

Original research article

Maternal Pregnancy Associated Plasma Protein A And Uterine Artery Doppler In Prediction Of Preeclampsia

Shreya Thind¹, Ripan Bala², Sangeeta Pahwa³¹ Resident, Department of Obstetrics and Gynaecology, SGRDUHS, Amritsar² Professor, Department of Obstetrics and Gynaecology, SGRDUHS, Amritsar³ Professor and Head, Department of Obstetrics and Gynaecology, SGRDUHS, Amritsar

Corresponding author: Shreya Thind

Email : shreya126a@gmail.com

ABSTRACT

Introduction: Preeclampsia is a multisystem disorder and is a major contributor of maternal and perinatal morbidity and mortality. Identifying women, who are at risk is important to prompt gestational management. Uterine artery waveform and biomarkers like pregnancy-associated plasma protein-A (PAPP-A) may reflect the pathophysiology of preeclampsia.

Aim: We aim to find out whether abnormal uterine artery pulsatility index (PI) and low serum PAPP-A in the first trimester can be used to predict preeclampsia.

Material And Methods: Antenatal women at 11-13⁺⁶ weeks of gestation visiting Sri Guru Ram Das University Of Health And science, Amritsar were enrolled after informed consent. Uterine artery Doppler was done with the early anomaly scan at 11-13⁺⁶ weeks. Serum levels of PAPP-A were analyzed. The women were followed up at intervals up to delivery. Incidence of preeclampsia was noted.

RESULTS: The incidence of preeclampsia was 26%. The mean uterine artery PI among those who developed preeclampsia was 2.03, which was significantly higher than the unaffected group (p=0.001). The first-trimester uterine artery PI as a screening tool showed a sensitivity of 84.67% and specificity of 75.68%. The mean PAPP-A MoM of the affected group was 0.91 which was lower than the unaffected group (p=0.028). The first trimester PAPP-A as a screening tool showed a sensitivity of 15.38%, specificity of 91.89%.

Conclusion: Both the tests were concluded to be good predictors of preeclampsia. Identification of high-risk factors, screening, and surveillance are important for timely prediction of preeclampsia and initiation of preventive therapy.

Keywords: Prospective study, preeclampsia, uterine artery Doppler, PAPP-A.

INTRODUCTION

Pre-eclampsia (PE) is a pregnancy-specific syndrome that can affect virtually every organ system. It affects 5-10% of pregnancies worldwide and 4.6% of pregnancies in India¹. It forms a member of the deadly triad, along with haemorrhage and infection that contribute greatly to maternal morbidity and mortality (14% of maternal deaths worldwide and 29.54% of maternal deaths in India^{2,3}).

Studies have shown that defective trophoblastic invasion of the placenta plays a crucial role in the pathogenesis of preeclampsia. This leads to incomplete spiral artery remodeling and increased resistance to flow in the uteroplacental unit, which is transmitted upstream to the uterine arteries⁴. This results in an increased pulsatility index (PI). Thus, uterine artery Doppler waveform analysis has the potential to predict pregnancy complications associated with uteroplacental insufficiency before the onset of clinical features⁵.

Poor placentation is associated with an imbalance of circulating vasoactive factors and, in turn, leads to maternal vascular maladaptation with associated systemic endothelial dysfunction. Placental products are released as part of the placentation process. Levels of these biochemical markers reflect the pathophysiology of defective placentation, and, as a result are assuming an increasing role in early gestation screening tests for later pregnancy complications. PAPP-A (pregnancy associated plasma protein A) is a protease for insulin like growth factor binding protein-4 (IGFBP-4). The expression and secretion of PAPP-A increase during differentiation of villous cytotrophoblasts to syncytiotrophoblasts⁶. A low level of PAPP-A is associated with higher IGFBP-4 and lower free Insulin like growth factor (IGF). IGF is known to influence fetal growth by controlling uptake of amino acids and glucose as well as having an autocrine and paracrine role in trophoblast invasion. Maternal serum PAPP-A has been shown to be relatively low in the first trimester of pregnancies complicated by IUGR and/or pre-eclampsia.

Our objective is to find out whether abnormal uterine artery Doppler and/or maternal PAPP-A levels at 11 to 13+6 weeks can predict preeclampsia.

Material And Methods

This was a prospective analytical study done in the Sri Guriu Ram Das University Of Health Sciences(SGRDUHS), Amritsar, after getting approval from the Institute Ethics Committee. The study was conducted from April 2021 to July 2022. The study included all antenatal women attending SGRDUHS out-patient department (OPD) at or before 11-13⁺⁶ weeks gestation, willing to follow-up and give consent for the study.

Total 104 women were enrolled in the study after obtaining the written informed consent and obtaining clearance from ethical committee. Out of these 4 loss to follow up . Thus, a total of 100 study participant's data was subjected for the final analysis

Inclusion Criteria:

1. All pregnant women with spontaneous conception at 11 to 13⁺⁶ weeks of gestation

Exclusion Criteria:

1. Chronic hypertension
2. Multiple pregnancy
3. Molar pregnancy
4. Chromosomal abnormalities of fetus
5. Comorbid condition (diabetes mellitus/renal, cardiovascular and thyroid disorder)
6. Body Mass Index ≥ 30

7. Previous history of pre eclampsia

After taking informed consent for participation in the study, detailed history, a general and systemic examination was done at the first visit. Particulars like age, parity, body mass index (BMI), education, socioeconomic status and residence was noted. After confirming dates and fetal cardiac activity, antenatal women were advised to undergo uterine artery Doppler along with the routine nuchal translucency (NT)/ nasal bone (NB) scan at 11-13⁺⁶ weeks. The uterine artery pulsatility index (UtA-PI) was noted. The values of PAPP-A in multiples of median (MoM) were noted from the dual markers report.

The study population was divided into four groups; the first one being patients with abnormal first-trimester uterine artery Doppler and normal PAPP-A, the second one being patients with abnormal PAPP-A and normal first-trimester uterine artery Doppler, the third one where both investigation results were abnormal, and last those where both investigation results were normal.

Follow-up visits were as follows: once every four weeks until 28 weeks gestation, once every 2 weeks until week 36, and weekly until week 40 or until delivery. In each follow-up visit, the blood pressure and urine dipstick was noted. Diagnosis and definition of preeclampsia was made as per the American College of Obstetricians and Gynecologists (ACOG) 2013 criteria⁶.

Statistical Analysis:

Statistical analyses were performed using a Statistical Package for Social Sciences software (SPSS) version 22. Student t-test (independent t-test) was applied to compare the PAPP-A MoM and UtA-PI between the normotensive and those who developed hypertensive disorders.

The Chi-square test was applied to see the association between outcome and demographic characteristics. The Receiver Operating Curve (ROC) was constructed for PAPP-A MoM and UtA-PI values.

For all statistical analyses, $p < 0.05$ was considered significant, and $p < 0.001$ was considered highly significant.

Results:

After considering the inclusion and exclusion criteria, 104 women were enrolled in the study after taking informed consent. Out of these four were lost to follow-up and were excluded during the analysis of data, and thus a total of 100 women's data were subjected for the final analysis.

Table 1: Distribution of the Study Population According to outcome

Outcome	No. of cases	%age
Normotensive	74	74.0
Preeclampsia	26	26.0
Total	100	100.0

In the present study, 26 out of 100 cases (26%) developed pre eclampsia and 74(74%) were normotensive.

Table 2: Comparison of mean uterine artery PI (first trimester) among hypertensive disorders of preeclampsia and normotensive cases

Outcome	PI	
	Mean	SD
Preeclampsia	2.0335	0.31039
Normotensive	1.4438	0.28950
t-value	-8.761	
p-value	0.001	

PI: pulsatility index, SD: standard deviation

The mean of the first-trimester uterine artery PI values of those developing preeclampsia(2.03) is significantly higher ($p=0.001$) than the mean uterine PI of those who did not (1.44), as shown in Table 2

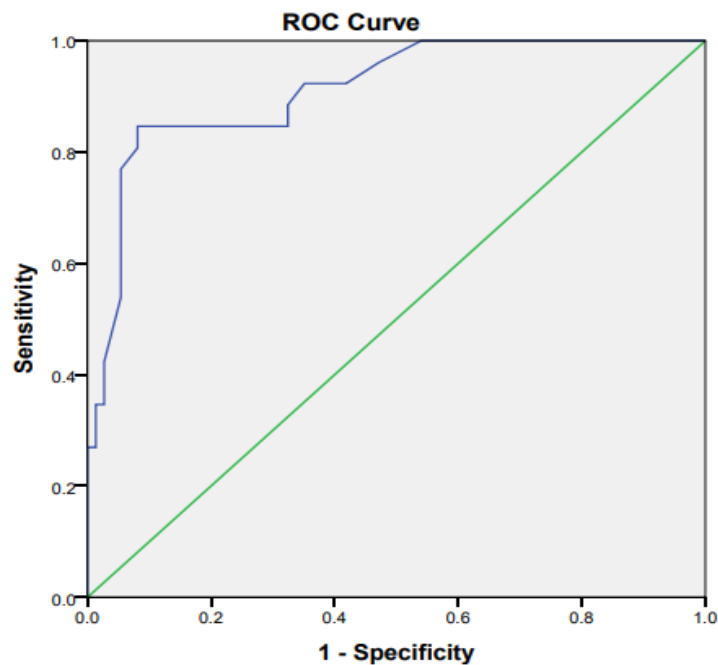


Figure 1: Receiver operator characteristic (ROC) curve of uterine artery pulsatility index. From the receiver operator characteristic curve of uterine artery pulsatility index (Figure 1), the area under the curve was 0.912. The best cut-off that maximized sensitivity and specificity was 1.50. The first-trimester uterine artery PI as a screening tool had a sensitivity

of 84.67%, specificity of 75.68%, positive predictive value (PPV) of 55%, negative predictive value (NPV) of 93.33%, and accuracy of 78%

Table 3: Comparison of mean PAPP-A MoM levels among hypertensive disorders of pregnancy and normotensive

Outcome	PAPP-A	
	Mean	SD
Preeclampsia	0.9188	0.31869
Normotensive	1.0645	0.27476
t-value	2.229	
p-value	0.028	

MoM: Multiples of Median, SD: Standard Deviation, PAPP-A: pregnancy-associated plasma protein-A

The mean first trimester PAPP-A MoM values of those who developed preeclampsia(0.91) was lower than the mean PAPP-A MoM of those who did not (1.06, $p=0.028$) (Table:3).

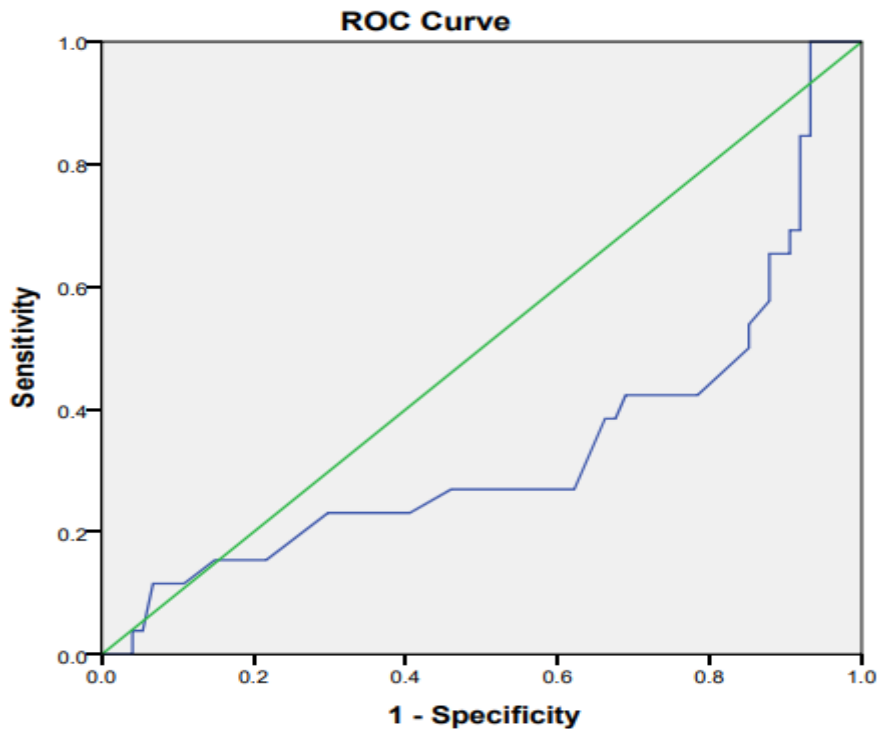


Figure 2: Receiver operator characteristic (ROC) curve for PAPP-A MoM

MoM: Multiples of Median, PAPP-A: pregnancy-associated plasma protein-A

As per the receiver operator characteristic (ROC) curve for PAPP-A MoM (Figure 2), the area under the curve was 0.336. The best cut-off that maximized sensitivity and specificity was 0.5. The first trimester PAPP-A as a screening tool had a sensitivity of 15.38%, specificity of 91.89%, PPV of 40%, NPV of 75.56%, and accuracy of 72%.

Table 4: Comparison of hypertensive disorders of pregnancy among the study groups

Screen characteristics	Outcome				Total	
	Normotensive		Preeclampsia			
	No.	%age	No.	%age	No.	%age
Both abnormal	2	2.70	2	7.69	4	4.00
PI abnormal, PAPP-A normal	16	21.62	20	76.92	36	36.00
PI normal, PAPP-A abnormal	4	5.41	2	7.69	6	6.00
Both normal	52	70.27	2	7.69	54	54.00
Total	74	100.00	26	100.00	100	100.00

X^2 : 31.66; df:3; p=0.001

PI: uterine artery pulsatility index, PAPP-A: pregnancy-associated plasma protein-A

The incidence of preeclampsia was 50% when both the screening parameters were abnormal. The incidence of preeclampsia was 3.7% when both parameters were normal. When combined, their association with preeclampsia was highly significant (p=0.001) (Table 4).

Discussion:

This study has demonstrated an approach for combining biophysical and biochemical parameters in the first-trimester of pregnancy to predict patient-specific risks for subsequent development of hypertensive disorders.

We chose 11 + 0 to 13 + 6 weeks as the gestational age for screening because this is being established as the first hospital visit of pregnant women at which combined sonographic and biochemical testing for chromosomal and other major defects is carried out. At this visit a record is made of maternal characteristics, such as age, ethnic origin, BMI, smoking status and medical and obstetric history; an ultrasound scan is carried out to determine the number of fetuses, confirm the gestation from the fetal CRL, exclude major defects, measure the NT thickness and other first-trimester markers of chromosomal defects; and maternal blood is taken for measurement of free β -hCG and PAPP-A.

Out of the 100 pregnant women included in the study, 26 (26%) developed preeclampsia during pregnancy (table 1) which was comparable to the study done by Sharanya Satish et al ⁷ (24%).

The mean uterine artery PI value among those who developed preeclampsia in pregnancy was 2.03, which was significantly higher than the unaffected group (p=0.001) (Table). Satish et al ⁷, Gomez et al.⁸, and Narang et al.⁹ also had a similar mean PI among the affected group: 2.34, 2.04, and 1.94, respectively.

Goetzinger et al. ¹⁰ did not find any significant difference in uterine artery PI values between affected and unaffected groups.

Uterine artery PI at 11-13⁶ weeks was considered a good predictor for pre eclampsia in pregnancy with a sensitivity of 84.67% and specificity of 75.68 % at a cut-off of 1.50 (as obtained from the ROC curve, Figure 1). A similar cut-off (1.52) was also obtained in a study by Staboulidou et al.¹¹. Narang et al.⁹ conducted a study in Uttar Pradesh, India, and showed similar sensitivity (75.9%) and specificity (79.6%). Similar cut-off(1.48) was also obtained by E das et al.¹² in a study conducted at AIIMS, Raipur, India with sensitivity of 68%, specificity of 52.99%. Sharanya Satish⁷ et al showed Sensitivity and specificity of uterine artery PI in their study as 98% and 31%

At the 95th percentile of uterine artery PI, Martin et al.¹³ and Gomez et al.⁸ showed lower sensitivity (27% and 23.9%, respectively). Goetzinger et al.¹⁰ also showed a lower sensitivity of 52%.

The PPV was 55%, and NPV was 93.33% for uterine artery PI in the screening for preeclampsia, according to this study. Singh et al.¹⁴ conducted a similar study in India with PPV 97.33% and NPV 97.33%. E das¹² et al. showed positive predictive value (PPV) of 23.61%, negative predictive value (NPV) of 88.57% for uterine artery PI in their study.

In this study, the mean PAPP-A MoM of the affected group (preeclampsia) was 0.91 (Table 4), which was comparable to the studies of Goetzinger et al.¹⁰ and Spencer et al.¹⁵ with mean PAPP-A MoM of 0.88 and 0.772.

From the ROC curve (Figure 2), the cut-off value for PAPP-A MoM at 11-13⁶ weeks was 0.5 with a sensitivity of 15.38% and specificity of 91.89% in this study. Staboulidou et al.¹¹ had found a similar cut-off value of PAPP-A MoM at 0.58 for preeclampsia. Zhong et al.¹⁶ showed similar sensitivity and specificity of 16% and 93%, respectively. E das et al.¹² had found a cut off of 0.41 with a sensitivity of 28% and specificity of 90.6% Odibo et al.¹⁷ showed a higher sensitivity of 58% for PAPP-A.

The present study showed PPV of 40% and NPV of 75.56% for PAPP-A. Patil et al.¹⁸ showed a PPV of 52% comparable to our study.

As shown in Table 4, the incidence of preeclampsia is 50 % when both the screening parameters are abnormal. The incidence of preeclampsia becomes respectively in the affected group 3.7% when both the parameters are normal which is comparable to the study done by E Das et al.¹². When combined, their association with preeclampsia is highly significant (p=0.001). Similar observations were made by Staboulidou et al.¹¹ and Satish et al.⁷.

A Pilalis et al.¹⁹ also concluded in their study that the combination of maternal history with abnormal uterine artery Doppler and low PAPP-A level at 11–14 weeks achieves better results than does either test alone in the prediction of pre-eclampsia.

However, according to Odibo et al.¹⁷, the median uterine artery MoM was higher in the group with early preeclampsia; it was not statistically significant. The PAPP-A MoM was significantly lower in the affected group. Thus a combination of all the parameters did not improve the screening capacity.

Poon et al.²⁰ found PAPP-A to be a good predictor of early-onset preeclampsia. There was no significant improvement by the addition of PAPP-A to the combination of maternal factors, mean arterial pressure (MAP), and uterine artery in the prediction of late PE and gestational hypertension. Goetzinger et al.¹⁰ demonstrated that at 11-14 weeks gestation, ADAM12, PAPP-A, and uterine artery Doppler in combination with maternal characteristics identified 50%, 48%, and 52% of patients who developed preeclampsia, respectively. Thus a combination of all the parameters did not improve the predictability.

Conclusion:

Preeclampsia is a life-threatening disorder of pregnancy. Thus early detection of the disease at a low cost is importance. Uterine artery Doppler in the first trimester done along with early anomaly scan at 11-13⁺⁶ weeks has been found to be a good predictor of preeclampsia with moderate sensitivity and specificity. It is convenient and cost-effective to use PAPP-A as a biomarker since PAPP-A levels are routinely checked as a part of aneuploidy screening. It also has a high specificity for preeclampsia screening.

Identification of high-risk factors, screening, and surveillance are of utmost importance in order to predict preeclampsia. Preventive therapy, if initiated early on the basis of these screening tests, will help save the antenatal woman from the complications of preeclampsia.

References :

1. Cunningham FG, Lenovo KJ, Bloom SL, Spong KY, Dashe JS, Hoffman BL, Casey BM, Sheffield JS. Williams Obstetrics. Twenty-Fourth Edition. United States of America: McGraw-Hill Education; 2014.
2. Say L, Chou D, Gemmill A, et al.: Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. 2014, 2:323-33. 10.1016/S2214-109X(14)70227-X
3. Konar H, Chakraborty AB: Maternal mortality: a FOGSI study (based on institutional data). *J Obstet Gynaecol India*. 2013, 63:88-95. 10.1007/s13224-012-0258-1
4. Redman CW, Sargent IL: Placental debris, oxidative stress and pre-eclampsia. *Placenta*. 2000, 21:597-602.
5. Dascau V, Furu G, Furu C, et al.: Uterine artery doppler flow indices in pregnant women during the 11 weeks + 0 days and 13 weeks + 6 days gestational ages: a study of 168 patients. *Maedica (Bucur)*. 2017, 12:36-41.
6. American College of Obstetricians and Gynecologists' Task Force: Hypertension in pregnancy. *Obstet Gynecol*. 2013, 122:1122-31.
7. Satish, Sharanya, et al. "Maternal pregnancy associated plasma protein-A (PAPP-A) and uterine artery Doppler changes as predictors of pre-eclampsia: a prospective observational study from a teaching hospital in Mysore, Karnataka, India." *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*, vol. 8, no. 4, Apr. 2019, pp. 1317
8. O. Gómez, J. M. Martínez, F. Figueras et al., "Uterine artery Doppler at 11-14 weeks of gestation to screen for hypertensive disorders and associated complications in an

- unselected population,” *Ultrasound in Obstetrics & Gynecology*, vol. 26, no. 5, pp. 490–494, 2005
9. Narang S, Agarwal A, Das V, Pandey A, Agrawal S, Ali W: Prediction of pre-eclampsia at 11-14 weeks of pregnancy using mean arterial pressure, uterine artery Doppler and pregnancy-associated plasma protein-A. *Int J Reprod Contracept Obstet Gynecol*. 2016, 5:3948-53.
 10. Goetzinger KR, Zhong Y, Cahill AG, Odibo L, Macones GA, Odibo AO: Efficiency of first-trimester uterine artery Doppler, a-disintegrin and metalloprotease 12, pregnancy-associated plasma protein a, and maternal characteristics in the prediction of preeclampsia. *J Ultrasound Med*. 2013, 32:1593-600.
 11. Staboulidou I, Galindo A, Maiz N, Karagiannis G, Nicolaides KH: First-trimester uterine artery Doppler and serum pregnancy-associated plasma protein-a in preeclampsia and chromosomal defects. *Fetal Diagn Ther*. 2009, 25:336-9.
 12. Das E, Singh V, Agrawal S, Pati SK. Prediction of Preeclampsia Using First-Trimester Uterine Artery Doppler and Pregnancy-Associated Plasma Protein-A (PAPP-A): A Prospective Study in Chhattisgarh, India. *Cureus*. 2022 Feb 8;14(2).
 13. Martin AM, Bindra R, Curcio P, Cicero S, Nicolaides KH. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler at 11-14 weeks of gestation. *Ultrasound Obstet Gynecol*. 2001 Dec;18(6):583-6.
 14. Singh P, Sharma B, Singh N: Early prediction of pregnancy induced hypertension by colour Doppler and role of antioxidants. *Int J Reprod Contracept Obstet Gynecol*. 2016, 5:26779.
 15. Spencer K, Cowans NJ, Nicolaides KH: Low levels of maternal serum PAPP-A in the first trimester and the risk of pre-eclampsia. *Prenat Diagn*. 2008, 28:7-10.
 16. Zhong Y, Zhu F, Ding Y: Serum screening in first trimester to predict pre-eclampsia, small for gestational age and preterm delivery: systematic review and meta-analysis. *BMC Pregnancy Childbirth*. 2015, 15:191.
 17. Odibo AO, Zhong Y, Goetzinger KR, Odibo L, Bick JL, Bower CR, Nelson DM: First-trimester placental protein 13, PAPP-A, uterine artery Doppler and maternal characteristics in the prediction of pre-eclampsia. *Placenta*. 2011, 32:598-602.
 18. Patil M, Panchanadikar TM, Wagh G: Variation of papp-a level in the first trimester of pregnancy and its clinical outcome. *J Obstet Gynaecol India*. 2014, 64:116-9.
 19. Pilalis A, Souka AP, Antsaklis P, Daskalakis G, Papantoniou N, Mesogitis S, Antsaklis A. Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler and PAPP-A at 11–14 weeks' gestation. *Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2007 Feb;29(2):135-40.
 20. Poon LC, Stratieva V, Piras S, Piri S, Nicolaides KH. Hypertensive disorders in pregnancy: combined screening by uterine artery Doppler, blood pressure and serum PAPP-A at 11–13 weeks. *Prenatal Diagnosis: Published in Affiliation With the International Society for Prenatal Diagnosis*. 2010 Mar;30(3):216-23.