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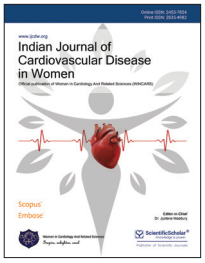

Original Article *Cardiovascular*

Pre-eclampsia Paradigm: Analyzing Angiogenic Markers, Cardiac Biomarkers, and Maternal Myocardial Indices

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ABSTRACT

Objectives: Pre-eclampsia (PE) is a pregnancy-specific hypertensive condition characterized by angiogenic imbalance, abnormal placentation, and elevated maternal cardiovascular stress. Placental dysfunction and disease severity are indicated by soluble fms-like tyrosine kinase-1 to placental growth factor ratio (sFlt-1/PLGF), while myocardial strain is specified by N-terminal pro-brain natriuretic peptide (NT-proBNP) and myocardial work. Conventional echocardiography may fail to identify early cardiac involvement in PE. Myocardial work indices resulting from left ventricular pressure–strain loops provide load-adjusted assessment of myocardial performance and enable detection of subclinical myocardial dysfunction. The integration of angiogenic and cardiac biomarkers, myocardial work indices in prediction, and maternal and fetal outcomes needs to be assessed. The objective of the study is to evaluate the correlation "between angiogenic marker (sFlt-1/PLGF ratio), cardiac biomarker (NT-proBNP), and myocardial work indices in women with PE and to assess their relationship with adverse maternal and neonatal" outcomes.

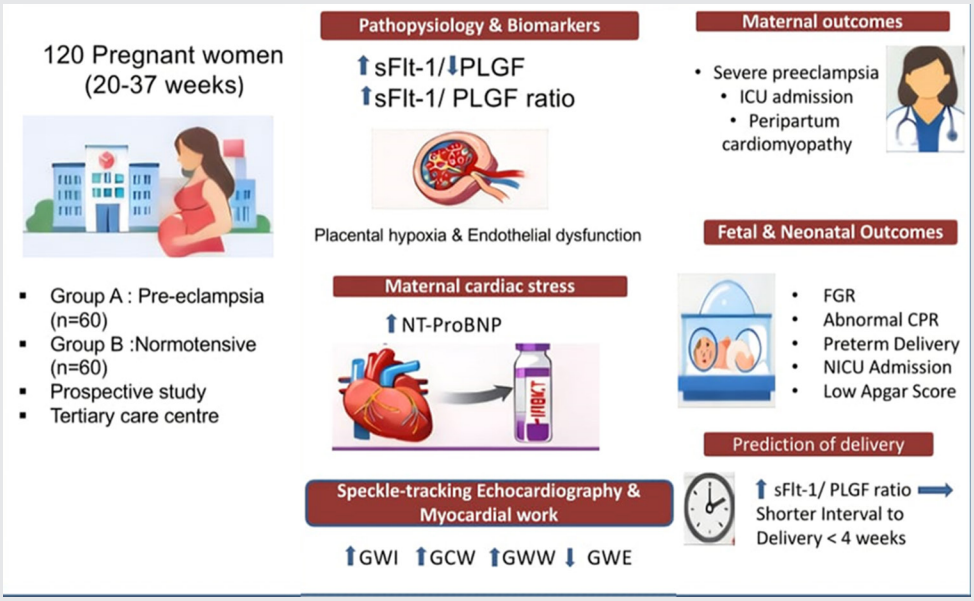
Materials and Methods: It was a prospective cohort study conducted in a tertiary care center from May 1, 2025, to July 31, 2025. A total of 120 pregnant women from 20 to 37 weeks were enrolled. They were divided into two groups of 60 each: Group A: women with PE; Group B: normotensive women. The serum sFlt-1/PLGF ratio and NT-proBNP levels have all been determined through ECLIA on the cobas analyzer (Roche Diagnostics). Global work index (GWI), global work efficiency (GWE), global constructive work (GCW), global wasted work (GWW), utilizing non-invasive pressure-strain loop analysis, and comprehensive transthoracic echocardiography were calculated. Maternal and neonatal outcomes were noted until delivery. A cohort-specific sFlt-1/PLGF cutoff of 102 was identified using receiver operating characteristic analysis. Statistical analysis encompassing Spearman correlation, Chi-square test, Mann–Whitney U test, receiver operating characteristic (ROC) analysis, exhibiting $P < 0.05$, is regarded as significant.

Results: Women with PE demonstrated statistically significant values of sFlt-1/PLGF ratios, NT-proBNP concentrations, and spot protein–creatinine ratios compared with normotensive women ($P < 0.001$). Left ventricular ejection fraction was preserved in both groups. GWE was decreased while GWI, GCW, and GWW were all elevated, indicating a significant change in all myocardial work indices ($P = 0.001$). GWE demonstrated a significant inverse correlation with sFlt-1/PLGF ratio. Higher sFlt-1/PLGF ratios were related to a shorter interval to delivery, with a median delivery interval of approximately 4 weeks. ROC analysis demonstrated the highest sensitivity of global wasted work. Women with PE had more frequent adverse maternal and neonatal outcomes.

Conclusion: PE is associated with marked angiogenic imbalance, elevated NT-proBNP levels, and impaired myocardial work, reflecting early cardiovascular involvement despite preserved systolic function. Combined assessment of angiogenic biomarkers, cardiac biomarkers, and myocardial work indices provides complementary information for risk stratification and long-term cardiovascular diseases in PE.

Keywords: Angiogenic imbalance, Global wasted work, Global work efficiency, Myocardial work indices, N-terminal pro-brain natriuretic peptide, Perinatal outcomes, Pre-eclampsia, Soluble fms-like tyrosine kinase-1/Placental growth factor ratio

ABSTRACT IMAGE



INTRODUCTION

The incidence of pre-eclampsia (PE) is 3–8%. In low-resource settings, approximately 16% of maternal mortality occurs due to hypertensive disorders of pregnancy.[1] The complications of PE are HELLP syndrome, maternal eclampsia, and long-term cardiovascular disease. Fetal risks include preterm delivery, fetal growth restriction (FGR), and stillbirth due to placental insufficiency.[2] Early detection of women at risk can prevent cardiovascular and other complications.[1,2]

The underlying pathophysiology of PE is abnormal placentation, endothelial dysfunction, and imbalance among angiogenic factors, namely placental growth factor, along with anti-angiogenic factors, mainly soluble fms-like tyrosine kinase-1.[3] The angiogenic imbalance leads to diastolic dysfunction and cardiovascular diseases.[4] N-terminal pro-brain natriuretic peptide (NT-proBNP) levels are an early predictor of cardiovascular health since it increases with increased cardiac stress.[5] Myocardial work indices (global work index [GWI], global constructive work [GCW], global wasted work [GWW], global work efficiency [GWE]) are an indicator of left ventricular performance. They have been shown to detect early alterations in cardiac mechanics in PE, complementing both angiogenic and natriuretic biomarkers.[3-6]

Integrating biomarkers such as NT-proBNP, soluble fms-like tyrosine kinase-1 (sFlt-1)/placental growth factor (PLGF) ratio, with advanced echocardiographic measures like myocardial work can predict risk stratification and contribute to better maternal and fetal outcomes.[3-6]

This is a pilot study to integrate angiogenic markers, natriuretic peptides, and myocardial work indices as a combined diagnostic framework in predicting cardiovascular disease in PE.

Aims and objectives

Aim of the study

To evaluate "the correlation between sFlt-1/PLGF ratio, NT-proBNP levels, and myocardial work indices, in patients with PE and their relationship with adverse maternal and fetal outcomes.

Objectives of the study

1. To evaluate the correlation between the Angiogenic marker (sFlt-1/PLGF ratio), cardiac biomarkers (NT-proBNP), myocardial work parameters, in patients with PE
2. To evaluate the relationship of these biomarkers with adverse maternal and fetal outcomes
3. To assess the predictive value of angiogenic markers, cardiovascular biomarkers, and myocardial work indices in PE.

MATERIALS AND METHODS

The Department of Obstetrics and Gynecology conducted a prospective study in Dayanand Medical College and Hospital. Approval for the study was obtained from hospital's "Ethical committee" with Ref.no. (IEC/2025/1018).

The inclusion criteria were all antenatal women between 20 and 37 weeks of gestation singleton live intrauterine pregnancy. The exclusion criteria are intrauterine fetal demise, fetal congenital anomaly, multiple pregnancy, <20 weeks, >37weeks period of gestation, any other medical co-morbidity, including chronic hypertension.

A total of 120 antenatal women from 20 to 37 weeks were recruited from May 1, 2025, to July 31, 2025. The patients were categorized into two groups: group A (60 women with PE) and group B (60 normotensive women).

A comprehensive clinical evaluation was undertaken for each patient, including assessment of maternal age, obstetric history, and relevant risk factors. Obstetric and general physical examination was performed. Routine antenatal investigations, angiogenic markers (sFlt/PLGF ratio), biochemical cardiac markers (NT-proBNP), and echocardiography were done for all participants.

An ECLIA on a cobas analyzer (Roche Diagnostics) assessed serum "PLGF" and "sFlt-1" (pg/mL). Established thresholds indicate a normal sFlt-1/PlGF ratio as ≤38, whereas ≥85 indicates PE. In our investigation, a raised sFlt-1/PLGF ratio >102 was considered abnormal (derived from receiver operating characteristic [ROC] curve analysis).[7] Serum levels of NT-proBNP (pg/mL) were assessed with ECLIA assays on the cobas platform (Roche Diagnostics).[8] A cut-off value >300 pg/mL based on ROC curve analysis was used to indicate myocardial stress. Myocardial work indices were evaluated through speckle-tracking echocardiography, and thresholds were evaluated by ROC analysis. The indices such as global work index <1901 mmHg%, global constructive work <2250 mmHg%, global wasted work >176 mmHg%, and global work efficiency <94.1% have been assessed.[6] Antenatal care was provided in accordance with standard operating procedures. Fetal and maternal outcomes were followed up until delivery.[6-8]

Statistical analysis

Data were summarized using range, mean ± standard deviation, median (interquartile range), absolute frequencies (number of cases), relative frequencies (percentages), as appropriate. Differences in quantitative variables between study groups were assessed employing Mann–Whitney U test.

The Chi-square (χ^2) test has been employed for evaluating categorical variables, and Fisher's exact test was applied when expected cell frequencies were < 5. For determining optimal cut-off value based on sensitivity and specificity, ROC curve analysis was also used and area under curve was computed. Spearman's correlation coefficient was used. Statistical significance was deemed at $P < 0.05$. The statistical analysis was done using the Statistical Package for the Social Sciences (SPSS), version 26.0 (SPSS Inc., Chicago, IL, USA), for Microsoft Windows.

RESULTS

A total of 120 pregnant women were recruited; 60 women with PE constituted Group A, and 60 normotensive women comprised Group B. Baseline demographic characteristics were comparable regarding maternal age, thyroid status, and diabetes status. Primigravidity was observed with significantly greater frequency in Group B ($P = 0.025$). Women with PE had significantly greater systolic and diastolic blood pressures ($P < 0.001$). NT-proBNP concentrations, the spot protein–creatinine ratio, and angiogenic markers like sFlt-1/PLGF ratio were significantly higher in Group A [Table 1].

Echocardiographic evaluation demonstrated significant left ventricular remodeling in increased "left ventricular mass index and left atrial volume index in group A. Diastolic dysfunction was evident with increased A-wave velocity, reduced E-wave velocity, and elevated E/e′ ratio, while left ventricular ejection fraction" remained preserved. The global longitudinal strain (GLS) analysis revealed a statistically significant difference between the study groups [Table 2].

A statistically significant difference in myocardial parameters, GWI, GCW, GWW, and GWE was observed between two groups ($P = 0.001$) [Table 2].

The sFlt-1/PLGF ratio can be used to predict interval to delivery, which has been recorded [Table 3]. Women with higher sFlt-1/PLGF ratios (>150) delivered within 2–4 weeks of assessment, compared with those with ratios between 38 and 150 ($P = 0.080$).

The ROC-derived cut-off values revealed the highest sensitivity and specificity of GWW >176 mmHg% and a GWE under 94.1%, respectively. NT-proBNP levels exceeding 300 pg/mL demonstrated high sensitivity, while a sFlt-1/PLGF ratio >102 showed high specificity in identifying PE [Table 4].

The diagnostic performance of myocardial work indices, angiogenic markers, and NT-proBNP done with area under the curve (AUC) values (0.90–1.00) [Figure 1]. Among the myocardial work parameters, both GWW and GWI demonstrated the highest diagnostic accuracy.

Scatter plot analysis revealed a statistically significant correlation among sFlt-1/PLGF ratio and GWE. Higher sFlt-1/PLGF ratios have been associated with a progressive decrease in GWE [Figure 2].

Adverse maternal outcomes such as severe PE, ICU admission, and peripartum cardiac complications were more frequent in group A [Figure 3]. Neonatal outcomes

Table 1: Comparative demographic characteristics and maternal risk factors among study groups.

Demography			
Parameters	**Group A (*n*=60)**	**Group B (*n*=60)**	***P*-value**
Age in years Median [IQR]			
<30 yrs (%)	28 (20.0)	31 (15)	0.585
>30 yrs (%)	32 (25.0)	29 (18.3)	
Severe pre-eclampsia *n* (%)	16 (26.7)	0 (0)	0.001
SBP (mmHg), Median [IQR]	150 (150–160)	110 (100–120)	0.001
DBP (mmHg), Median [IQR]	100 (90–110)	70 (60–70)	0.001
sFlt-1 (pg/mL), Median [IQR]	14345.5 (11123–17045)	1900 (1500–2400)	0.001
Spot urine P: C, Median [IQR]	0.55 (0.4–0.9)	0.10 (0.1–0.1)	0.001
NT-ProBNP (pg/mL), Median [IQR]	961.00 (578.75–1532.25)	70.50 (53.5–98.75)	0.001

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, IQR: Interquartile range, sFlt-1: Soluble fms-like tyrosine kinase-1, NT-ProBNP: N-terminal pro-brain natriuretic peptide. Statistically significant threshold is 0.05.

Table 2: Comparison of echo indices and myocardial work parameters.

Echocardiographic parameters										
Parameters	**Group A (*n*=60)**				**Group B (*n*=60)**				**Z**	***P*-value**
	Mean	**SD**	**Median**	**IQR**	**Mean**	**SD**	**Median**	**IQR**		
Echo indices										
LEVDVI (m^l/m^2)	64.02	8.11	65.85	59.05–68.8	50.17	5.80	48.90	45.1–55.45	−7.743	0.001
RWT	0.46	0.11	0.46	0.435–0.54	0.22	0.04	0.23	0.2–0.24	−9.004	0.001
LVMI (g/m^2)	116.62	12.14	118.10	105.475–125.475	78.48	7.01	78.55	72.55–84.075	−9.448	0.001
LAVI (m^l/m^2)	21.03	3.91	22.10	19.1–23.4	13.47	1.62	13.75	12.075–15	−8.157	0.001
E	1.00	0.15	1.02	0.89–1.115	0.92	0.06	0.91	0.88–0.99	−3.405	0.001
A {m/s)	0.80	0.13	0.83	0.6725–0.8875	0.69	0.07	0.69	0.62–0.74	−5.069	0.001
E/e	16.00	3.72	15.85	12.425–19.825	8.91	1.23	9.00	7.825–9.8	−9.329	0.001
EF (%)	55.19	2.79	55.20	52.625–57.875	62.77	3.37	64.00	60.5–65	222.000	0.001
GLS (%)	−14.92	4.15	−15.41	−16.0225–−14.77	−20.20	1.09	−20.26	−21.13–−19.265	−9.448	0.001
Myocardial work										
GWI (mm/Hg%)	2202.10	220.75	2189.00	1989–2353.25	1748.58	99.33	1767.00	1678–1800.75	−9.041	0.001
GCW (mm/Hg%)	2668.40	221.57	2683.50	2498.5–2845	2064.12	1289.69	1868.50	1810–1989	−9.083	0.001
GWW (mm/Hg%)	314.03	71.60	300.00	256.25–376	117.50	23.72	110.00	100–130	−9.453	0.001
GWE (mm/Hg%)	90.75	2.78	90.95	88.825–93	95.98	1.19	96.10	95.1–96.975	−9.181	0.001

LVEDI: Left ventricular end diastolic volume index, LVMI: Left ventricular mass index, LAVI: Left atrial volume index, E: E wave, A: A wave, E/e: Early diastolic transmittal flow velocity, EF: Ejection fraction, GLS: Global longitudinal strain, GWI: Global work index, GCW: Global constructive work, GWW: Global wasted work, GWE: Global work efficiency, IQR: Interquartile range, SD: Standard deviation. Statistically significant threshold is 0.05.

such as Apgar scores, preterm delivery, low birth weight, and neonatal intensive care unit admission were significantly increased in the PE group [Figure 4].

DISCUSSION

Angiogenic markers, cardiac biomarkers, and myocardial work were analyzed to predict cardiovascular impact in PE. The sFlt-1/PLGF ratio significantly increased in placental hypoxia and endothelial dysfunction.[3] The ISSHP 2021 guidelines highlight that sFlt-1/PLGF ratio <38 effectively rules out PE, while higher values predict the development of PE within 1–4 weeks.[9] This ratio also aids in monitoring disease progression and predicting adverse outcomes, notably FGR, preterm birth, and stillbirth. Research by Giorgione *et al*. observed that elevated sFlt-1/PLGF ratios are correlated with cardiac remodeling in hypertensive pregnancies.[3,9,10]

In our study, NT-proBNP levels were statistically significantly greater in women having PE in comparison to normotensive

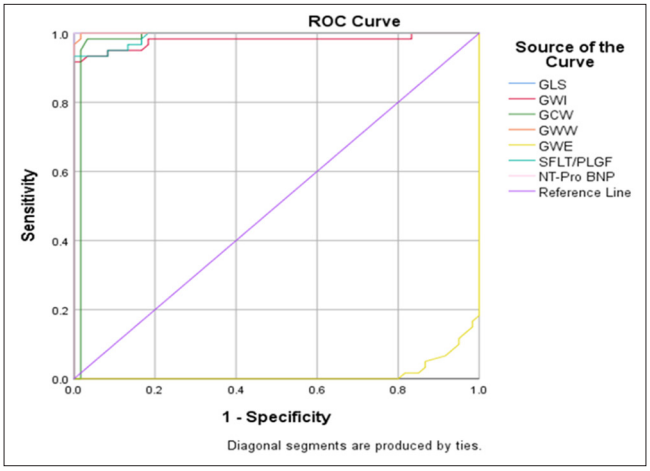


Figure 1: Receiver operating characteristic (ROC) curve analysis of myocardial work indices, angiogenic markers, and cardiac biomarkers. (GLS: Global longitudinal strain, GWI: Global work index, GCW: Global constructive work, GWW: Global wasted work, GWE: Global work efficiency, sFLT/PLGF: Soluble fms like tyrosine kinase, PlGF: Placental like growth factor, NT-proBNP: N-Terminal pro-B-type natriuretic peptide).

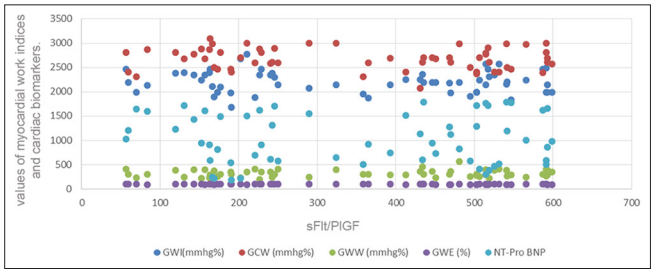


Figure 2: Correlation of myocardial work and cardiac biomarkers with angiogenic markers. GWW: Global wasted work, GCW: Global constructive work, (GWW: Global waste work, GWE: Global work efficiency, NT-proBNP: N-Terminal pro-B type natriuretic peptide).

pregnant women, reflecting increased myocardial stress. NT-proBNP is elevated in response to ventricular stretch, and causing greater risk of maternal cardiovascular disease.[5] Zeng *et al.* also observed that NT-proBNP is a useful biomarker for diagnosing and evaluating cardiac involvement in pre-eclamptic women.[5]

Our research demonstrated that PE women had higher left ventricular filling pressures (P = 0.001). The E/e′ ratio is a validated marker of diastolic function, and higher values reflect impaired relaxation and elevated filling pressures. These findings are consistent with a systematic review as well as meta-analysis by the American Heart Association, which also reported similar findings.[4] A statistically significant increase of left ventricular mass index (LVMI) and relative wall thickness (RWT) (P = 0.001) was observed. These changes suggest a compensatory remodeling response for maintaining left ventricular performance under increased

Table 3: Association between sFlt-1/PlGF ratio and interval to delivery.

Interval to delivery (in weeks)	sFlt-1/PlGF				Total	Chi-square value	*P*-value
	38–150		>150				
	n	%	*n*	%			
0–2	2	28.6	20	37.7	22	6.753	0.080
2–4	0	0.0	15	28.3	15		
4–6	1	14.3	9	17.0	10		
>6	4	57.1	9	17.0	13		

sFlt-1: Soluble fms-like tyrosine kinase-1, PLGF: Placental growth factor ratio. Statistically significant threshold is 0.05.

cardiac workload. Underscored a strong positive correlation between BNP levels, LVMI, and RWT in women having PE.[4] GLS represents the longitudinal deformation of the myocardium and provides additional insights into systolic function. Although it was not a predefined primary endpoint of this study, the changes observed in GLS might suggest early functional alterations in the myocardium among the study participants.

Myocardial work indices, such as "global constructive work," "global wasted work," and "global work index," have been significantly greater in PE women in current research (P = 0.001), suggesting significant alterations in cardiac mechanics. Piao *et al.* reported similar increases in myocardial work parameters among pre-eclamptic women, supporting their relevance in identifying subclinical myocardial dysfunction.[6] The observed rise in GWI and GCW reflects myocardial contractile effort required to compensate for increased afterload, while elevated GWW suggests greater myocardial wall stress and reduced mechanical efficiency. These parameters can be beneficial in predicting cardiovascular diseases.[6,11]

ROC analysis demonstrated a statistically significant inverse correlation of GWE with sFlt-1/PLGF ratio (r = −0.275, P = 0.034). This indicates that progressive angiogenic dysregulation is accompanied by a gradual decline in myocardial work efficiency. Unlike absolute myocardial work indices that primarily reflect compensatory increases in workload, GWE incorporates both constructive and wasted myocardial work, thereby providing an integrated measure of overall cardiac efficiency. The worsening placental dysfunction parallels escalating maternal cardiovascular stress, even when left ventricular ejection fraction remains preserved. Current finding supports the role of GWE as a marker of disease severity.[3]

In our study, myocardial work indices effectively differentiated PE from normotensive pregnancy, with global wasted work demonstrating optimal diagnostic accuracy (AUC = 1.00) in detecting early myocardial involvement despite preserved ejection fraction. NT-proBNP as well as sFlt-1/PLGF ratio

Table 4: Diagnostic accuracy of myocardial work indices, angiogenic markers, and cardiac biomarkers in pre-eclampsia.

Diagnostic accuracy	GWI		GCW		GWW	
Statistic	**Value (%)**	**95% CI**	**Value (%)**	**95% CI**	**Value (%)**	**95% CI**
Sensitivity	91.67	81.61–97.24	98.33	91.06–99.96	100.00	94.04–100.00
Specificity	100.00	94.04–100.00	96.67	88.47–99.59	98.33	91.06–99.96
Positive predictive value	100.00	93.51–100.00	96.72	88.30–99.14	98.36	89.57–99.76
Negative predictive value	92.31	83.83–96.52	98.31	89.25–99.75	100.00	93.94–100.00
Accuracy	95.83	90.54–98.63	97.50	92.87–99.48	99.17	95.44–99.98
Diagnostic accuracy	**GWE**		**NT-ProBNP**		**SFLT/PLGF**	
Statistic	**Value (%)**	**95% CI**	**Value (%)**	**95% CI**	**Value (%)**	**95% CI**
Sensitivity	93.33	83.80–98.15	91.67	81.61–97.24	93.33	83.80–98.15
Specificity	91.67	81.61–97.24	100.00	94.04–100.00	95.00	86.08–98.96
Positive predictive value	91.80	82.83–96.30	100.00	93.51–100.00	94.92	86.08–98.26
Negative predictive value	93.22	84.17–97.26	92.31	83.83–96.52	93.44	84.66–97.35
Accuracy	92.50	86.24–96.51	95.83	90.54–98.63	94.17	88.35–97.62

GWI: Global work index, GCW: Global constructive work, GWW: Global wasted work, GWE: Global work efficiency, IQR: Interquartile range, SD: Standard deviation, SFlt-1: Soluble fms-like tyrosine kinase-1, NT-ProBNP: N-terminal pro-brain natriuretic peptide, PLGF: Placental growth factor ratio, CI: Confidence interval. The statistically significant threshold is < 0.05.

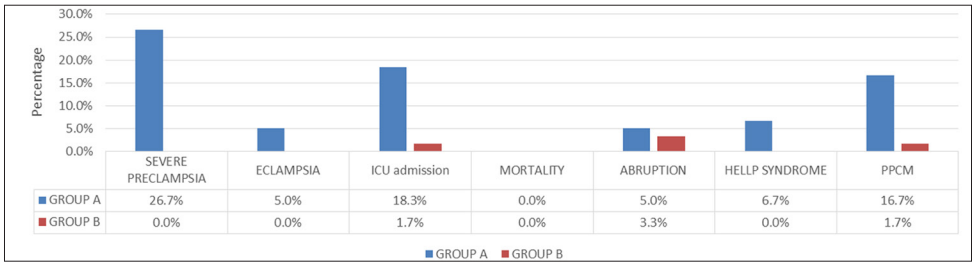


Figure 3: Maternal morbidity and critical care requirements across study groups. (PPCM: Postpartum cardiomayopathy).

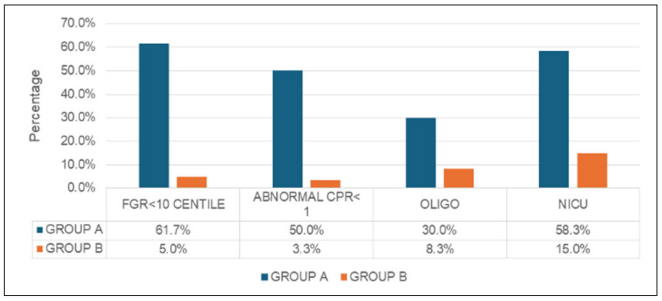


Figure 4: Comparison of neonatal and fetal outcomes between the two study groups. (OLIGO: Oligohydramnios, NICU: Neonatal intensive care unit).

demonstrated strong diagnostic performance, indicating angiogenic imbalance and myocardial stress in PE, respectively.[3,5,6,12]

In women having PE, sFlt-1/PLGF ratio appears to be useful marker for forecasting the need for an earlier delivery. In the present study, higher sFlt-1/PLGF ratios were associated with significantly shorter intervals to delivery, with a median delivery interval of approximately four weeks. This relationship likely reflects progressive angiogenic imbalance resulting from worsening placental ischemia, leading to widespread maternal endothelial dysfunction. Dröge *et al.*, similarly described that increased sFlt-1/PLGF ratio reliably predicts delivery within a four-week window in women with PE.[3,9,13]

Overall sFlt-1/PLGF ratio, NT-proBNP, and myocardial work indices (GWI, GWW, GCW) were all significantly elevated with PE. GWE was significantly decreased in PE. All these findings were associated with adverse maternal and neonatal outcomes.

CONCLUSION

The current research highlights that women with PE display significant angiogenic imbalance, increased NT-proBNP levels, and impaired myocardial work. These abnormalities were closely related to adverse maternal and fetal outcomes.

The relevance of integrating angiogenic markers, cardiac biomarkers, and myocardial work indices can predict subclinical cardiovascular involvement.

To the best of our knowledge, our study seems to be the pilot study to integrate angiogenic markers, cardiac biochemical, and myocardial work in PE; more extensive research is required for validation of these results.

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Ethical approval: The research/study was approved by the Institutional Review Board at Dayanand Medical College & Hospital, number IEC NO: 2025-1018, dated April 30, 2025.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Use of artificial intelligence (AI)-assisted technology for manuscript preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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