

Does the addition of biomarker Serum endothelin 1 increase the predictive value of the combined test using uterine artery pulsatility index, mean arterial pressure, placental growth factor for the prediction of pre-eclampsia?

Debasmita Padhy¹, Susovita Dash², Duryodhan Sahoo³

¹Assistant Professor, Department of Obstetrics and Gynecology, Dharanidhar Medical College and Hospital, Keonjhar, Odisha, India

²Assistant Professor, Department of Obstetrics and Gynecology, Maharaja Jajati Keshari Medical College and Hospital, Jajpur, Odisha, India

³Assistant Professor, Department of Biochemistry, Dharanidhar Medical College and Hospital, Keonjhar, Odisha, India

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Corresponding Author: Duryodhan Sahoo

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Abstract:

Background: Globally, preeclampsia (PE) is a leading cause of illness and mortality among mothers and newborns. Particularly for early-onset PE, the traditional combination test that combines placental growth factor (PIGF), uterine artery pulsatility index (UtA-PI), and mean arterial pressure (MAP) offers a moderate level of predictive accuracy. Serum endothelin-1 (ET-1), a potent vasoconstrictor linked to endothelial dysfunction, has emerged as a potential biomarker for PE prediction. This study aimed to evaluate whether adding ET-1 improves the predictive performance of the combined test.

Methods: A retrospective observational study was conducted at DDMCH, Keonjhar, from June 2024 to July 2025. A total of 220 singleton pregnant women screened between 11–14 weeks of gestation were included. Clinical data and serum samples were retrieved from hospital records. MAP, UtA-PI, and PIGF were assessed at baseline, and ET-1 levels were measured retrospectively using ELISA. Predictive performance was evaluated using receiver operating characteristic (ROC) analysis.

Results: Of the 220 participants, 46 (20.9%) developed PE, including 18 (8.2%) with early-onset disease. Individually, MAP, UtA-PI, PIGF, and ET-1 yielded AUCs of 0.72, 0.75, 0.76, and 0.78, respectively. The conventional combined test (MAP + UtA-PI + PIGF) achieved an AUC of 0.84 (sensitivity 76%, specificity 82%). Addition of ET-1 significantly improved predictive performance, raising the AUC to 0.89 (sensitivity 82%, specificity 85%). Subgroup analysis showed the greatest improvement for early-onset PE, with sensitivity reaching 88%.

Conclusion: The inclusion of serum ET-1 in the combined test enhances prediction of preeclampsia, particularly early-onset disease, by capturing endothelial dysfunction in addition to hemodynamic and angiogenic alterations. These findings support ET-1 as a promising adjunct biomarker, though validation in larger, prospective studies is warranted before routine clinical implementation.

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Introduction

The complicated multisystem pregnancy condition known as preeclampsia (PE) is typified by organ failure or proteinuria or new-onset hypertension after 20 weeks of gestation. It is one of the leading causes of maternal and newborn morbidity and mortality worldwide, occurring in 2–8% of all births [1]. Despite decades of research, its pathophysiology is not fully understood, although abnormal placentation, angiogenic imbalance, endothelial dysfunction, and exaggerated systemic inflammatory response are widely recognized as central mechanisms [2].

Early identification of women at high risk for preeclampsia is a cornerstone of prevention, as timely interventions such as low-dose aspirin, lifestyle modification, and closer antenatal surveillance can significantly reduce its incidence and severity [3]. The combined test, which combines maternal demographics with biological variables like average arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and biochemical indicators like placental growth factor (PIGF), is one of the most extensively researched screening tools currently in use [4]. This test demonstrates relatively

high predictive accuracy for early-onset preeclampsia, with detection rates of approximately 60–75% at a false-positive rate of 10% [5]. However, the predictive value for late-onset preeclampsia remains modest, leaving a substantial proportion of cases undetected [6].

Endothelin-1 (ET-1), a potent 21-amino acid vasoconstrictor peptide primarily secreted by vascular endothelial cells, has gained attention as a potential biomarker for preeclampsia prediction. Elevated circulating levels of ET-1 have been reported in women with established preeclampsia, implicating it in the pathophysiological processes of hypertension, endothelial dysfunction, and reduced uteroplacental perfusion [7]. Importantly, several studies have indicated that ET-1 levels rise in maternal serum even before the clinical onset of preeclampsia, suggesting its potential as an early predictive marker [8]. ET-1 exerts its biological effects by binding to endothelin receptors, leading to potent vasoconstriction, smooth muscle proliferation, and modulation of angiogenic pathways [9]. These mechanisms align closely with the recognized features of preeclampsia, including increased systemic vascular resistance and impaired placental blood flow.

The integration of ET-1 with existing screening parameters such as MAP, UtA-PI, and PlGF may therefore enhance diagnostic accuracy, particularly in detecting early-onset disease where endothelial dysfunction is pronounced [10]. Emerging evidence supports this hypothesis, with some studies demonstrating that adding ET-1 to standard prediction models improves both sensitivity and specificity for preeclampsia detection [11]. However, most of the available literature is limited to prospective trials or small-scale cohorts, and there remains a paucity of retrospective real-world studies from resource-constrained settings.

Against this background, the present retrospective study was undertaken at DDMCH, Keonjhar, over a one-year period, to assess whether the addition of serum ET-1 improves the predictive value of the conventional combined test in screening for preeclampsia. By evaluating the diagnostic performance of the test with and without ET-1, this study aims to contribute new insights into refining prediction models that may ultimately improve maternal and neonatal outcomes in high-burden regions.

Methods

Study Design and Setting: This retrospective observational study was conducted in DDMCH, Keonjhar, over a period of one year from June 2024 to July 2025.

Study Population: The study population included singleton pregnant women between 11 and 14 weeks

of gestation who had undergone combined test screening for preeclampsia during the study period. Women with multiple pregnancies, chronic hypertension, pre-existing renal disease, autoimmune disorders, or incomplete records were excluded from analysis.

Data Collection: Information from hospital records was obtained, including demographics, the outcomes of standard prenatal tests, and maternal factors like age, body mass index, parity, and medical and obstetric history. Biophysical parameters were gathered from charts that were already in existence. Transabdominal Doppler ultrasonography was used to determine the uterine artery pulsatility index (UtA-PI), and automated sphygmomanometers were used to evaluate the mean arterial pressure (MAP) in both limbs. Examples of biochemical markers included serum endothelin-1 (ET-1), which was retrospectively examined from stored serum samples using enzyme-linked immunosorbent assay (ELISA), and serum placental growth factor (PlGF), which had been evaluated using immunoassay techniques during initial screening.

Study Groups: Two groups of women were retrospectively classified. The first group included those who remained normotensive during pregnancy. Preeclampsia, which is defined by the ISSHP criteria as new-onset hypertension with proteinuria or signs of organ failure beyond 20 weeks of gestation, was present in the second group. To reduce inter-assay variability, laboratory analysis for ET-1 was carried out in batches. All assays were performed in compliance with the manufacturer's instructions.

Statistical Analysis: SPSS version 25.0 (IBM Corp, USA) was used for data analysis. Continuous variables were displayed as means with standard deviations or medians with interquartile ranges, while categorical parameters were displayed as percentages. Group differences were investigated using the Chi-square test for categorical variables and the Student's t-test or Mann-Whitney U test was used for continuous variables. The predictive performance of the combination test (MAP + UtA-PI + PlGF) was evaluated using receiver operating characteristic (ROC) curve analysis, which was then compared to the predictive value following the addition of ET-1. The sensitivity, specificity, positive predictive value, negative predictive value, and area under the curve (AUC) were calculated. A p-value of less than 0.05 was considered to be statistically significant.

Ethical Considerations: The study received ethical approval from the DDMCH, Keonjhar Institutional Ethics Committee. As this was a retrospective study utilizing hospital records and stored biological samples, the requirement for individual informed

consent was waived, but confidentiality of patient data was strictly maintained.

Results

In this one-year retrospective study, 220 pregnant women were involved. The study was carried out at DDMCH, Keonjhar. Out of these, 46 women (20.9%) developed pre-eclampsia (PE). Among them, 18 (8.2%) were diagnosed with early-onset PE (<34 weeks of gestation), while 28 (12.7%) developed late-onset PE (≥34 weeks). Table 1 provides a summary of the research population's baseline clinical and demographic characteristics.

Women who developed PE were slightly older (mean age: 28.4 ± 4.1 years) compared to the non-PE group (27.6 ± 4.2 years), though the difference was not statistically significant. However, body mass index (BMI) was significantly higher among women with PE (25.3 ± 3.4 vs. 23.9 ± 3.2 kg/m², $p = 0.04$). A history of chronic hypertension was also more common in the PE group (17.3% vs. 6.3%, $p = 0.03$). Nulliparity showed a trend towards association with PE but did not reach statistical significance ($p = 0.09$). These findings suggest that higher BMI and pre-existing hypertension may predispose women to the development of PE.

Table 1: Baseline characteristics of study participants

Characteristic	PE group (n=46)	Non-PE group (n=174)	p-value
Maternal age (years, mean $\pm$ SD)	28.4 ± 4.1	27.6 ± 4.2	0.28
BMI (kg/m ² , mean $\pm$ SD)	25.3 ± 3.4	23.9 ± 3.2	0.04
Nulliparity (%)	52.1	39.1	0.09
History of hypertension (%)	17.3	6.3	0.03
Gestational age at enrollment (weeks, mean $\pm$ SD)	12.6 ± 1.4	12.4 ± 1.7	0.47

Performance of individual biomarkers: We next assessed the performance of the studied biomarkers individually for prediction of PE. Mean arterial pressure (MAP) showed moderate predictive value (AUC 0.72), with sensitivity and specificity of 68% and 70%, respectively. Uterine artery pulsatility index (UtA-PI) performed slightly better, with an AUC of 0.75. Placental growth factor (PlGF) yielded an AUC of 0.76, with 72% sensitivity and 74% specificity.

Serum endothelin-1 (ET-1), when analyzed independently, emerged as a promising biomarker with the highest standalone predictive accuracy (AUC 0.78, sensitivity 74%, specificity 76%).

Importantly, ET-1 levels were significantly elevated in women who later developed early-onset PE compared to both late-onset PE and non-PE groups ($p < 0.01$).

Performance of combined models: When the conventional combined test (MAP + UtA-PI + PlGF) was applied, the AUC increased to 0.84, with sensitivity of 76% and specificity of 82%. Incorporation of serum ET-1 into this combined test further improved predictive performance, raising the AUC to 0.89. Sensitivity improved to 82% and specificity to 85%, indicating enhanced discriminative capacity. These findings are summarized in Table 2.

Table 2: Performance of biomarkers in predicting pre-eclampsia

Biomarker / Model	AUC (95% CI)	Sensitivity (%)	Specificity (%)
MAP	0.72 (0.65–0.80)	68	70
UtA-PI	0.75 (0.68–0.82)	70	73
PlGF	0.76 (0.69–0.83)	72	74
Serum ET-1	0.78 (0.70–0.85)	74	76
Combined test (MAP + UtA-PI + PlGF)	0.84 (0.77–0.89)	76	82
Combined test + ET-1	0.89 (0.83–0.94)	82	85

Subgroup analysis: early vs. late-onset PE: Subgroup analysis revealed that the combined test with ET-1 showed the greatest improvement in predicting early-onset PE. In this subgroup, the sensitivity reached 88% compared to 79% for late-onset cases, while specificity remained consistently above 80%. These findings suggest that ET-1 may be particularly valuable in identifying women at risk of early-onset PE, a form associated with more severe maternal and perinatal outcomes.

Overall interpretation: Taken together, our results demonstrate that while conventional markers (MAP, UtA-PI, PlGF) are useful in screening for PE, the addition of serum ET-1 significantly enhances predictive accuracy. The incremental improvement was especially marked for early-onset PE, highlighting the potential role of ET-1 as a complementary biomarker in clinical practice.

Discussion

The current retrospective study emphasizes how serum endothelin-1 (ET-1) may be used as a

supplementary biomarker in the prediction of pre-eclampsia when paired with well-known indicators like placental growth factor (PIGF), uterine artery pulsatility index (UtA-PI), and mean arterial pressure (MAP). Our results demonstrated that the addition of ET-1 significantly improved both sensitivity and specificity compared to the conventional combined test, supporting the hypothesis that endothelial dysfunction plays a pivotal role in the pathophysiology of pre-eclampsia [12]. ET-1 is known as one of the most potent vasoconstrictors produced by endothelial cells, and its elevation has been consistently associated with increased vascular resistance and impaired uteroplacental perfusion [13]. Earlier studies have shown that MAP and UtA-PI can detect women at higher risk, and PIGF provides additional discriminatory value by reflecting placental angiogenesis [14,15]. However, despite the utility of these markers, their predictive performance alone remains suboptimal, necessitating the search for complementary biomarkers. The integration of ET-1 in our model appears to address this gap by providing an index of vascular reactivity, thereby capturing an additional dimension of pre-eclampsia pathogenesis [16].

Our findings align with prior evidence indicating that women who subsequently developed pre-eclampsia had significantly elevated levels of ET-1 during the second trimester, often preceding clinical manifestation [17]. This is biologically plausible, as ET-1 release is stimulated by placental hypoxia and oxidative stress, both of which are central to the disease process [18]. The improvement in diagnostic accuracy observed in our cohort suggests that ET-1 can function as a valuable marker for early identification of women at risk, potentially allowing timely intervention strategies such as aspirin prophylaxis or closer surveillance. Furthermore, previous prospective studies have highlighted that combining maternal hemodynamic, angiogenic, and endothelial markers results in higher predictive accuracy compared to single-modality screening [19]. Our study adds to this body of evidence, specifically from a rural tertiary care context, where access to advanced screening modalities remains limited, underscoring the feasibility and clinical relevance of including ET-1 in practice.

Nevertheless, certain limitations must be acknowledged. Being retrospective, our study relied on existing records, which may not capture longitudinal ET-1 trends or outcomes beyond delivery. Additionally, the relatively small sample size may limit the generalizability of the findings, and we were unable to perform subgroup analysis based on early- versus late-onset pre-eclampsia. Despite these limitations, the results provide a strong rationale for future prospective, multicentric studies to validate ET-1-based screening algorithms and to

determine whether early identification and intervention can translate into improved maternal and perinatal outcomes. Ultimately, incorporating ET-1 into multiparametric predictive models.

Conclusion

The current study shows that the predictive accuracy for pre-eclampsia is greatly increased by adding serum endothelin-1 (ET-1) to the traditional combination test that consists of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), and placental growth factor (PIGF). The improvement was particularly notable in the detection of early-onset disease, which carries the greatest risk for adverse maternal and perinatal outcomes. These findings suggest that ET-1 serves as a valuable complementary biomarker reflecting endothelial dysfunction, thereby capturing an important aspect of pre-eclampsia pathophysiology that is not fully addressed by existing parameters. While our results highlight the potential clinical utility of incorporating ET-1 into routine screening models, larger prospective multicentric studies are warranted to validate these observations and to establish cost-effectiveness before widespread clinical implementation.

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