

# Efficacy of Uterine Artery Doppler Changes, Platelet Indices and Combination of both in Prediction of Preeclampsia in Pregnant Women: A Prospective Observational Study

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## ABSTRACT

**Introduction:** Preeclampsia is a pregnancy-specific medical disorder characterised by an abnormal vascular response to placentation. Uterine artery Doppler ultrasound has emerged as a predictive tool in preeclampsia. Abnormal Doppler waveforms have been associated with impaired placental perfusion and an increased risk of developing preeclampsia. Preeclampsia is associated with alterations in platelet function and activation. The estimation of platelet indices is an easy and economical method for screening preeclampsia. Abnormal uterine artery Doppler findings and abnormal platelet indices are both related to the etiological pathways of preeclampsia.

**Aim:** To compare the efficacy of uterine artery Doppler changes, platelet indices alone and their combination in predicting preeclampsia among pregnant women.

**Materials and Methods:** This was a prospective observational study conducted Department of Obstetrics and Gynaecology, Gandhi Hospital in Secunderabad, Telangana, India, over 18 months, including 160 pregnant women aged 18-35 years with singleton pregnancies between 20-24 weeks of gestational age.

Doppler ultrasound and platelet indices were measured and patients were followed-up until delivery for the development of preeclampsia. Receiver Operating Characteristic (ROC) curves were constructed and sensitivity, specificity and accuracy were determined to predict preeclampsia.

**Results:** The mean age of the study population was  $25.9 \pm 4.04$  years. The sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and accuracy of platelet indices in predicting preeclampsia alone were 67.71%, 59.38%, 71.43%, 55.07% and 64.38%, respectively. The sensitivity, specificity, PPV, NPV and accuracy of the uterine artery Doppler indices in predicting preeclampsia alone were 77.08%, 68.75%, 78.72%, 66.67% and 73.75%. The combined assessment of uterine artery Doppler study and platelet indices in the prognostication of preeclampsia had a sensitivity of 85.42%, specificity of 82.81%, PPV of 88.17% and NPV of 79.10%, with improved accuracy of 84.38%.

**Conclusion:** A combination of uterine artery Doppler ultrasound with platelet indices is easy to use, affordable, readily available in clinical settings and more effective in predicting preeclampsia than when used individually.

**Keywords:** Diastolic notch, Mean platelet volume, Platelet distribution width, Platelet large cell ratio, Pulsatility index, Resistance index

## INTRODUCTION

Preeclampsia, affecting 2%-5% of pregnant women worldwide [1], is a pregnancy-specific disorder characterised by an abnormal vascular response to placentation, associated with increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system and endothelial cell dysfunction [2].

Uterine artery Doppler ultrasound is a non invasive tool for predicting preeclampsia [3]. Abnormal uterine artery Doppler waveforms, characterised by increased resistance indices such as Pulsatility Index (PI) and Resistance Index (RI), have been associated with impaired placental perfusion and an increased risk of developing preeclampsia [4].

Endothelial dysfunction, inflammation and platelet activation are thought to contribute to the pathogenesis of preeclampsia, leading to alterations in platelet function and activation, which in turn cause changes in platelet indices [5]. Platelet indices, including Platelet Count (PC), Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW), have been investigated as potential predictive markers for preeclampsia [6].

Abnormal uterine artery Doppler findings and abnormal platelet indices are both related to the etiological pathways of preeclampsia and their combination may improve the prediction of the disease compared to using either one separately [7].

There is a lack of standardised protocols for integrating Doppler and platelet indices into routine clinical practice due to variability in interpreting measurements. By using standardised measurement protocols and analysis methods, the present study seeks to address the variability in current practice and improve the reliability of predictions by including a diverse population and employing robust statistical methods to validate and refine predictive models.

The integration of Doppler and platelet indices into predictive models may have significant clinical implications by potentially improving early risk assessment, monitoring and management of preeclampsia, thus enhancing maternal and foetal outcomes.

The present study aimed to evaluate the potential synergistic effects of combining these markers to improve the prediction of preeclampsia.

## MATERIALS AND METHODS

This was a prospective observational study conducted Department of Obstetrics and Gynaecology, Gandhi Hospital in Secunderabad, Telangana, India, from September 2022 to March 2023. A total of 160 pregnant women with singleton normal pregnancies between the ages of 18 and 35 were included. Institutional Ethics Committee committee approval from the was obtained from the study Institute (IEC/GMC/2022/08/120).

**Inclusion and Exclusion criteria:** Pregnant women with singleton normal pregnancies aged 18-35 years at 20-24 weeks of gestational age presenting to study Institute were included in the study. Women with systemic diseases such as diabetes mellitus, hypertension, collagen tissue disease, heart disease, renal disease, hepatic disease, diseases affecting platelet indices such as immune thrombocytopenic purpura and systemic lupus erythematosus, those using anticoagulant drugs, women with foetal anomalies, multifoetal gestations and patients already on any prophylactic medication for the prevention of preeclampsia were excluded from the study.

**Sample size calculation:** A simple random sampling technique was adopted. A total of 160 women underwent uterine artery Doppler studies. A complete blood count analysis at 20-24 weeks was performed using an automated haematology analyser and the platelet indices were measured.

### Study Procedure

When the Doppler study showed persistence of a diastolic notch (unilateral or bilateral) or an elevated PI or RI, it was considered a positive predictor index. For statistical purposes, the cut-off for elevated PI was set at  $\geq 1.44$  and elevated RI at  $\geq 0.65$ , according to the 95<sup>th</sup> percentile of the mean uterine artery PI/RI for the second trimester provided by the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG) [8].

Altered indices were considered if any one index was not within the normal range, as follows: Platelet Count (PC):  $155-409 \times 10^3$ /microlitre; MPV: 7.8-10.2 femtolitres; Platelet Distribution Width (PDW): 9.8-16%; and Platelet Large Cell Ratio (PLCR): 13.0-43.0 [9].

These patients were followed-up until delivery for the development of preeclampsia. The diagnosis of preeclampsia was made according to the criteria established by the International Society for the Study of Hypertension in Pregnancy (ISSHP) [10].

### STATISTICAL ANALYSIS

Data were entered into Microsoft Excel (Windows 10; Version 2019) and analyses were conducted using the Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0; SPSS Inc, Chicago). Descriptive statistics such as mean and Standard Deviation (SD) for continuous variables, as well as frequencies and percentages for categorical variables, were calculated. The association between variables was analysed using the Chi-square test for categorical variables. An unpaired t-test was used to compare the means of continuous variables between study groups. The level of significance was set at 0.05. Receiver Operating Characteristic (ROC) curves were constructed and sensitivity, specificity and accuracy were determined to predict preeclampsia.

### RESULTS

The mean age of the study population was  $25.9 \pm 4.04$  years. The majority (45%) of the cases belonged to the 18-23 years age group. Most of the study subjects were primigravidas (26.25%) [Table/Fig-1]. A total of 96 (60%) pregnant women developed preeclampsia at delivery, while 64 (40%) remained normotensive [Table/Fig-2].

The mean PI, mean RI, presence of a diastolic notch and alterations in platelet indices is compared in [Table/Fig-3]. The combined mean values for all parameters, except for Platelet Count (PC), were found to be higher in the preeclampsia group than in the normotensive group and these differences were statistically significant.

Of the 96 patients with preeclampsia, 91 had abnormal platelet indices, 94 had abnormal Doppler findings and 93 had both abnormal Doppler and platelet indices [Table/Fig-4].

The combined uterine artery Doppler study and platelet indices in prognosticating preeclampsia had a sensitivity of 85.42%, specificity of 82.81%, PPV of 88.17% and NPV of 79.10%, with an accuracy of 84.38% [Table/Fig-5].

Parameters	Frequency (n)	Percentage (%)
<b>Age group (in years)</b>		
18-23	72	45
24-29	61	38.13
30-35	27	16.87
Grand total	160	100
<b>Parity</b>		
Primigravida	42	26.25
Parity 1	35	21.87
Parity 2	24	15
Parity 3	30	18.75
Parity 4	29	18.12
Grand total	160	100

**[Table/Fig-1]:** Distribution of study subjects according to age group and parity (N=160).

Preeclampsia group at delivery	Normotensive group at delivery	Total
96 (60%)	64 (40%)	160

**[Table/Fig-2]:** Distribution of study subjects according to preeclampsia and normotensive groups at delivery (n=160).

Parameters	Preeclampsia group (n=96)	Normotensive group (n=64)	p-value
Mean Pulsatility Index (PI) Cut-off $\geq 1.44$	1.49 $\geq 1.44$	0.88 <1.44	0.0012*
Mean Resistance Index (RI) Cut-off $\geq 0.65$	0.78 $\geq 0.65$	0.50 <0.65	0.008*
Persistent diastolic notch	89 (92.7%)	5 (5.2%)	0.01#
Platelet Count (PC)	208103.6771 microlitre	254350.4688 microlitre	0.461
Mean Platelet Volume (MPV)	9.48 femtolitre	8.66 femtolitre	0.041*
Platelet Distribution Width (PDW)	13.98%	13.45%	0.035*
Platelet Large Cell Ratio (PLCR)	21.05	21.01	0.028*

**[Table/Fig-3]:** Comparison between doppler parameters and platelet indices in the preeclampsia and normotensive groups.

#: Chi-square test was used; \*: Unpaired t-test was used

Parameters	Preeclampsia group (n=96)	Normotensive group (n=64)
<b>Platelet indices</b>		
Abnormal (n=91)	65	26
Normal (n=69)	31	38
<b>Uterine artery doppler</b>		
Abnormal (n=94)	74	20
Normal (n=66)	22	44
<b>Combined uterine artery doppler and platelet indices</b>		
Abnormal (n=93)	82	11
Normal (n=67)	14	53

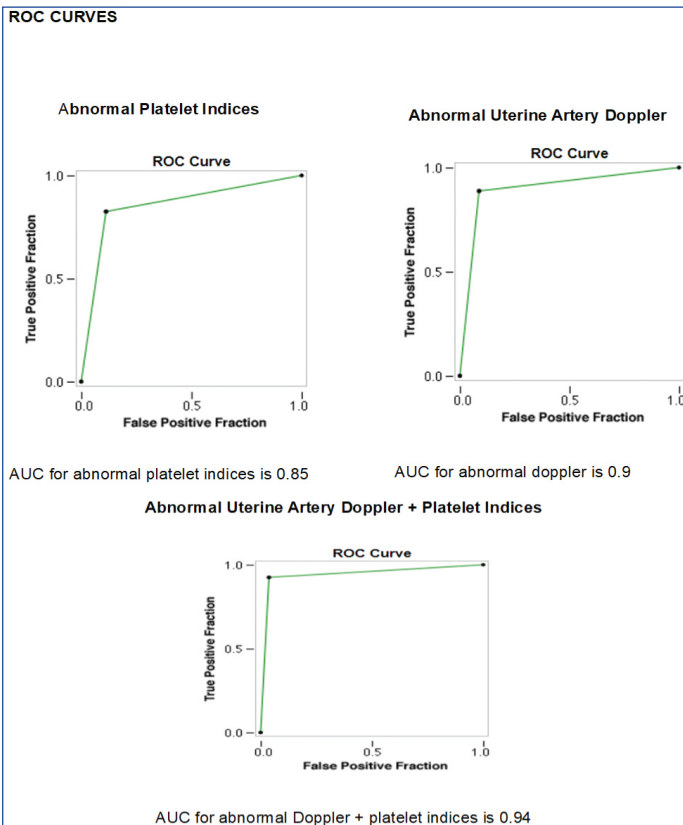
**[Table/Fig-4]:** Performance of uterine artery doppler ultrasound and platelet indices in prediction of preeclampsia.

Statistics	Platelet indices	Uterine artery doppler ultrasound	Combination of both
Sensitivity 95% CI	67.71% 57.39% to 76.90%	77.08% 67.39% to 85.05%	85.42% 76.74% to 91.79%
Specificity 95% CI	59.38% 46.37% to 71.49%	68.75% 55.94% to 79.76%	82.81% 71.32% to 91.10%
Positive likelihood ratio 95% CI	1.67 1.20 to 2.31	2.47 1.69 to 3.60	4.97 2.88 to 8.56
Negative likelihood ratio 95% CI	0.54 0.38 to 0.77	0.33 0.22 to 0.50	0.18 0.11 to 0.29
Positive predictive value 95% CI	71.43% 64.32% to 77.61%	78.72% 71.69% to 84.39%	88.17% 81.23% to 92.78%

Negative predictive value 95% CI	55.07% 46.26% to 63.58%	66.67% 57.22% to 74.94%	79.10% 69.73% to 86.15%
Accuracy 95% CI	64.38% 56.43% to 71.78%	73.75% 66.22% to 80.38%	84.38% 77.80% to 89.63%

**[Table/Fig-5]:** Validity of platelet indices, uterine artery doppler ultrasound and combination of uterine artery doppler ultrasound with platelet indices in prognostication of preeclampsia.

The Area Under the Curve (AUC) for abnormal platelet indices, abnormal Doppler findings and their combination in predicting preeclampsia is shown in [Table/Fig-6]. The AUC for abnormal platelet indices was 0.85, for abnormal Doppler findings it was 0.90 and for the combination of abnormal Doppler and platelet indices, it was 0.94, indicating a greater probability of predicting preeclampsia when both uterine artery Doppler findings and abnormal platelet indices are combined.



**[Table/Fig-6]:** AUC curve for abnormal platelet indices, abnormal doppler and their combination in predicting preeclampsia.

## DISCUSSION

In the present study, 96 (60%) pregnant women developed preeclampsia, while 64 (40%) remained normotensive until delivery. The mean age of the study population was  $25.9 \pm 4.04$  years. These results correlated well with the study by Patel RB et al., which reported a mean age of their study population as  $27.11 \pm 4$  years [11]. Of the 160 patients included in the study, 42 women (26.25%) were primigravidas, similar to a study by Missfelder-Lobos H et al., where 26.6% of the women studied were primigravidas [12].

The mean PI and RI in the women who developed preeclampsia at delivery were 1.49 and 0.88, respectively, which were higher than the mean PI and RI of the normotensive group (mean PI: 0.88, mean RI: 0.50). This finding aligns with a study by Aboufotouh M et al., who reported mean PI and RI values of  $1.51 \pm 0.359$  and  $0.726 \pm 0.099$ , respectively, in the preeclampsia group and  $0.935 \pm 0.268$  and  $0.573 \pm 0.102$  in the normotensive group [13]. Of the 96 women with preeclampsia in the present study, 89 (92.7%) exhibited a persistent diastolic notch, which correlated well with the study by Abdel Razik M et al., in which a persistent diastolic notch was observed in 94.6% of women who developed preeclampsia

and only in 5.1% of normotensive women, with a statistically significant value [9].

The MPV, mean Platelet Distribution Width (PDW) and Platelet Large Cell Ratio (PLCR) in women who developed preeclampsia were significantly altered when compared to the normotensive group. This is similar to the findings of Aboufotouh M et al., who reported the mean Platelet Count (PC), mean MPV, mean PDW and mean PLCR as 2.37 lac/mm<sup>3</sup>, 9.72 femtolitres, 17.3% and 20.11 in the preeclampsia group, compared to 2.52 lac/mm<sup>3</sup>, 7.88 femtolitres, 13.74% and 22.39 in the normotensive group, respectively [13].

The sensitivity, specificity, PPV, NPV and accuracy of platelet indices alone in predicting preeclampsia were 67.71%, 59.38%, 71.43%, 55.07% and 64.38%, respectively. These results were found to be similar to a study by Aboufotouh M et al., who reported sensitivity of 57.14%, specificity of 91.3%, PPV of 66.67%, NPV of 87.5% and accuracy of 83.33% [13].

The sensitivity, specificity, PPV, NPV and accuracy of uterine artery Doppler alone in predicting preeclampsia were 77.08%, 68.75%, 78.72%, 66.67% and 73.75%, respectively. These findings were similar to a study by Aboufotouh M et al., who reported sensitivity of 85.71%, specificity of 91.3%, PPV of 75%, NPV of 95.45% and accuracy of 90% [13].

The combined uterine artery Doppler study and platelet indices in prognosticating preeclampsia had a sensitivity of 85.42%, specificity of 82.81%, PPV of 88.17% and NPV of 79.10%, with an improved accuracy of 84.38%. Similar findings were reported by Aboufotouh M et al., where the combination yielded a sensitivity of 85.7%, specificity of 100%, PPV of 100% and NPV of 95.8%, with an accuracy of 96.7% [13].

In a recent literature review by Takaa M et al., it was concluded that the integration of Doppler and platelet indicators improves the accuracy of predictions in the early identification of hypertensive disorders, which has the potential to decrease both maternal and foetal morbidity [14]. However, further investigations are needed to evaluate prognostic models for practical implementation. The strength of the study lies in the concept of combining biomarkers to enhance the efficacy of predicting preeclampsia, which is cost-effective and can be universally accepted in the near future.

## Limitation(s)

Further validation of the biomarkers used in the present study on a larger population is necessary.

## CONCLUSION(S)

Currently, identifying pregnant women who are at an elevated risk of preeclampsia is one of the most essential obstetrical aims. Furthermore, the identification of sensitive and specific biomarkers would enable the identification of individuals at risk of preeclampsia, allowing for early diagnosis, initiation of preventive therapies, vigilant monitoring and appropriate prenatal intervention. In this regard, platelet indices combined with uterine artery Doppler stand out as an excellent option since it is an easy-to-use technique that is more affordable and readily available in clinical settings. However, to establish a cut-off for platelet indices, we need a larger sample size. The present study has found that platelet indices in preeclampsia are significantly altered compared to the normal range.

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**PLAGIARISM CHECKING METHODS:** [Jain H et al.]

- Plagiarism X-checker: Jun 06, 2024
- Manual Googling: Aug 21, 2024
- iThenticate Software: Aug 29, 2024 (13%)

**ETYMOLOGY:** Author Origin**EMENDATIONS:** 6**AUTHOR DECLARATION:**

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jun 01, 2024**Date of Peer Review: **Jul 25, 2024**Date of Acceptance: **Aug 30, 2024**Date of Publishing: **Nov 01, 2024**