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ORIGINAL RESEARCH

Role of PAPP-A (Pregnancy Associated Plasma Protein-A), PlGF (Placental Growth Factor) and uterine artery doppler in prediction of preeclampsia

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ABSTRACT
Preeclampsia poses significant risks to maternal and fetal health, necessitating reliable methods for early prediction to facilitate timely intervention and mitigate adverse outcomes. This study investigates the predictive value of Pregnancy-Associated Plasma Protein-A (PAPP-A), Placental Growth Factor (PlGF), and uterine artery Doppler (UAD) in identifying preeclampsia risk. A Hospital-based Cross-sectional study was conducted among 90 antenatal cases attending to Obstetric clinic of MMC over a duration of twelve months. Receiver Operating Characteristic (ROC) curve analysis was employed to assess the diagnostic efficacy of PAPP-A, PlGF, and pulsating index (PI) in predicting preeclampsia. Among the biomarkers evaluated, PI exhibited the highest Area Under the Curve (AUC) value of 0.793, surpassing both PAPP-A (AUC = 0.272) and PlGF (AUC = 0.127). PAPP-A concentration below 0.5 MoM demonstrated a sensitivity of 50% and specificity of 82%, while a PlGF concentration below 0.75 MoM exhibited a sensitivity of 50% and specificity of 92% in predicting preeclampsia. Pl >2 had a sensitivity of 87.5% but a specificity of only 34%. In conclusion, lower levels of PAPP-A and PlGF, along with higher Pulsatility Index, are associated with an increased risk of pre-eclampsia.

Key words: Preeclampsia, Pregnancy-Associated Plasma Protein-A, Placental Growth Factor, uterine artery Doppler, Pulsating index

INTRODUCTION:
Pre-eclampsia (PE) is a multi-system disorder characterized by the new onset of hypertension and proteinuria or end-organ dysfunction, or both during the second half of pregnancy. Although most pregnancies with PE are associated with delivery at term or near term, with good maternal and fetal outcomes, these pregnancies have a high risk for maternal and/or fetal mortality or serious morbidity.[1,2]

Preeclampsia (PE) accounts for 5-10% of pregnancies worldwide and 4.6% of pregnancies in India.[3,4] It forms one member of the deadly triad, along with hemorrhage and infection that contribute greatly to maternal morbidity and mortality (14% worldwide, 29.5%in India).[5,6]

Preeclampsia begins during the first half of the first trimester but only becomes evident during the second half of pregnancy. Some risk factors have been associated with the development of preeclampsia, but widespread factors, such as nulliparity, multiple gestation, diabetes mellitus (DM), a history of renal diseases, a maternal age higher than 35 or lower than 20 years, obesity, previous preeclampsia, mutation of factor V Leiden, mutations in the angiotensinogen and prothrombin genes, and antiphospholipid antibody syndrome, also characterize a risk cohort for pregnant women.[7,8]

Studies have shown that defective trophoblastic invasion of the placenta plays a crucial role in the pathogenesis of preeclampsia. Poor placentation is associated with an imbalance of circulating vasoactive factors and, in turn, leads to maternal vascular maladaptation with associated systemic endothelial dysfunction.[9,10] Placental products are released as part of the placentation process. Levels of these biochemical markers reflect the pathophysiology of defective placentation, and, as a consequence, are assuming an

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increasing role in early gestation screening tests for later pregnancy complications. These biomarkers include pregnancy-associated plasma protein-A (PAPPA), placental growth factor (PlGF), soluble FMS-like tyrosine kinase-1 (sFlt-1), soluble endoglin (sEng), activin-A, inhibin-A, a disintegrin and metalloprotease 12 (ADAM12), and placental protein 13 (PP13).

Early prediction of preeclampsia is still a challenge. Several markers have been studied by researchers in the past. Based on the literature review PAPP-A, PlGF and uterine artery Doppler in the first trimester have shown promising results in the prediction of preeclampsia. However, most of the studies available were conducted on the Caucasian and African-American populations. Data from the Indian population is still insufficient. The present study is conducted with an objective to find out whether abnormal uterine artery Doppler, PAPP-A and PIGF levels in first trimester can predict preeclampsia.

MATERIALS AND METHODS

A Hospital-based Cross-sectional study was conducted at the Department of Obstetrics and Gynaecology, Muzaffarnagar Medical College, located in Muzaffarnagar, Uttar Pradesh. The study population comprises 90 antenatal cases attending the Obstetric clinic of MMC over a duration of twelve months. The sample size is set at 90, and a systematic randomized sampling technique was employed by selecting every 10th antenatal case till the required level of sample size achieved. Inclusion criteria encompass all volunteer gravid women attending the antenatal OPD in the first trimester of pregnancy, as well as high-risk groups for preeclampsia during their first trimester. Exclusion criteria involve medical disorders such as renal insufficiency, congestive heart disease, and chronic respiratory insufficiency, along with pregnant women presenting fetal chromosomal abnormalities and congenital anomalies.

The detailed medical history was taken in all cases. This was followed by a detailed medical examination.The schedule of investigations consists of initial routine examinations of blood especially haemoglobin percentage, total WBC count, ESR, urine routine, serological test for Syphilis, HIV, HbsAg, Blood grouping and Rh typing, Serum. Uric acid, Serum. LDH, Fasting Lipid profile, PAPP-A (PREGNANCY ASSOCIATED PLASMA PROTEIN), PlGF (PLACENTAL GROWTH FACTOR) and uterine artery Doppler.

Uterine artery Doppler Ultrasound was performed to evaluate uterine artery's flow velocity waveforms. It used to calculate the presence of diastolic notch and resistance index (RI). At each antenatal visit, the risk factors for Preeclampsia such as Blood Pressure, proteinuria, and signs and symptoms was noted. Women was labelled to have Preeclampsia if they developed hypertension (BP >140/90) after 20 weeks of gestation in combination with proteinuria. Plasma samples was collected at the time of each Antenatal visit scheduled for four-week intervals from the first or early second trimester until delivery. All patients will provide written informed consent prior to sample collection. The plasma protein of each patient was profiled in two to six samples collected from each patient and was included, and for some of the cases the sample was collected after the diagnosis of early preeclampsia.The data collected after diagnosis was displayed in longitudinal plots, all analyses reported here was based only on samples collected. A Papp-A level more than or equal to 0.5 MOM was considered normal, while levels less than 0.5 MOM are marked as low. PIGF level below 5th percentile was considered low. Data collected was entered into MS-Excel 2013 spreadsheet and analysed using IBM statistical package for social sciences (IBM SPSS) version 26. Chi-square test and Unpaired t-test was used find the significant factors causing preeclampsia. Receiver operating characteristic [ROC] analysis is used to assess the diagnostic performance of PAPP-A, PlGF and uterine artery Doppler and $P < 0.05$ was considered as statistically significant.

RESULTS

Out of 90 pregnant women studied 8(8.9%) developed pre-eclampsia during their follow-up period. The average age of participants without pre-eclampsia was 22.7 ± 3.9 years, whereas those with pre-eclampsia had an average age of 25.7 ± 3.7 years, with a significant difference between two groups (p=0.03). A significant association was observed between working status and pre-eclampsia (p=0.03), with higher rates among women who were employed (25%) compared to housewives (4.7%) or labourers (10%). Other factors such as education level, gravidity, and pregnancy type did not show significant associations with pre-eclampsia as shown in table 1.

Table 1: Association between various independent factors and Pre-eclampsia

		Pre-eclampsia		
		No [82]	**Yes [8]**	**p-value**
Age [years]		22.7 ± 3.9	25.7 ± 3.7	0.036 [sig.]
Education	Illiterate	42 [95.5%]	2 [4.5%]	0.289 [NS]
	Up to 12th	25 [89.3%]	3 [10.7%]	
	egree andabove	15 [83.3%]	3 [16.7%]	
Working status	Housewife	61 [95.3%]	3 [4.7%]	0.038 [Sig.]
	Labourer	9 [90%]	1 [10%]	
	Working	12 [75%]	4 [25%]	
Gravida	Primi	32 [84.2%]	6 [15.8%]	0.265 [NS]
	G2	30 [96.8%]	1 [3.2%]	
	G3	18 [94.7%]	1 [5.3%]	

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	G4	2 [100%]	0	
Pregnancy type	Single	78 [91.8%]	7 [8.2%]	0.369 [NS]
	Twin	4 [80%]	1 [20%]	

The mean level of PAPP-A MoM was significantly lower in individuals with pre- eclampsia (0.66 ± 0.36) compared to those without (0.99 ± 0.44), with a p-value of 0.045. The mean level of PlGF MoM was significantly lower in individuals with pre-eclampsia (0.72 ± 0.17) compared to those without (0.97 ± 0.14), with a highly significant p-value of 0.000. The mean Pulsatility Index was significantly higher in individuals with pre-eclampsia (2.27 ± 0.31) compared to those without (1.69 ± 0.53), with a statistically significant p-value of 0.003 as shown in table 2.

Table 2: Comparing mean PAPP-A MoM, PIGF MoM and PI with Pre-eclampsia

	Pre-eclampsia		
	No	**Yes**	
PAPP-A MoM	0.99 ± 0.44	0.66 ± 0.36	0.045 [Sig.]
PIGF MoM	0.97 ± 0.14	0.72 ± 0.17	0.000 [Sig.]
PI	1.69 ± 0.53	2.27 ± 0.31	0.003 [Sig.]

Fig 1: ROC curve of PAPP-A for predicting pre-eclampsia

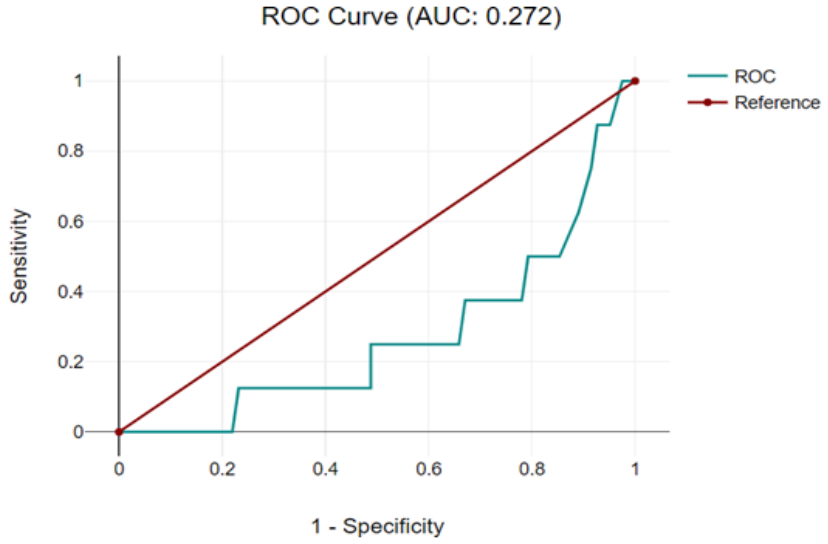

Fig 2: ROC curve of PIGF for predicting pre-eclampsia

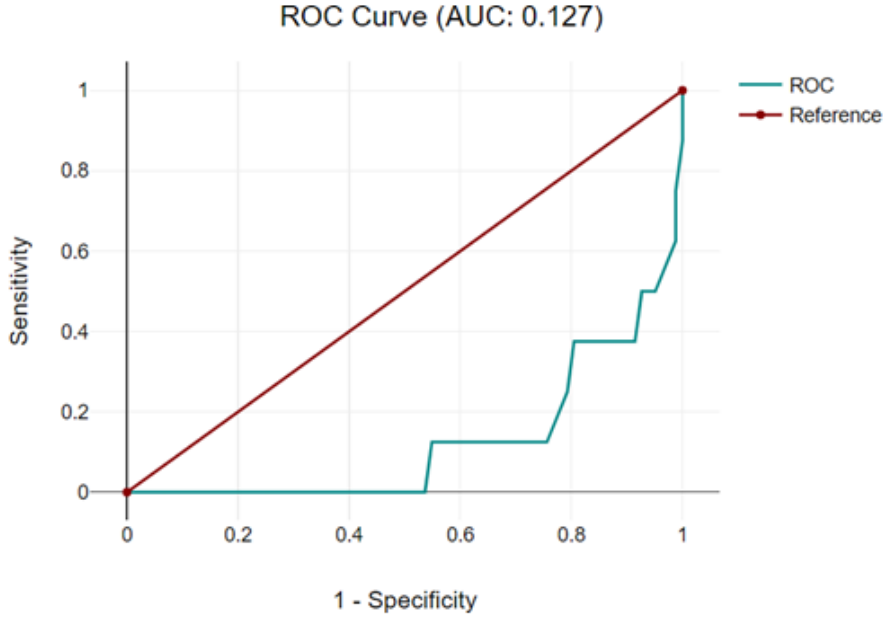

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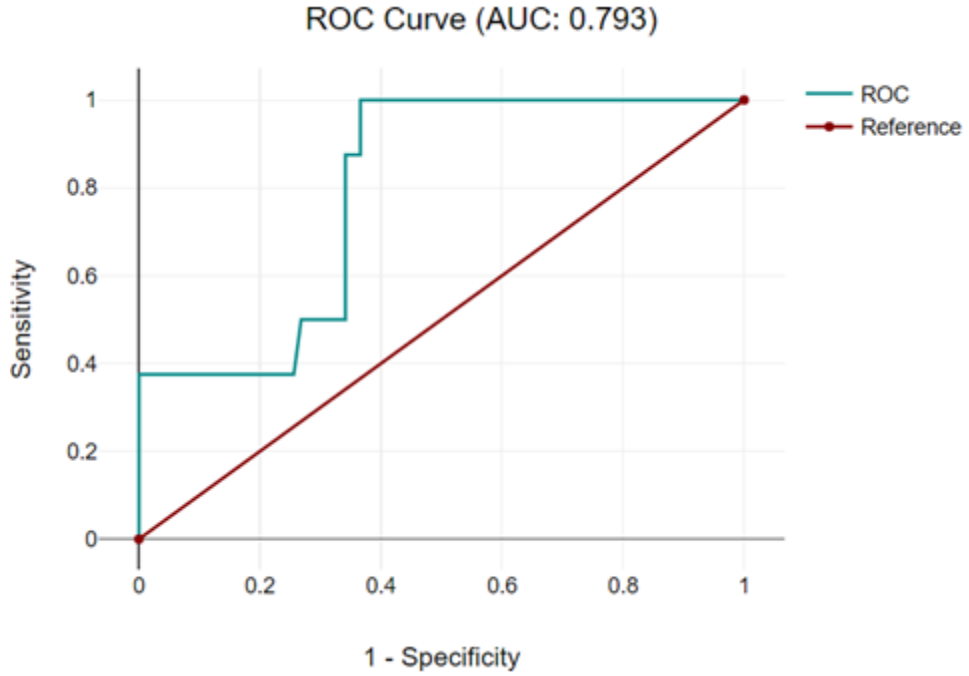
Fig 3: ROC curve of pulsating index (PI) for predicting pre-eclampsia



Receiver Operating Characteristic (ROC) curve analysis was conducted to evaluate the diagnostic performance of PAPP-A, PlGF and PI for predicting preeclampsia. The AUC of PI (AUC – 0.793) was higher than that of PAPP-A (AUC – 0.272) and PIGF (AUC – 0.127). PAPP-A concentration <0.5 MoM had a sensitivity of 50% and a specificity of 82% for the prediction of preeclampsia. At PlGF concentration <0.75 MoM had a sensitivity of 50% and a specificity of 92% for the prediction of preeclampsia. A Pl >2 had a sensitivity of 87.5% and a specificity of 34% for the prediction of preeclampsia.

DISCUSSION

Timely identification of preeclampsia is crucial for ensuring successful pregnancy outcomes, particularly for women at risk. Early detection enables clinicians to administer targeted intensive care in the early stages of pregnancy, thereby reducing the severe morbidity and mortality associated with the condition. In the present study involving 90 pregnant women, 8 (8.9%) developed preeclampsia during their follow-up period. The observed difference in average age between participants with and without pre-eclampsia highlights age as a potential risk factor for the development of this condition. This finding is consistent with Sun et al.,[11] indicating that advanced maternal age is associated with an increased risk of pre-eclampsia. Narang S et al.,[12] had reported that the mean age of the women who developed complications was 26.48 years and those who did not was 25.61 years. Furthermore, the significant association between working status and pre-eclampsia suggests that occupational factors may play a role in the pathogenesis of the condition. Specifically, a higher prevalence of pre-eclampsia among employed women compared to housewives or labourers underscores the importance of further exploring the impact of occupational stressors on maternal health during pregnancy.

The mean level of PAPP-A MoM was significantly lower in individuals with pre- eclampsia (0.66 ± 0.36) compared to those without (0.99 ± 0.44), with a p-value of 0.045. Narang S et al.,[12] had reported that the mean PAPP-A of the women who developed preeclampsia and related complications was 14.20 ± 11.05 and that of women who did not develop complications were 13.89 ± 7.13 with no statistically significant difference between two groups. In Das E et al.,[13] study the mean PAPP-A MoM of the affected group (preeclampsia) was 0.67, which was comparable to the studies of Goetzinger et al.,[14] and Spencer et al.,[15] with mean PAPP-A MoM of 0.88 and 0.772.

The mean level of PlGF was significantly lower in individuals with pre-eclampsia (0.72± 0.17) compared to those without (0.97 ± 0.14), with a highly significant p-value of 0.000. Contrary to study findings Sung KU et al.,[16] had reported that PIGF MoM and PAPP-A MoMhad no association with pre-eclampsia. Keikkala E et al.,[17] found that PlGF MoM was lower in women with subsequent pre-eclampsia, but statistical significance was not reached

The mean Pulsatility Index was significantly higher in individuals with pre-eclampsia (2.27 ± 0.31) compared to those without (1.69 ± 0.53), with a statistically significant p-value of 0.003. Narang S et al.,[12] had reported that the mean PI of the women who developed preeclampsia and related complications was 1.94 ± 0.55 and that of women who did not develop complications was 1.42 ± 0.44 with a statistically significant difference between two groups. Das E et al.,[13] had also reported that mean uterine artery PI value among those who developed preeclampsia was 2.007, which was significantly higher than the unaffected group (p=0.01). Satish et al.,[18] and Gomez et al.,[19] also had a similar mean PI among the affected group: 2.34 and 2.04 respectively.

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Regarding biomarkers, the significantly lower levels of Pregnancy-associated plasma protein-A (PAPP-A) and Placental Growth Factor (PlGF) in individuals with pre-eclampsia compared to those without the condition indicate the potential utility of these biomarkers as diagnostic tools for pre-eclampsia. PAPP-A MoM concentration <0.5 had a sensitivity of 50% and a specificity of 82% for the prediction of preeclampsia. Similarly, Luewan S et al.,[20] study found that pregnancies with low PAPP-A levels were significantly associated with an increased risk of preeclampsia, especially early-onset preeclampsia. However, Narang S et al.,[12] and Shah KH et al.,[21] found that PAPP-A was not as a predictive factor for preeclampsiaand its associated complications. Das E et al.,[13] had reported that the cut-off value for PAPP-A MoM at 11-13 +6 weeks was 0.41 with a sensitivity of 28% and specificity of 90.6% in this study. Zhong et al.,[22] showed similar sensitivity and specificity of 16% and 93%, respectively. Odibo et al.,[23] showed a higher sensitivity of 58% for PAPP-A. Staboulidou et al.,[24] had found a cut-off value of PAPP-A MoM at 0.58 for preeclampsia. Patil et al.,[25] showed a PPV of 52% compared to 38.89% of our study at a cut-off of 0.5. These findings are in line with Sun et al.,[11] and Mendoza et al.,[26] study demonstrating alterations in PAPP-A and PlGF levels in pre- eclampsia. Luewan S et al.,[20] had reported that the sensitivity and specificity of PAPP-A in predicting preeclampsia was 26% and 90% respectively. The predictive value of PAPP-A for early detection of preeclampsia as reported by Shah H et al.,[21] was 37%.

PlGF MoM <0.75 had a sensitivity of 50% and a specificity of 94% for the prediction of preeclampsia. Keikkala E et al.,[17] had also reported that AUC values for prediction of early-onset pre-eclampsia were 0.692 (P = 0.021) for PlGF and 0.783 (P = 0.001) for PAPP-A. Noel L et al.,[27] had found that the sensitivity of PAPP-A and PIGF for early detection of preeclampsia was 46% and 52% respectively.

In the present study pulsating index at cutoff >2 had a sensitivity of 87.5% and a specificity of 34% for the prediction of preeclampsia. Das E et al.,[13] had found that Uterine artery PI at first trimester was considered a good predictor for hypertensive disorders of pregnancy with a sensitivity of 68% and specificity of 52.99% at a cut-off of 1.48. A similar cut-off (1.52) was also obtained in a study by Staboulidou et al.,[24] which showed similar sensitivity (75.9%) and specificity (79.6%). Similar sensitivity (64%) was also shown by Odibo et al.[23] Similarly, Narang S et al.,[12] had reported that the AUC (area under curve) of the meanPI ROC was 0.787 for a cut off of 1.7 with sensitivity of mean PI at 11-14 weeks of pregnancy for predicting complications is 75.9% and specificity is 79.6%.

Overall, The Receiver Operating Characteristic (ROC) curve analysis demonstrates the varying diagnostic performance of PAPP-A, PlGF, and PI for predicting pre-eclampsia, with PI exhibiting the highest Area Under the Curve (AUC). These findings underscore the importance of incorporating multiple biomarkers and diagnostic tools in pre-eclampsia prediction and management strategies.

CONCLUSION

These results indicate that lower levels of PAPP-A and PlGF, along with higher Pulsatility Index, are associated with an increased risk of pre-eclampsia. These biomarkers may serve as valuable tools for predicting and diagnosing pre-eclampsia, aiding in the early identification and management of this condition during pregnancy.

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