคลอดก่อนกำหนด (ร้อยละ 15.8 เทียบกับร้อยละ 7.2) การเกิดความดันโลหิตสูงขณะตั้งครรภ์ (ร้อยละ 12.5 เทียบกับร้อยละ 5.3) และการเจริญเติบโตช้าของทารกในครรภ์ (ร้อยละ 10.8 เทียบกับร้อยละ 3.7) สูงกว่าอย่างมีนัยสำคัญ สำหรับค่า cutoff ที่ 0.4 MoM ค่าความไว ความจำเพาะ ค่าทำนายเมื่อผลเป็นลบ และค่าทำนายเมื่อผลเป็นบวกในการทำนายการคลอดก่อนกำหนดอยู่ที่ร้อยละ 12.18, 94.64, 92.72 และ 16.10 ตามลำดับ โดยค่า area under the receiver operative characteristic สำหรับการคลอดก่อนกำหนด ความดันโลหิตสูง และการเจริญเติบโตช้าของทารกในครรภ์ เท่ากับ 0.597, 0.578 และ 0.585 ตามลำดับ*
สรุป: *ระดับ PAPP-A ที่ต่ำมีความสัมพันธ์กับการคลอดก่อนกำหนด ความดันโลหิตสูงขณะตั้งครรภ์ และการเจริญเติบโตช้าของทารกในครรภ์อย่างมีนัยสำคัญ อย่างไรก็ตาม เนื่องจากมีประสิทธิภาพในการทำนายต่ำ PAPP-A จึงไม่ควรใช้เป็นเครื่องมือเดียวในการตัดสินใจทางคลินิก*

คำสำคัญ: *Pregnancy-Associated Plasma Protein-A, PAPP-A, ภาวะแทรกซ้อนในระหว่างตั้งครรภ์, การคลอดก่อนกำหนดกำหนด*

Introduction

Pregnancy-associated plasma protein-A (PAPP-A) is a large glycoprotein produced by the syncytiotrophoblast and decidua and released into maternal blood circulation immediately after implantation. Its concentration increases steadily throughout gestation, reaching a peak at term(1, 2). PAPP-A plays a crucial role in breaking down insulin-like growth factor binding protein (IGFBP), thereby releasing insulin-like growth factors (IGFs), which are essential for placental and fetal growth since IGF promotes trophoblast invasion and enhances glucose and amino acid uptake(3). If this process occurs abnormally, it is associated with miscarriage, FGR, pregnancy-induced hypertension, stillbirth, preterm birth, and cesarean section due to either fetal or maternal compromise(4). Impaired syncytiotrophoblasts function or reduced placental volume can lead to decreased PAPP-A production(5, 6); therefore, low PAPP-A levels may indicate compromised placental function as low PAPP-A level will be inadequate to cleave IGF, then IGF will remain in an inactive bound form causing poor fetal and placental growth ending up with adverse pregnancy outcomes(4, 7).

Numerous studies have reported an association between low PAPP-A levels and adverse pregnancy outcomes, including miscarriage, stillbirth, gestational diabetes mellitus, gestational hypertension, preeclampsia, fetal growth restriction, and preterm birth(4, 8-34). However, the definitions of low PAPP-A levels vary across these studies, with cutoff points ranging from 0.39 to 0.73 multiples of median (MoM), limiting the consistency and applicability of the finding in clinical practice.

Moreover, PAPP-A levels are influenced by several factors, such as maternal weight, ethnicity, smoking status, diabetes mellitus, and method of conception(35-37), further complicating their universal application. Previous studies have shown that PAPP-A levels are generally higher in pregnant Asian women compared to Western women(38-42). Moreover, even within the same ethnic group, regional variation exists. For example, PAPP-A levels among pregnant women in northern Thailand were found to differ from those in the southern region(40-42).

Given these inconsistencies, this study was conducted to evaluate the association between low PAPP-A levels and poor pregnancy outcomes in our population. The primary objective was to investigate the relationship between low PAPP-A levels and the risk of preterm birth since it has been a major problem causing neonatal morbidity and mortality in our population for decades. Secondary objectives included examining associations between low PAPP-A levels and other adverse outcomes, including miscarriage, stillbirth, gestational diabetes mellitus, gestational hypertension, preeclampsia, and fetal growth restriction, as well as identifying factors influencing PAPP-A levels.

Materials and methods

Following approval from the Siriraj Institutional Review Board (SIRB 754/2567), this retrospective diagnostic study was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand. Electronic medical records were reviewed for all women with singleton pregnancies undergoing the combined first trimester Down syndrome screening test between 11 and 14 weeks of gestation, from January 2014 to December 2023. Inclusion criteria required complete medical data, including age, body mass index (BMI), gestational age, gravida, ethnicity, smoking status, mode of conception, underlying medical conditions, PAPP-A levels (expressed as MoM), and obstetric outcomes. For participants who gave birth elsewhere, obstetric outcomes were obtained via telephone follow-up. Pregnant women whose birth outcomes could not be followed-up were excluded from the study. PAPP-A measurements were performed in batches using a commercial kit for an automated assay (BRAHMS PAPP-A KRYPTOR; ThermoFisher Scientific, Hennigsdorf, Germany), which was a homogeneous immunoassay (sandwich enzyme-linked immunosorbent assay (ELISA) principle using time resolved amplified cryptate emission

(TRACE) technology. The intra-assay and inter-assay coefficient variations were less than 10% and 12%, respectively.

The sample size was calculated based on a study by Shah et al[14], which evaluated the relationship between low PAPP-A levels and pregnancy complications in India. In that study, preterm birth was 25% in the low PAPP-A group compared to 14% in the normal PAPP-A group. Using a 2-sided type I error of 0.05, 80% power, percent preterm in the low and normal PAPP-A of 25% and 15% respectively and n2 (normal PAPP-A): n1 (low PAPP-A) = 15:1 (based on our data), sample size n1: n2 of 123: 1,845 (total = 1,968) was required. Therefore, retrospective data of about 2,000 subjects with PAPP-A were studied.

Gestational age was determined based on a certain last menstrual period in women with regular cycles, if consistent with first-trimester ultrasound findings. If not, gestational age was based solely on the first-trimester ultrasound performed before 14 weeks of gestation. Maternal medical conditions of interest included diabetes mellitus, chronic hypertension, systemic lupus erythematosus, and antiphospholipid syndrome. The obstetric outcomes assessed were miscarriage, stillbirth, gestational diabetes mellitus, gestational hypertension, preeclampsia, and fetal growth restriction, and preterm birth.

Miscarriage was defined as spontaneous pregnancy loss before 24 weeks of gestation[43]. Stillbirth was defined as fetal death at or beyond 20 weeks of gestation[44]. Gestational diabetes mellitus was diagnosed using either the one-step 2-hour 75-gram oral glucose tolerance test (OGTT) based on the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria[45], or the two-step method recommended by the American College of Obstetricians and Gynecologists (ACOG)[46], which includes a 50-gram, 1-hour glucose challenge test followed by a 100-gram, 3-hour OGTT for values ≥ 140 mg/dL. Gestational hypertension was defined as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, measured on two occasions at least four hours apart, arising after 20 weeks of gestation without proteinuria[47]. Preeclampsia was diagnosed in women meeting the criteria for gestational hypertension in addition to one or more of the following: proteinuria (urine dipstick ≥ 2+, protein-to-creatinine ratio ≥ 0.3, or 24-hour urine protein ≥ 300 mg), thrombocytopenia (platelet count < 100,000/μL), elevated liver enzymes (transaminases > 2 times the upper normal limit), new-onset renal insufficiency (serum creatinine > 1.1 mg/dL or doubling the baseline), pulmonary edema, or new-onset cerebral or visual disturbances[47]. Fetal growth restriction was defined as an estimated fetal weight below the 10th percentile[48]. Preterm birth was defined as delivery before 37 weeks of gestation whereas early preterm birth was defined as delivery before 34 weeks of gestation[49].

Regarding PAPP-A categorization, a cutoff value of 0.4 MoM was used, in accordance with most previous studies[9, 10, 13, 17, 23, 26, 27, 29], however, various cutoff points would also be studied. Women with serum PAPP-A levels < 0.4 MoM served as the case group, while those with levels ≥ 0.4 MoM served as the control group.

Statistical analysis

Descriptive statistics were presented as appropriate, including n (%), mean ± standard deviation (SD), and median with interquartile range (IQR). The chi-square test was used to compare categorical variables between the low and normal PAPP-A groups. A p value of less than 0.05 was considered statistically significant. The predictive performance of various PAPP-A cutoff levels were evaluated using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for both primary and secondary outcomes. Spearman correlation and receiver operating characteristic (ROC) curve analyses were used to assess relationships between independent variables. The area under the ROC curve (AUROC) was interpreted using standard academic benchmarks: 0.5 to 0.6 = fail, 0.6 to 0.7 = poor, 0.7 to 0.8 = fair, 0.8 to 0.9 = good, 0.9 to 1.0 = excellent predictive ability[50]. All statistical analyses were performed using SPSS software, version 29.0.2.0 (IBM Corp., Armonk, NY, USA).

Results

Among 2,023 pregnant women who underwent first trimester Down syndrome screening, 120 (5.9%) were found to have low PAPP-A levels. PAPP-A MoM interpretation was unavailable in 12 cases (Fig. 1). The incidence of preterm delivery was notably higher in the low PAPP-A group compared to the normal PAPP-A group (15.8 % vs 7.2 %).

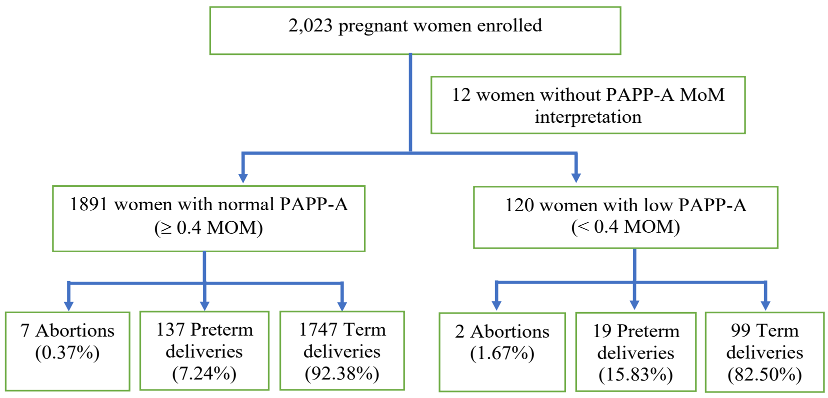

Fig. 1. Flow diagram of participants with and without preterm delivery

PAPP-A: pregnancy-associated plasma protein-A, MoM: multiples of median

As shown in Table 1, baseline characteristics were generally similar between the two groups, with notable differences: women in the low PAPP-A group had higher BMI (26.1 kg/m^2 vs 23.1 kg/m^2), lower mean gestational age at delivery (37.2 weeks vs 38.1 weeks), and higher rates of hypertension (5.8% vs 1.8%), and diabetes mellitus (5.8% vs 1.2%). Factors associated with reduced PAPP-A levels included higher BMI, multiparity, diabetes mellitus, and hypertension (Table 2).

Table 1. Baseline characteristics of the participants (n = 2,023).

Baseline characteristics	PAPP-A group: mean ± SD (min-max)			p value
	Total (n = 2,023)	Normal (n = 1,891)	Low (n = 120)	
Age (year)	29.9 ± 4.6 (18 - 44)	29.9 ± 4.6	30.0 ± 4.5	0.760
BMI (kg/m^2)	23.3 ± 4.8 (14.4 - 52.1)	23.1 ± 4.7	26.1 ± 6.7	< 0.001
Gestational age (weeks)	38.1 ± 2.0 (14 - 41)	38.1 ± 1.9	37.2 ± 3.0	0.001
Gravida, n (%)				0.189
Nulliparity	927 (45.8)	873 (46.2)	48 (40.0)	
Multiparity	1,096 (54.2)	1,018 (53.8)	72 (60.0)	
Southeast Asian, n (%)	2,023 (100)	1,891 (100)	120 (100)	1.000
Smoking, n (%)	6 (0.3)	5 (0.3)	1 (0.8)	0.309
Mode of conception, n (%)				1.000
Natural	1,999 (98.8)	1,868 (98.8)	119 (99.2)	
ART	24 (1.2)	23 (1.2)	1 (0.8)	
Medical conditions, n (%)				
Hypertension	41 (2.0)	34 (1.8)	7 (5.8)	0.009
Pregestational DM	30 (1.5)	23 (1.2)	7 (5.8)	0.001
SLE	10 (0.5)	10 (0.5)	0	1.000

PAPP-A: pregnancy-associated plasma protein-A, SD: standard deviation, BMI: body mass index, ART: assisted reproductive technology, SLE: systemic lupus erythematosus, DM: diabetes mellitus

Table 2. Effects of baseline characteristics on PAPP-A MoM in 2011 subjects.

Baseline characteristics	n	PAPP-A MoM: Mean ± SD	p value
BMI (kg/m²)			< 0.001
• < 18.50	266	1.27 ± 0.61	
• 18.50 - 24.99	1,160	1.13 ± 0.59	
• 25 - 29.99	393	0.92 ± 0.47	
• ≥ 30	192	0.81 ± 0.43	
Gravida			0.010
• Nulliparity	921	1.11 ± 0.57	
• Multiparity	1,090	1.04 ± 0.57	
Mode of conception			0.108
• Natural	1,987	1.07 ± 0.57	
• ART	24	1.26 ± 0.77	
Smoking			0.431
• No	2,005	1.07 ± 0.57	
• Yes	6	0.89 ± 0.41	
Hypertension			0.025
• No	1,970	1.08 ± 0.57	
• Yes	41	0.88 ± 0.59	
DM			< 0.001
• No	1,981	1.08 ± 0.57	
• Yes	30	0.66 ± 0.48	
SLE			0.040
• No	2,001	1.07 ± 0.57	
• Yes	10	1.45 ± 0.69	

PAPP-A: pregnancy-associated plasma protein-A, MoM: multiples of median, SD: standard deviation, BMI: body mass index, ART: assisted reproductive technology, DM: diabetes mellitus, SLE: systemic lupus erythematosus

Regarding adverse pregnancy outcomes (Table 3), women with low PAPP-A levels had significantly higher rates of preterm birth (15.8% vs 7.2%), gestational hypertension, and fetal growth restriction (10.8% vs 3.7%). Other adverse pregnancy outcomes were more frequent in the low PAPP-A group but did not reach statistical significance.

Table 3: Adverse pregnancy outcomes in patients with normal versus low PAPP-A levels (< 0.4 MoM).

Pregnancy outcomes	PAPP-A group: Number (%)		RR (95% CI)	p value
	Normal (n = 1891)	Low (n = 120)		
Outcome				< 0.001
Abortion	7 (0.4)	2 (1.7)	4.50 (0.95, 21.44)	
Preterm birth	137 (7.2)	19 (15.8)	2.19 (1.40, 3.40)	
Early preterm (GA < 34)	22 (1.2)	6 (5.0)	4.30 (1.78, 10.40)	
Late preterm (GA ≥ 34)	115 (6.1)	13 (10.8)	1.78 (1.04, 3.07)	
Term	1747 (92.4)	99 (82.5)	0.89 (0.82, 0.97)	
Stillbirth	7 (0.4)	2 (1.7)	4.50 (0.95, 21.44)	0.097
Gestational diabetes mellitus	298 (15.8)	26 (21.7)	1.37 (0.96, 1.96)	0.088
Gestational hypertension	101 (5.3)	15 (12.5)	2.34 (1.41, 3.90)	0.001
Preeclampsia	16 (0.8)	2 (1.7)	1.97 (0.46, 8.47)	0.292
Fetal growth restriction	70 (3.7)	13 (10.8)	2.93 (1.67, 5.14)	< 0.001

MoM: multiples of median, PAPP-A: pregnancy-associated plasma protein-A, RR: relative risk, CI: confidence interval, GA: gestational age

Table 4 presents the diagnostic performance of various PAPP-A cutoff points for predicting preterm birth, gestational hypertension, and fetal growth restriction. Using the 0.4 MoM threshold, the sensitivity, specificity, NPV, and PPV for predicting preterm birth were 12.18%, 94.64%, 92.72%, and 16.10%, respectively. Higher cutoff values led to increased sensitivity, while specificity and PPV declined, while NPV remained relatively stable. Among all adverse pregnancy outcomes, fetal growth restriction showed the highest NPV and lowest PPV, followed by gestational hypertension and preterm birth. Nevertheless, Youden's index was notably low among all cutoff values.

Table 4. Diagnostic performance of PAPP-A MoM in predicting preterm birth, gestational hypertension, and fetal growth restriction.

Pregnancy outcomes	PAPP-A (MoM)	Percent				
		Sensitivity	Specificity	Youden's index	NPV	PPV
Preterm birth	< 0.4	12.2	94.6	6.8	92.7	16.1
	< 0.5	19.9	88.9	8.8	92.9	13.2
	< 0.6	26.9	82.2	9.1	93.0	11.4
	< 0.7	38.5	74.3	12.8	93.5	11.2
	< 0.8	46.2	65.3	11.5	93.5	10.1
	< 0.9	55.8	56.8	12.6	93.8	9.8
	< 1.0	64.1	48.8	12.9	94.1	9.6
Gestational hypertension	< 0.4	12.9	94.5	7.4	94.7	12.5
	< 0.5	18.1	88.6	6.7	94.6	8.9
	< 0.6	28.4	82.0	10.4	94.9	8.8
	< 0.7	36.2	73.7	9.9	95.0	7.8
	< 0.8	44.8	64.8	9.6	95.0	7.2
	< 0.9	55.2	56.4	11.6	95.4	7.2
	< 1.0	62.1	48.2	10.3	95.4	6.8
Fetal growth restriction	< 0.4	15.7	94.5	10.2	96.3	10.8
	< 0.5	21.7	88.6	10.3	96.3	7.6
	< 0.6	26.5	81.7	8.2	96.3	5.9
	< 0.7	33.7	73.4	7.1	96.3	5.2
	< 0.8	43.4	64.6	8.0	96.4	5.0
	< 0.9	53.0	56.1	9.1	96.5	4.9
	< 1.0	59.0	47.9	6.9	96.5	4.7

PAPP-A: pregnancy-associated plasma protein-A, NPV: negative predictive value, PPV: positive predictive value

The ROC curves for predicting preterm birth, gestational hypertension and fetal growth restriction using PAPP-A levels are shown in Figure 2. The AUROC values were 0.597 for preterm birth, 0.578 for gestational hypertension, and 0.585 for fetal growth restriction, respectively.

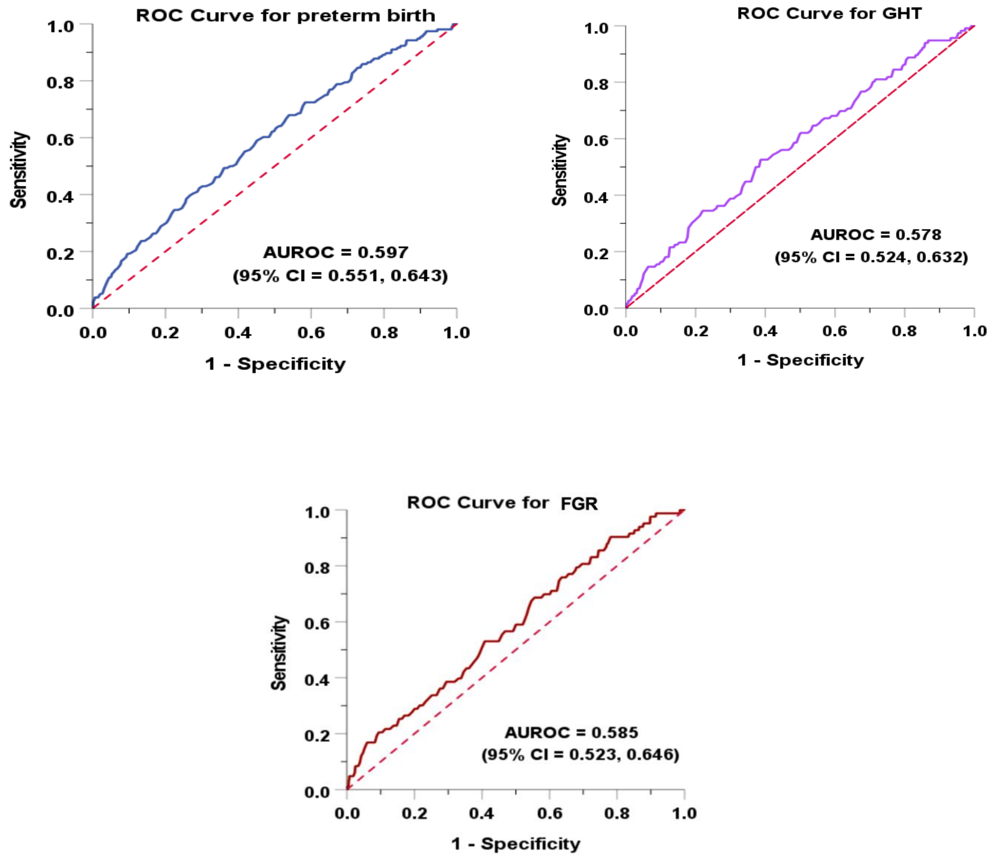

Fig. 2. Receiver operating characteristic (ROC) curves for low PAPP-A (< 0.4 MoM) in predicting preterm birth, gestational hypertension, and fetal growth restriction

PAPP-A: pregnancy-associated plasma protein-A, MoM: multiples of median

Discussion

This study demonstrated a significant association between low PAPP-A levels (< 0.4 MoM) and adverse pregnancy outcomes, specifically preterm birth, gestational hypertension, and fetal growth restriction. There was no obvious optimal cutoff point to define low PAPP-A levels in this study.

PAPP-A is an IGFBP protease leading to the release of IGF which is paramount in fetal growth[51] through the process of trophoblast invasion, regulation of glucose and amino acid transport in chorionic villi[52]. If this process occurs abnormally, it is associated with miscarriage, fetal growth restriction, pregnancy-induced hypertension, stillbirth, preterm birth, and cesarean section due to either fetal or maternal compromise[4]. Consequently, low PAPP-A level will be inadequate to cleave IGF, then IGF will remain in an inactive bound form causing poor fetal and placental growth ending up with adverse pregnancy outcomes[4, 7].

Pregnant women in the low PAPP-A group tended to have a higher BMI, consistent with findings from previous studies[35, 37]. Lower PAPP-A levels observed in earlier gestational ages were also in line with studies showing the trend of rising PAPP-A levels throughout pregnancy[1, 2]. Additionally, medical conditions, such as diabetes mellitus and hypertension were associated with reduced PAPP-A levels, likely reflecting poor placental growth and lower PAPP-A levels. These associations, particularly the link between diabetes mellitus and PAPP-A levels has been reported in prior research[37]. Similarly, smokers and multiparous women had lower PAPP-A levels, as shown in previous studies[37]; however, the small number of smokers in our cohort may have limited statistical significance.

In contrast to earlier studies, we found no significant association between mode of conception and PAPP-A levels, which was different from a previous study that showed that women who conceived with assisted reproductive technology (ART) had lower PAPP-A levels, with increases observed in the third trimester (IVF pregnancies)[37]. This could be due to a small number of ART cases leading to inadequate power for detection.

Regarding adverse pregnancy outcomes, low PAPP-A levels were strongly associated with preterm birth, aligning with previous studies that used cutoff values ranging from 0.35-0.59 MoM[4, 10, 11, 14-19, 25-27, 29]. Notably, this association remained consistent when only studies using the 0.4 MoM threshold were considered. Likewise, increased incidences of gestational hypertension and fetal growth restriction in the low PAPP-A group were consistent with prior findings[4, 11, 13, 14, 16, 17, 24, 25, 28, 29]. However, some studies found a higher occurrence of gestational hypertension in women with low PAPP-A without reaching statistical significance[12, 23, 31, 32], which may be due to differing cutoff definitions or the grouping of gestational hypertension and preeclampsia into a single outcome. Although miscarriage was more frequent among women with low PAPP-A levels in our study, the association was not statistically significant, in line with findings reported of another study[23]. This contrasted with the results of Movahedi et al[8], who reported a significant link between low PAPP-A levels and miscarriage, possibly due to a larger proportion of miscarriages in their sample. Lata et al[25] conversely found a higher rate of miscarriage in normal PAPP-A level group, however, there was only one miscarriage case in that group and the definition of miscarriage was based on ACOG guideline using a diagnostic cutoff point of 24 weeks' gestation. A similar trend was observed in stillbirths: while rates were higher in the low PAPP-A group, the difference was not statistically significant, echoing the results of previous studies[14, 29]. However, a contrasting outcome was reported in another Thai study, where a stronger association was likely influenced by a higher incidence of stillbirth in their population[11].

Our study found no significant association between low PAPP-A levels and gestational diabetes mellitus, despite a higher incidence of adverse outcomes — consistent with prior studies[14, 25]. This contrasted with previous studies[30-34] that demonstrated a significant link possibly due to the inhibitory effect of low PAPP-A on IGF-1, impairing glucose homeostasis and increasing insulin resistance. However, these studies used a much higher cutoff point of 0.995 MoM. Preeclampsia was observed approximately twice as common in the low PAPP-A group, though the difference did not reach statistical significance which could be explained by a small number of cases due to insufficient sample size. Similar findings have been reported in other studies as well[23, 28, 33], while several other studies found a significant association[8, 9, 11-13, 16, 17, 20, 29].

This study clearly demonstrated that all obstetric complications were higher in women with low PAPP-A levels, even when statistical significance was not achieved in some cases, likely due to limited sample size for certain outcomes.

When evaluating the predictive performance of low PAPP-A levels (cutoff 0.4 MoM), the test showed poor accuracy for predicting preterm birth, gestational hypertension, and fetal growth restriction. This aligned with a previous study[16], which reported AUROC values around 0.6 for both preterm delivery and small-for-gestational-age (SGA) infants, although SGA was defined as weight < 5th percentile which was lower than in our study. Likewise, Goetzinger et al reported an AUROC of 0.63, using a cutoff of 0.59 MoM for predicting preterm birth before 35 weeks. Dane et al[18], however, reported better predictive performance (AUROC = 0.74) for preterm delivery using a lower cutoff point of 0.35 MoM and defining preterm birth as delivery before 34 weeks.

Given that PAPP-A levels tend to be higher among Asian populations compared to Caucasians, our study also explored alternative cutoff points to determine whether higher cutoff ones would be of value. Although previous Thai studies used 0.53 MoM as the threshold(11, 15), different PAPP-A values were observed among different regions(40-42). Nonetheless, there was no obvious optimal cutoff point for defining low PAPP-A levels in predicting adverse pregnancy outcomes in this study based on Youden's index.

A key strength of this retrospective study was the large and adequate sample size, allowing for robust analysis of the primary outcome. In addition, there was no missing data, making the conclusion reliable. To our knowledge, this is the first study to evaluate various higher PAPP-A cutoff points to identify the optimal threshold in a Thai population. However, some limitations were observed. The sample size may have been insufficient to detect significant associations between low PAPP-A level and adverse pregnancy outcomes. Additionally, women with low PAPP-A levels in this study were not classified by the presence or absence of known risk factors for preterm birth, which may have influenced the results. Preterm birth cases were not categorized into spontaneous and indicated as well. Also, a small number of women (7.3%) were followed-up by a telephone interview so the obtained adverse pregnancy outcomes especially pregnancy-induced hypertension may be less reliable giving rise to lower-than-expected prevalence of preeclampsia in this study. Moreover, gestational diabetes mellitus diagnosis was based on two diagnostic criteria which might affect the prevalence rate of both groups in our study.

Since this study is based on a PAPP-A level serum marker, its use in clinical management is limited since there are a lot of other risk factors for adverse pregnancy outcomes. Therefore, it cannot replace current screening tools such as those used for preeclampsia risk. However, PAPP-A could serve as an early marker for guiding further follow-up for preterm birth, gestational hypertension, and fetal growth restriction, especially among those without other risk factors for developing adverse outcomes. Future research should stratify women by risk profile to accurately assess independent impact of low PAPP-A on specific pregnancy complications.

Conclusion

Low PAPP-A levels were associated with an increased risk of preterm birth, gestational hypertension, and fetal growth restriction. However, the overall predictive performance was limited so PAPP-A should not be used as the sole indicator for clinical decision-making.

Potential conflicts of interest

The authors declare no conflicts of interest.

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