Section: Obstetrics and Gynaecology

Original Research Article

A PROSPECTIVE STUDY TO MAKE AN EARLY PREDICTION OF PREECLAMPSIA TO IMPROVE FETO-MATERNAL OUTCOME BY USING BIOCHEMICAL MARKERS (PAPP-A, PLGF, SFLT), UTERINE ARTERY DOPPLER AND CONGO RED SPOT TEST IN 11 -13 WEEKS OF PREGNANCY

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Received *: 02/08/2025*
Received in revised form *: 19/09/2025*
Accepted *: 04/10/2025*

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DOI: 10.70034/ijmedph.2025.4.513

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (4); 2868-2871

ABSTRACT

Background: Pre-eclampsia affects 8% -10% of pregnancies in India, is a major cause of maternal and perinatal morbidity. It is very important to diagnose preeclampsia early in pregnancy to reduce the maternal morbidity associated with it. The performance of screening can be improved by combining history with a series of biochemical and biophysical markers which are altered from as early as the first trimester of pregnancy in cases that subsequently develop Preeclampsia. So the current study was designed to predict pre-eclampsia and prevent its sequelae using maternal history, biophysical markers (PAPP-A, PLGF, SFLT), Amyloid protein by Congo Red and uterine artery doppler at 11-13 weeks of gestation.

Materials and Methods: Current study was prospective observational study conducted in the Department of Obstetrics and Gynaecology, S.M.S medical college, Jaipur. A total 500 pregnant woman with gestational age of 11-13 were included and followed up. Data analysis was done using licensed SPSS software version 21.0 (Chicago, Illinois). A p-value <0.05 was considered as statistically significant.

Results: Incidence of preeclampsia was found to be 34% (Figure 1). This study found that Congo red test was positive in 98.2% of preeclamptic patients. PAPP-A and PLGF was found to be statistically significant low in pre-eclamptic woman, Congo red test positivity, SFLT and uterine artery PI was found to be statistically significant high in pre-eclamptic woman. Accuracy of congo red test was found to highest and overall sensitivity of all tests was found to be 100%.

Conclusion: Our findings suggest that low serum PAPP-A and PLGF levels, as well as high SFLT and uterine artery PI, positive congo red test can be used to predict pre-eclampsia. Overall combined sensitivity of all these test was found to be 100% but specificity was found to be low. More research on bigger and more diverse populations is needed to evaluate the use of these integrated techniques in pre-eclampsia prediction.

Keywords: Pre-eclampsia, PAPP-A, PLGF, SFLT, Congo Red. uterine artery doppler etc.

INTRODUCTION

Preeclampsia is one of the leading causes of maternal morbidity and mortality in the world. Globally, about 12% of mothers die only from preeclampsia. As estimated by WHO, the occurrence of preeclampsia is seven times higher in developing countries

compared to developed countries. The prevalence of preeclampsia ranges between 1.8 and 16.7% in developing countries.[1,2] In Asia and Africa, nearly one tenth of all maternal deaths are associated with hypertensive disorder of pregnancy.[1] In India, the incidence of preeclampsia is reported to be 8-10% among the pregnant women. Pre-eclampsia affects 8% -10% of pregnancies in India, is a major cause of maternal and perinatal morbidity.[3] It is very important to diagnose preeclampsia early in pregnancy to reduce the maternal morbidity associated with it.[2] The performance of screening can be improved by combining history with a series of biochemical and biophysical markers which are altered from as early as the first trimester of pregnancy in cases that subsequently develop Preeclampsia.[3] These markers are thought to be involved in placentation or in the cascade of events leading from impaired placentation to development of clinical symptoms of preeclampsia. There is evolving evidence that both the degree of impaired placentation and the incidence of adverse fetal and maternal short and long-term consequences of Preeclampsia are inversely related to the gestational age at the onset of the disease.[4]

The aim of such early identification of women at high risk is to allow intensive maternal and fetal monitoring leading to early diagnosis of PE with the potential for mitigating an adverse outcome5. Additionally, there is evidence from randomized studies on the prophylactic use of aspirin that this may reduce the incidence of PE by about 50% provided treatment is initiated before 16 weeks.[5,6]

So the current study was designed to predict pre-eclampsia and prevent its sequelae using maternal history, biophysical markers (PAPP-A, PLGF, SFLT), Amyloid protein by Congo Red and uterine artery doppler at 11-13 weeks of gestation.

MATERIALS AND METHODS

Current study was prospective observational study conducted in the Department of Obstetrics and Gynaecology, S.M.S medical college, Jaipur. Sample size was calculated at 95% confidence level and 80% study power expecting 91% detection rate of early pre-eclampsia by using maternal factors plus all biophysical markers as found in seed article by Ranjit Akolekar et al.[7] Assuming 2.3% incidence of preeclampsia in all pregnancies as per results of seed article and 20% relative allowable error in detection rate, minimum 436 pregnant women are required as sample size in present study which is further enhanced and rounded off to 500 pregnant women as a final sample size expecting 15% dropouts / loss to follow-up / attrition.

A complete history was taken regarding present and previous pregnancies as well in the first visit (at 11 to 13 weeks). A detailed history was taken and all the relevant investigations was done. Transabdominal ultrasound (TAS) was performed at 11-13 weeks to measure the pulsatility index (PI) in right and left uterine artery. Transabdominal 2D color Doppler probe of Voluson 730 pro V machine was used to confirm a live fetus and to determine the gestational age. We was also measure the levels of PAPPA, Sflt, and PLGF in these patients. Blood pressure will be measured in both arms simultaneously by automated BP instrument.

PAPP-A test was done by Sandwich-CLIA method and detection range is from 0.156-10 ng/mL.

SFLT test was done by Automated immunofluorescent assay and detection range is 22-90000 pg/mL.

PLGF test was done by Automated immunofluorescent assay and detection range is 3.6–7000 pg/ml.

In the second trimester, we did congo red spot test in these women to see congophilia. The test is based on selective binding of Congo Red dye to misfolded proteins present in the urine.

Data analysis was done using licensed SPSS software version 21.0 (Chicago, Illinois). Descriptive statistics were used to calculate frequencies of categorical variables, and measures of central tendencies and dispersion were used to describe continuous variables. Independent t-test was used to compare the continuous variable and chi-square test was used for categorical variables. A p-value <0.05 was considered as statistically significant. Approval from Institutional Ethical Committee of SMS medical college & Hospital was taken before the start of the study.

RESULTS

In our study, mean age of study participants was 25.4±3.9 years, maximum 258 (51.6%) were in age group of 18-25 years followed by 176 (35.2%) in age of 26-30 years and most of (75.4%) were multigravida. [Table 1]

Incidence of preeclampsia was found to be 34% [Figure 1]. This study found that Congo red test was positive in 98.2% of preeclamptic patients. PAPP-A and PLGF was found to be statistically significant low in pre-eclamptic woman, Congo red test positivity, SFLT and uterine artery PI was found to be statistically significant high in pre-eclamptic woman. [Table 2].

Accuracy of congo red test was found to highest and overall sensitivity of all tests was found to be 100%. [Table 3].

Table 1: Sociodemographic and clinical profile of study participants (N=500)

Variable	Frequency	Percent
Age (Mean±SD)	25.4±3.9	
Age group:		
18-25 years	258	51.6

26-30 years	176	35.2
>30 years	66	13.2
Gravida:		
Primigravida	123	24.6
Multigravida	377	75.4

Table 2: Association of pre-eclampsia with various parameters

	Pre-eclampsia absent (n-330)		Pre-eclampsia present (n-170)		p-value
	Count	%	Count	%	
Age					
18-25 years	169	51.2%	89	52.4%	0.656
26-30 years	120	36.4%	56	32.9%	
>30 years	41	12.4%	25	14.7%	
Gravida:					
Primigravida	81	24.5%	42	24.7%	0.558
Multigravida	249	75.5%	128	75.3%	
Congo red test:					
Negative	327	99.1%	3	1.8%	<0.001
Positive	3	0.9%	167	98.2%	
Biophysical marker (Mean±SD)					
PAPP-A	1.60±1.06		1.24±1.07		0.041
PLGF	2430.68±557.1		1832.1±272.9		0.010
SFLT	29010.5±2197.4		42093.0±996.1		0.002
Uterine artery PI	1.32±0.87		1.54±0.96		0.009

Table 3: Accuracy of different tests to diagnose preeclampsia

Test	Sensitivity	Specificity	PPV	NPV
PAPP-A	74.9%	93.6%	85.9%	87.7%
SFLT-1	74.9%	80.5%	66.7%	86.0%
PLGT	73.7%	90.3%	79.7%	86.8%
Congo Red	97.7%	99.9%	98.2%	98.8%
Uterine artery PI	81.3%	93.6%	86.9%	90.6%
Combined of all	100%	68.0%	62.0%	100%

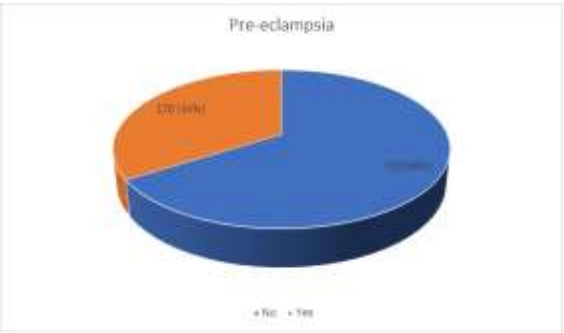

Figure 1: Incidence of pre-eclampsia

DISCUSSION

This study aimed to make an early prediction of pre-eclampsia and prevent its sequalae using maternal history, biophysical markers (PAPP-A, PLGF, SFLT), and uterine artery doppler at 10 -13 weeks of period of gestation. A total 500 pregnant woman with gestational age of 11-13 were included and followed up.

Pre-eclampsia and PAPP-A: In our study, incidence of pre-eclampsia was found to be 34% and PAPP-A was found to be statistically significant low in pre-eclamptic woman. So low PAPP-A can be early predictor of pre-eclampsia. Sensitivity, specificity, NPV and PPV was found to be 74.9%, 93.6%, 85.9% and 87.7% respectively.

Akolekar R et al,[7] also find similar results and revealed that plasma levels of PAPP-A has decreased in all trimesters of pregnancy, similarly Spencer K et al,[8] also found a statistically low PAPP-A in preeclamspia and concluded an early predictor of pre-eclampsia and the levels of PAPP-A were significantly reduced in the early onset PE while in case of late onset PE the levels did not differ from the control group. However, Romero R et al,[9] revealed that PAPP-A is not useful in predicting late onset PE and larger trials are required to confirm these preliminary predictions.

Pre-eclampsia and Placental growth factor: Our study revealed that PLGF was found to be statistically significant low in pre-eclamptic woman. Sensitivity, specificity, NPV and PPV was found to be 73.7%, 90.3%, 79.7% and 86.8% respectively.

Similarly Lam C et al,[10] have demonstrated that maternal serum levels of PLGF are lower in both early and late onset PE.

Pre-eclampsia and Soluble FMS-like tyrosine kinase -1 (SFLT-1):

In our study, SFLT was found to be statistically significant high in pre-eclamptic woman. So low SFLT can be early predictor of pre-eclampsia. Sensitivity, specificity, NPV and PPV was found to be 74.9%, 80.5%, 66.7% and 86.% respectively.

Romero R et al9 compared with control subjects, the women who develop PE, a significant rise in serum levels of sFlt-1. However, LAM C et al,[10] showed the lower specificity and poor predictive value of sFlt-1 in the early stages of pregnancy. Baumann et al,[11] reported the predictive role of sFlt1 and sEngin PE.

Pre-eclampsia and Congo red test: In our study out of the 500 participants, 170 (34%) were congo red test positive and a statistically significant high pre eclampsia was found among the participants who were positive for Congo red test. Sensitivity, specificity, NPV and PPV was found to be 97.7%, 99.9%, 98.2% and 98.8% respectively. Sailakshmi MPA et al,[12] found the sensitivity and the specificity of the test was 66.18% and 96.45% respectively. The positive predictive value (PPV) and negative predictive value (NPV) was 80.36% and was 92.86% respectively. Study by Nagarajappa et al,[13] results showed that there is a significant difference in the level of urinary congophilia between early onset and late onset PE and congophilia is not affected by factors such as gestational age of onset, severity or superimposed eclampsia.

Pre-eclampsia and uterine artery doppler: In our study, a statistically significant high uterine artery PI was found among the participants had pre-eclampsia. Sensitivity, specificity, NPV and PPV was found to be 81.3%, 93.6%, 86.9% and 90.6% respectively. Salem MAA et al,[14] Gomaa et al,[15] they found that at 11–13 weeks of pregnancy the mean PI of uterine arteries was significantly higher in preeclamptic which supported the current result. Cnossen JS et al,[16] did a meta-analysis regarding the role of uterine artery Doppler study in prediction of pre-eclampsia confirmed that using this procedure in the second trimester of pregnancy is better than in the first trimester, and it had a major role in predicting severe or early-onset pre-eclampsia in low-risk population. Raised PI of the uterine artery has a sensitivity of 78% and specificity of 95% in predicting severe pre-eclampsia if used in the second trimester.

CONCLUSION

Our findings suggest that low serum PAPP-A and PLGF levels, as well as high SFLT and uterine artery PI, positive congo red test can be used to predict pre-eclampsia. Overall combined sensitivity of all these test was found to be 100% but specificity was found to be low. More research on bigger and more diverse populations is needed to evaluate the use of these integrated techniques in pre-eclampsia prediction.

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