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Original Research Article

## Serum PAPP-A and uterine artery Doppler as predictors of preeclampsia

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### ABSTRACT

**Background:** Preeclampsia (PE) is a disorder that happens during pregnancy. It is marked primarily by symptoms such as high blood pressure and problems with organs that develop after 20 weeks of gestation. Recently, biomarkers like pregnancy-associated plasma protein A (PAPP-A) and uterine artery Doppler pulsatility index (PI) have been identified as new predictors of PE because they reflect the condition and throughput of the placenta. Therefore, the goal of this research was to determine how accurate maternal serum PAPP-A levels and uterine artery PI predict PE when used not only separately but also together.

**Methods:** This prospective cohort study was carried out in Department of Obstetrics and Gynecology and the Fetal-Maternal Medicine Department of Bangladesh Medical University (BMU) Dhaka during January 2024 to December 2024. The sample of the study consisted of 99 pregnant women who visited outpatient departments, their gestational age was between 12 and 20 weeks and they were normotensive. Statistical analysis was done through SPSS version 26.0. The association between PAPP-A levels and the development of PE, which was illustrated through odds ratios (ORs) with 95% confidence intervals (CIs), and a p-value less than 0.05 was regarded as statistically significant.

**Results:** ROC analysis showed that PAPP-A has moderate predictive ability for preeclampsia, with an AUC of 0.742 (95% CI:0.638-0.846, p=0.03). A cut-off value of  $\geq 0.55$  yielded good sensitivity (72.73-81.82%) and moderate specificity (68.18%), with a high negative predictive value (95.24-95.28%) but low positive predictive value (22.22%) and overall accuracy of 68.69%. Most PE cases (8 of 11) occurred in participants with PAPP-A  $< 0.55$ , supporting its role as a predictor. Similarly, elevated uterine artery PI ( $\geq 1.61$ ) was observed in 7 of 11 PE cases and showed high specificity (93.18%), high negative predictive value (95.35%), moderate sensitivity (63.64%), and overall accuracy of 89.90%, indicating a strong association between increased PI and the development of preeclampsia.

**Conclusions:** Low PAPP-A and high uterine artery PI show solid early signs of preeclampsia. Tracking these markers in first trimester pregnancies helps spot at-risk women. Early detection allows actions to be taken before complications arise. Interventions can reduce harm to mother and baby. The data supports real-time risk assessment without waiting for symptoms to appear.

**Keywords:** Serum PAPP-A, Uterine artery doppler, Preeclampsia

### INTRODUCTION

It starts with high blood pressure after 20 weeks, systolic at 140 mmHg or higher, diastolic at 90 mmHg or higher -

and protein in the urine or signs of organ damage. Now, this condition comes from too much inflammation in the mother's body and poor function of blood vessel lining.<sup>1,2</sup> At least in theory, it affects 8.5 million women globally

and accounts for 2, 8% of pregnancy problems. PE is second only to postpartum bleeding as a cause of maternal death, killing over 50,000 women each year.<sup>3-5</sup> Rates are in particular high among African-American and hispanic women. In developing countries, incidence is seven times greater than in rich nations. Bangladesh sees about 14.4% of pregnancies affected, with roughly 10% developing PE after 20 weeks without prior hypertension.<sup>6-8</sup> Solid complications include placental abruption, brain bleeding, blood clotting issues, early birth, and baby death. Even though its pathophysiology cannot be determined with certainty, impaired trophoblastic invasion and differentiation, oxidative stress, systemic inflammation autoantibodies platelet and thrombin activation, endothelial dysfunction as well as anti-angiogenic states have been identified.<sup>9-11</sup> Uterine artery doppler velocimetry (a screening method) measures pulsatility index (PI) between 12-20 weeks of gestation and is helpful in spotting impaired placental perfusion, with PI greater than the 95th percentile indicating the heightened probability of preeclampsia (PE).<sup>12,13</sup> Changes in the maternal serum, such as drops in pregnancy-associated plasma protein A (PAPP-A), which is a large glycosylated protein secreted by trophoblasts, are also great indicators; PAPP-A that is low represents placental malfunction and ischemia that lead to PE development via the release of anti-angiogenic and pro-inflammatory factors.<sup>2,14</sup>

In consequence, a combination of uterine artery PI Doppler assessment and early measurement of PAPP-A provides a very effective method for early recognition of women who are likely to develop preeclampsia. Low levels of PAPP-A promote the pathogenesis of preeclampsia by stimulating the release of bioactive substances that cause damage to maternal blood vessels, resulting in hypertension and organ complications.<sup>15</sup> Regulating insulin-like growth factors, PAPP-A influences fetal growth and placental development. Reduced levels weaken IGF signaling, raising the chance of preeclampsia. Clinically, low PAPP-A stands out as a key sign for PE risk, leading to more frequent checks and focused prenatal care. The rise of PE comes from many factors - no single cause fits all cases. Recent reviews stress the need for strong prospective studies on predictive tools: clinical signs, blood tests, and ultrasound readings, used separately or together with different levels of accuracy.<sup>16</sup> It seems hard to ignore that women with PE often have low serum PAPP-A and high uterine artery pulsatility index on doppler scans. Combining both markers improves early detection of preeclampsia.

## METHODS

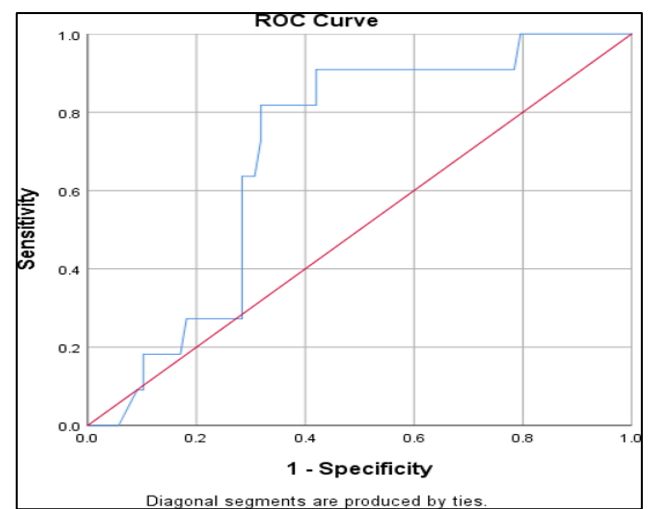
This prospective cohort study took place in the obstetrics and gynecology and fetal-Maternal Medicine departments at Bangladesh Medical University in Dhaka, from January to December 2024, after receiving IRB approval. Pregnant women visiting outpatient clinics between 12 and 20 weeks gestation who were normotensive made up the study group. A total of 99 women were chosen through

purposive sampling based on availability and meeting inclusion criteria: singleton live pregnancies, no proteinuria, and written consent. Women with chronic hypertension, diabetes, kidney disease, autoimmune conditions, pregnancy complications like PROM or chorioamnionitis, placenta previa, abruptio placentae, intrauterine fetal death, unexplained IUGR, or known fetal abnormalities were excluded. At enrollment, five milliliters of venous blood was drawn to check serum PAPP-A levels. Uterine artery doppler was performed by the same person to evaluate the pulsatility index this probably gives a clearer picture of vascular resistance during early pregnancy.

Participants followed the WHO antenatal care timeline to monitor for preeclampsia. It seems hard to ignore that lower PAPP-A and higher uterine artery PI are linked to the condition. Those with reduced serum PAPP-A and elevated PI were grouped separately from those with normal levels. Data analysis used SPSS 26.0, with results shown as mean (SD), median (IQR), or percentages. Pearson chi-square tested categorical data, t-tests handled continuous variables. Logistic regression found odds ratios for PAPP-A and PE development, with 95% CIs reported. A p-value under 0.05 marked importance. Thing is, the model does not account for comorbidities in all cases.

## RESULTS

The majority of participants in both groups were aged 26-34 years and were predominantly housewives. Most had a BMI within the normal to overweight range (18.5-29.9 kg/m<sup>2</sup>), with slightly higher obesity observed in the high PI group.



**Figure 1: Receiver operator characteristics (ROC) curve of PAPP-A to predict PE.**

However, no statistically significant differences were found between the groups regarding age, occupation, or BMI ( $p > 0.05$ ). Most participants in both groups were multigravida, with similar proportions of primigravida. The majority had no family history of preeclampsia, and

the mean gestational age was comparable between groups. No statistically significant differences were observed between Normal and Low PAPP-A groups in terms of gravidity, family history of PE, or duration of pregnancy

( $p>0.05$ ). The majority of participants in both groups were multigravida, with comparable proportions of primigravida.

**Table 1: Sociodemographic and obstetric characteristics of study subjects according to PAPP-A level and uterine artery PI (n=99).**

Variables	Categories	Normal PAPP-A N (%)	Low PAPP-A N (%)	P value	Normal uterine artery PI N (%)	High uterine artery PI N (%)	P value
Age (years)	18-25	—	—	—	32 (37.2)	4 (30.8)	0.55 <sup>a</sup>
	26-34	—	—	—	49 (57.0)	9 (69.2)	
	35-40	—	—	—	5 (5.8)	0 (0.0)	
Occupation	Housewife	—	—	—	55 (64.0)	10 (76.9)	0.54 <sup>a</sup>
	Student	—	—	—	17 (19.8)	1 (7.7)	
	Service	—	—	—	14 (16.3)	2 (15.4)	
BMI (kg/m <sup>2</sup> )	<18.5	—	—	—	8 (9.3)	0 (0.0)	0.63 <sup>a</sup>
	18.5-24.9	—	—	—	35 (40.7)	5 (38.5)	
	25-29.9	—	—	—	30 (34.9)	5 (38.5)	
	≥30	—	—	—	13 (15.1)	3 (23.1)	
Gravidity	Primi	23 (34.3)	12 (37.5)	0.75 <sup>a</sup>	30 (34.9)	5 (38.5)	0.80 <sup>a</sup>
	Multi	44 (65.7)	20 (62.5)		56 (65.1)	8 (61.5)	
Family history of PE	Yes	7 (10.4)	2 (6.3)	0.49 <sup>a</sup>	7 (8.1)	2 (15.4)	0.39 <sup>a</sup>
	No	60 (89.6)	30 (93.8)		79 (91.9)	11 (84.6)	
Duration of pregnancy (weeks)	Mean±SD	18.90±2.04	18.56±4.75	0.70 <sup>c</sup>	18.90±3.06	18.08±3.79	0.38 <sup>c</sup>

<sup>a</sup> Chi-square test; <sup>c</sup> Independent t-test; PE=Preeclampsia; NS=Non-significant.

**Table 2: Distribution of the participants according to biochemical parameters (n=99).**

Variables	Categories	Not developed PE N (%)	Developed PE N (%)	P value
PAPP-A	Normal	63 (94.0)	4 (6.0)	0.01 <sup>a</sup>
	Low	25 (78.1)	7 (21.9)	
Uterine artery PI	Normal	82 (95.3)	4 (4.7)	0.001 <sup>a</sup>
	High	6 (46.2)	7 (53.8)	

<sup>a</sup>Chi-square test; s=significant

**Table 3: Univariate logistic regression of risk factors for preeclampsia.**

Attribute	Categories	Co-efficient (B)	S. E.	OR	95% CI (lower-upper)	P value
PAPP-A	<0.5	1.48	0.670	4.41	1.18-16.39	0.02 <sup>s</sup>
	≥0.5**	—	—	Reference	—	
Uterine artery PI	≥1.61	3.17	0.756	23.91	5.43-105.27	0.001 <sup>s</sup>
	<1.61**	—	—	Reference	—	

\*\*Reference category; s=significant.

Most participants had no family history of preeclampsia, although a slightly higher prevalence was observed in the high PI group. The mean gestational age was similar between groups. Overall, no statistically significant differences were found between normal and high uterine artery PI groups regarding gravidity, family history of PE, or duration of pregnancy ( $p>0.05$ ) (Table 1). Low PAPP-A levels and high uterine artery PI were significantly associated with the development of preeclampsia.

Participants with low PAPP-A showed a higher proportion of PE compared to those with normal levels, while more than half of those with high uterine artery PI developed PE. These associations were statistically significant ( $p<0.05$ ) (Table 2). Univariate logistic regression analysis showed that both low PAPP-A (<0.5) and elevated uterine artery PI (≥1.61) were significant predictors of preeclampsia. Low PAPP-A increased the odds of developing PE by 4.41 times (95% CI:1.18-16.39; $p=0.02$ ), while high uterine

artery PI demonstrated a markedly stronger association, increasing the odds by 23.91 times (95% CI:5.43-105.27; p=0.001) (Table 3). ROC analysis of PAAP-A to predict PE, with an AUC value of 0.742 (95% CI 0.638-0.846), which was statistically significant (p value:0.03) (Table 4).

PAPP-A demonstrated moderate predictive ability for preeclampsia, with an AUC of 0.69 that was statistically significant (p=0.03).

**Table 4: Area under curve (AUC) of PAPP-A to predict preeclampsia.**

Parameters	Values
Area under the curve (AUC)	0.69
Standard error	0.067
P value	0.03
95% CI (lower-upper)	0.567-0.828

A cut-off value of  $\geq 0.55$  yielded good sensitivity (81.82%) and moderate specificity (68.18%), with high negative predictive value (95.28%) but low positive predictive value (22.22%). Overall diagnostic accuracy was 68.69% (Table 5).

**Table 5: Determination of cut-off value of PAPP-A using Youden index.**

Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
$\geq 0.55$	81.82	68.18	22.22	95.28	68.69

**Table 6: Cross-tabulation of preeclampsia (PE) with PAPP-A based on cut-off value.**

PAPP-A	PE developed (N)	Not developed (N)	Total
<0.55	8	28	36 (TP+FP)
$\geq 0.55$	3	60	63 (FN+TN)
<b>Total</b>	11 (TP+FN)	88 (FP+TN)	99

**Table 7: Diagnostic performance of PAPP-A cut-off for predicting preeclampsia (PE).**

Statistics	Values (%)	95% confidence interval
Sensitivity	72.73	39.03-93.98
Specificity	68.18	57.39-77.71
PPV	22.22	15.10-31.45
NPV	95.24	88.29-98.15
Accuracy	68.69	58.59-77.64

PPV=Positive predictive value; NPV=Negative predictive value.

The combination of low PAPP-A and high uterine artery PI demonstrated strong diagnostic performance for predicting preeclampsia.

Among 71 participants, 7 of 11 PE cases were correctly identified (true positives), while 3 participants were false positives. The test showed a sensitivity of 63.6% and a high

Most cases of preeclampsia were observed among the participants with lower PAPP-A values. Specifically, 8 out of 11 PE cases had PAPP-A levels below 0.55, indicating that reduced PAPP-A is associated with a higher likelihood of developing preeclampsia. This supports the role of low PAPP-A as a potential predictor for PE (Table 6). The derived cut-off value of PAPP-A demonstrated moderate diagnostic performance in predicting preeclampsia, with a sensitivity of 72.73% and specificity of 68.18%. The test showed a high negative predictive value (95.24%), indicating good ability to rule out PE, while the positive predictive value was low (22.22%).

Overall accuracy was 68.69% (Table 7). A higher proportion of preeclampsia cases was observed among participants with uterine artery PI  $\geq 1.61$ . Specifically, 7 out of 11 PE cases had elevated PI values, indicating a strong association between increased uterine artery PI and the development of preeclampsia (Table 8). The derived cut-off of uterine artery PI ( $\geq 1.61$ ) demonstrated high specificity (93.18%) and a high negative predictive value (95.35%) for predicting preeclampsia. Although sensitivity was moderate (63.64%), the overall accuracy was 89.90% (Table 9).

specificity of 95.0%, indicating excellent ability to correctly identify women without PE. The positive predictive value was 70.0%, and the negative predictive value was 93.4%, reflecting strong reliability in ruling out PE when results were normal (Table 10).

**Table 8: Cross-tabulation of preeclampsia (PE) with uterine artery PI based on cut-off value.**

Uterine artery PI	PE developed (N)	PE not developed (N)	Total
$\geq 1.61$	7	6	13 (TP+FP)
<1.61	4	82	86 (FN+TN)
<b>Total</b>	11 (TP+FN)	88 (FP+TN)	99

**Table 9: Diagnostic performance of uterine artery PI cut-off for predicting preeclampsia (PE).**

Statistics	Values (%)	95% confidence interval
Sensitivity	63.64	30.79-89.07
Specificity	93.18	85.75-97.45
PPV	53.85	32.34-74.01
NPV	95.35	90.35-97.82
Accuracy	89.90	82.21-95.05

PPV=Positive predictive value; NPV=Negative predictive value.

**Table 10: Diagnostic performance of combined low PAPP-A and high uterine artery PI in predicting preeclampsia (n=71).**

Test results	PE developed (N)	Not developed (N)	Total
<b>Abnormal (low PAPP-A+ high PI)</b>			
	7 (TP)	3 (FP)	10
<b>Normal</b>	4 (FN)	57 (TN)	61
<b>Total</b>	11	60	71
<b>Diagnostic measure</b>	Value	95% confidence interval	
<b>Sensitivity</b>	63.6%	30.79-89.07%	
<b>Specificity</b>	95.0%	86.07-98.95%	
<b>Positive predictive value (PPV)</b>	70.0%	41.51- 88.46%	
<b>Negative predictive value (NPV)</b>	93.4%	86.67-96.89%	
<b>Accuracy</b>	90.1%	80.73-95.94%	

## DISCUSSION

In this study, the majority of participants in both PAPP-A and uterine artery PI groups were aged 26–34 years, with smaller proportions in the 18–25 and 35–40 age brackets, and no statistically significant differences were observed ( $p$  values 0.55-0.58). Housewives formed the largest occupational group in both cohorts, with students and service workers less represented, again without significant differences ( $p=0.54-0.88$ ).

Regarding BMI, most participants fell within 18.5-24.9 or 25-29.9, with higher BMI ( $\geq 30$ ) slightly more frequent in the high PI group; differences were not statistically significant ( $p=0.07$ ), suggesting potential trends for further exploration. In terms of obstetric history, 34.3% of the Normal PAPP-A group and 37.5% of the Low PAPP-A group were experiencing their first pregnancy, with no significant difference ( $p=0.75$ ).

Similarly, 34.9% of the normal PI group and 38.5% of the high PI group were primigravida ( $p=0.80$ ). Family history of preeclampsia (PE) was reported in a minority of participants across all groups (Normal PAPP-A 10.4%, Low PAPP-A 6.3%, Normal PI 8.1%, High PI 15.4%), with no significant differences ( $p=0.39-0.49$ ).

Mean gestational age was comparable among groups (Normal PAPP-A 18.90 $\pm$ 2.04 weeks vs. Low 18.56 $\pm$ 4.75 weeks, Normal PI 18.90 $\pm$ 3.06 vs. High 18.08 $\pm$ 3.79 weeks), showing no statistical significance. The overall age distribution in this study showed 36.4% aged 18-25, 58.6%

aged 26-34, and 5.1% aged 35-40. This is comparable to Das et al, who reported 38.8% of women aged 26-30, 2.8% aged 18-20, and 2.8% aged 36–40.<sup>17</sup> Education levels were mainly primary (33.3%) or higher secondary (32.3%), similar to Das et al, where 35.9% had higher secondary education.<sup>17</sup> Most participants were housewives (65.7%), with students (18.2%) and service workers (16.2%), consistent with Das et al's findings of 75.3% homemakers.

Regarding income, most participants earned over 25,000 BDT (87.9%), with smaller proportions earning 10,000–25,000 BDT (10.1%) or below 10,000 BDT (2%). Primigravida participants constituted 35.4%, while 64.6% were multigravida, differing slightly from Das et al (65.5% primiparous, 34.5% multiparous), potentially due to higher multiparous attendance at outpatient clinics.<sup>17</sup>

A small proportion had a family history of PE (9.1%), comparable to Yücel et al (12.2% in PE group, 2.9% in controls).<sup>18</sup> BMI distribution in our study was 40.4% within 18.5–24.9 and 35.4% within 25–29.9, similar to Youssef et al, who reported 25.4 $\pm$ 3.1 in PE and 22.3 $\pm$ 2.4 in non-PE participants.

The study found statistically significant differences in mean PAPP-A levels and uterine artery PI between PE and non-PE groups. This contrasts with Yıldırım Köpük et al, who reported no significant difference in PAPP-A but significantly higher PI in the preeclamptic group ( $p=0.023$ ).<sup>19</sup>

In predicting PE, first-trimester PAPP-A levels demonstrated 72.73% sensitivity with 22.22% positive predictive value (PPV), comparable to literature reporting 23–51.7% sensitivity.<sup>20-22</sup>

For uterine artery PI, a cutoff of 1.61 (90th percentile) yielded 63.64% sensitivity, 93.18% specificity, and 89.90% overall accuracy. Yücel et al reported 63.41% sensitivity and 53.06% PPV for PAPP-A and 70.73% sensitivity, 95.32% specificity, and 58% PPV for PI at the 90th percentile.<sup>18</sup> These findings support the combined use of low PAPP-A and elevated uterine artery PI as a reliable early predictor of preeclampsia in high-risk pregnancies.

## Limitations

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

## CONCLUSION

In conclusion, the study highlights the low level of PAPP-A and high PI of the uterine artery doppler as potential biomarkers for predicting PE. These findings suggest that early monitoring of these parameters could be beneficial in identifying pregnant women at risk for PE, allowing for timely interventions to mitigate adverse outcomes.

## Recommendations

Given the significant association between low PAPP-A levels ( $<0.55$ ) and a high pulsatility index (PI) of the uterine artery ( $\geq 1.61$ ) with an increased risk of developing preeclampsia (PE), it is recommended that these markers be included in routine screening protocols for pregnant women, particularly during the first trimester. Women identified with low PAPP-A or elevated uterine artery PI should be considered high-risk and require close monitoring throughout pregnancy. Additionally, larger studies with increased sample sizes and diverse population subsets from different geographical regions of the country are needed to further validate and strengthen these findings.

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