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STUDY ON EVALUATION OF SFLT1/PLGF RATIO FOR PREDICTION OF PRE-ECLAMPSIA IN THE SECOND AND THIRD TRIMESTER OF PREGNANCY: AN OBSERVATIONAL STUDY.

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ABSTRACT

Background

Pre-eclampsia (PE) is a critical pregnancy complication leading to adverse perinatal outcomes like fetal growth restriction, stillbirth, oligohydramnios, eclampsia, and HELLP syndrome. An imbalance between pro-angiogenic (PlGF) and anti-angiogenic (sFLT-1) factors increases the sFLT-1/PlGF (sFlt1/PlGF) ratio, detectable about four weeks before the symptoms appear. The study was conducted to determine the predictive value of the sFlt1/PlGF ratio for the development of PE in high-risk pregnant women during the late 2nd and 3rd trimesters.

Methods

The study included 50 high-risk pregnant females between 24 and 32 weeks of gestation. Participants were selected based on criteria such as age > 30 years, BMI > 30 kg/m², previous history of PE, PAPPA < 0.4 MoM, increased UtA PI at 11-13 weeks, twin pregnancy, IVF conception, and history of FGR. The sFlt1/PlGF ratio was determined, and participants were monitored for the development of Pre-Eclampsia. The study determined the specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV).

Results

Among the participants, 70% were over 30 years of age, and 30% were under 30. The sFlt1/PlGF ratio demonstrated a high NPV of 96.7%, indicating a reliable prediction for the absence of PE within a week. The PPV was 63.5%, suggesting a strong indication of PE development with a high ratio (>38). The sensitivity of the ratio was 92.3%, and the specificity was 81.08%, confirming its effectiveness in correctly identifying both the presence and absence of pre-eclampsia.

Conclusion

The sFlt1/PlGF ratio is a valuable predictive tool for identifying the possibility of the development of PE in high-risk pregnancies, with high NPV, sensitivity, and specificity. It effectively aids in early identification and management, potentially improving maternal and fetal outcomes.

Recommendations

Clinicians should consider incorporating the sFlt1/PlGF ratio in the routine assessment of high-risk pregnant women to enhance early detection and intervention strategies for pre-eclampsia.

Keywords: *Pre-eclampsia, sFLT-1/PlGF Ratio, High-Risk Pregnancy, Predictive Value, Maternal Health.*
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INTRODUCTION

Pre-eclampsia is a leading cause of maternal and fetal morbidity and mortality, complicating about 5 to 15% of pregnancies in India. It is characterized by the development of Hypertension after 20 weeks of gestation with signs of maternal organ dysfunction, with or without proteinuria. The clinical presentation is variable, ranging from severe and rapidly progressive early-onset PE, which warrants preterm delivery, to late-onset PE which develops >34 weeks of gestation. The classical standards for the diagnosis of PE are not sufficient to encompass the complexity of the syndrome. Hence, for the optimum management of such high-risk pregnancies, early and reliable detection with intensified monitoring and timely referral to a specialized perinatal care center is essential to reduce maternal and perinatal morbidity and mortality [1]. Even while placental malfunction is widely acknowledged to play a key role, the etiology of PE is still not fully understood. Recent studies have highlighted the critical balance between pro- and anti-angiogenic variables in the pathogenesis of PE. Placental growth factor (PlGF), a pro-angiogenic factor, and soluble fms-like tyrosine kinase-1 (sFLT-1), an anti-angiogenic factor, are significant biomarkers involved in this balance. An elevated sFLT-1/PlGF (sFlt1/PlGF) ratio has been observed many weeks before the clinical onset of PE, suggesting its potential utility as an early prognostic

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indicator, thereby being helpful in the triage of high-risk pregnancies [2].

The diagnostic and prognostic significance of sFLt1/PlGF is becoming more widely known. Recent guidelines from the American College of Obstetricians and Gynecologists (ACOG) and the International Federation of Gynecology and Obstetrics (FIGO) recommend its adoption in specific clinical conditions to aid in PE management and prediction [3]. Studies reveal that a low sFlt1/PlGF ratio (<38) almost completely rules out the development of PE within a week, but a high ratio (>38) is associated with a greater likelihood of the condition manifesting rapidly [4, 5].

The utility of the sFLt1/PlGF ratio extends beyond prediction, as it also contributes to understanding the severity and prognosis of pre-eclampsia. For instance, higher ratios, > 85 between 20 – 33+6 weeks, and > 110 beyond 33+6 weeks, correlate with adverse outcomes such as fetal growth restriction and HELLP syndrome [6]. Additionally, incorporating this biomarker into clinical practice can help stratify patients' risk, enabling targeted surveillance and timely intervention, which are crucial for improving maternal and perinatal results [7].

The study aims to estimate the predictive value of the sFLt1/PlGF ratio for the development of PE in high-risk pregnant females during the late 2nd and 3rd trimesters.

METHODOLOGY

Study Design

It was a Prospective, Monocentric, Observational study.

Study Setting

The study was conducted at Holy Promise Hospital, East Patel Nagar, Patna. This tertiary care hospital has a dedicated Obstetrics and Gynaecology department equipped with the necessary facilities for high-risk pregnancy management. The study was carried out for a duration of 6 months from December 2023 to May 2024.

Participants

The study included 50 high-risk pregnant women attending the outpatient department (OPD) of the hospital between 24 and 32 weeks of gestation.

Inclusion Criteria

- Age > 30 years
- Body Mass Index (BMI) > 30 kg/m²
- Previous history of PE
- Pregnancy-associated plasma protein A (PAPPA) < 0.4 MoM (as per the Double Marker report)
- Increased uterine artery pulsatility index (UtA PI) at 11 to 13 weeks of gestation
- Twin pregnancy
- In vitro fertilization (IVF) conception
- History of fetal growth restriction (FGR) in the previous pregnancy

Exclusion Criteria

- Women with chronic hypertension
- Those with pre-existing diabetes mellitus
- Participants with known renal diseases

Sample size

To calculate the sample size for this study, the following formula was used for estimating a proportion of a population:

$$n = \frac{Z2 \times p \times (1-p)}{E2}$$

Where:

- n = sample size
- Z = Z-score corresponding to the desired level of confidence
- p = estimated proportion in the population
- E = margin of error

Bias

To minimize bias, laboratory personnel were blinded to clinical outcomes, standardized protocols were used for data collection and analysis, and consecutive patients meeting inclusion criteria were included to reduce selection bias. These measures ensured consistency and reliability in the study findings.

Variables

Variables included sFLt1/PlGF ratio, development of PE within a week of testing, Age, BMI, Parity, Method of conception, History of PE, History of FGR, UtA PI, PAPPA levels.

Data Collection

Data were collected through a combination of patient interviews, medical record reviews, and laboratory tests. Each participant's sFlT1/PlGF ratio was measured at the time of recruitment.

High-risk pregnant women were recruited from the OPD based on the specified inclusion and exclusion criteria. Demographic and clinical data, involving age, BMI, parity, method of conception, and medical history, were systematically collected. Blood samples were then drawn and analyzed to determine the sFLt1/PlGF ratio. Following the initial test, participants were closely monitored for one week to observe the development of pre-eclampsia.

Statistical Analysis

Software for statistical analysis was used. For the demographic and clinical profile, the study comprised frequency distributions, mean, and standard deviation. The sFLt1/PlGFratio's specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) were all assessed. Utilizing chi-square tests, a comparison of the sFLT-1/PlGF ratios between those who developed PE and those who did not was made. Statistical

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significance was attained when the p-value was less than 0.05.

Ethical considerations

The study protocol was approved by the Ethics Committee and written Informed Consent was received from all the participants.

RESULT

The distribution of participants based on demographic and clinical profiles is detailed in Table 1. Among the participants, 70% were over 30 years of age, and 30% were under 30. Regarding BMI, 48% had a BMI greater than 30 kg/m², while 52% had a BMI less than 30 kg/m². The parity distribution showed that 58% were primiparous, and 42% were multiparous. For the method of conception, 48% conceived spontaneously, and 52% (26 women) conceived through ART.

Table 1: Distribution of Participants According to Inclusion Criteria

Characteristic	Category	Frequency (n=50)	Percentage (%)
Age	> 30 years	35	70.0
	< 30 years	15	30.0
BMI	> 30 kg/m²	24	48.0
	< 30 kg/m²	26	52.0
Parity	Primi	29	58.0
	Multi	21	42.0
Method of Conception	Spontaneous	24	48.0
	ART	26	52.0
History of Pre-eclampsia in previous pregnancy	Present	18	36.0
	Absent	32	64.0
History of FGR in previous pregnancy	Present	12	24.0
	Absent	38	76.0
UtA PI at 11 -13+6 wks	> 95th centile	24	48.0
	< 95th centile	26	52.0
PAPP-A	< 0.4 MoM	19	38.0
	> 0.4 MoM	31	62.0

A significant portion of the participants, 36%, had a history of pre-eclampsia in previous pregnancies, whereas 64% did not. Additionally, 24% had a history of FGR in a previous pregnancy, and 76% did not. The UtA PI was above the 95th percentile at 48% and below the 95th percentile at 52%. Lastly, PAPP-A levels were below 0.4 MoM in 38% and above 0.4 MoM in 62%.

The predictive performance of the sF/P ratio for pre-eclampsia was assessed by categorizing participants based on their ratio values (Table 2). Among the women with an sF/P ratio below 38, only one developed PE, while 30 did not, resulting in a significant p-value of 0.001. Conversely, among those with an sF/P ratio above 38, 12 developed pre-eclampsia, while seven did not.

Table 2: Predictive Performance of sFLt1/PlGF Ratio

sFLT-1/PlGF Ratio	Pre-eclampsia		Total	p-value
	(+)	(-)		
< 38	1	30	31	0.001
> 38	12	7	19	
Total	13	37	50	

The sFLt1/PlGF ratio's PPV, NPV, sensitivity, and specificity were computed in the study. A low sFlT1/PlGF ratio (<38) is highly likely to correctly predict the absence of PE after a week, as indicated by the NPV of 96.7%. The chance that a high sFLt1/PlGF ratio (>38) accurately predicts the occurrence of PE is reflected in the PPV of 63.5%. The efficiency of the sF/P ratio in accurately identifying females who developed PE was demonstrated by its sensitivity of 92.3%. The ratio's specificity of 81.08% demonstrated its ability to reliably identify females who did not have PE.

- NPV = TN/ TN+ FN = 30/30+31 x 100 = 96.7%
- PPV = TP/TP+FP = 12/12+7 x100 = 63.5%
- Sensitivity = TP/TP+FN = 12/ 12+1 x100 = 92.3%
- Specificity = TN/ TN+FP = 30/30+7 x 100 = 81.08%

DISCUSSION

The study results indicated that the sFLt1/PlGF ratio is a highly effective predictive tool for the development of PE. The majority of participants were over 30 years old (70%), with nearly equal distribution across BMI categories and parity (primiparous and multiparous). A significant

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number of participants had a previous history of PE (36%) and FGR (24%).

The predictive performance of the sFLt1/PlGF ratio was measured by categorizing participants based on their ratio values, with a cut-off value of 38. Among females with an sFLt1/PiGF ratio below 38, only one developed pre-eclampsia, while 30 did not, resulting in a significant p-value of 0.001. Conversely, among those with sFLt1/PlGF ratio above 38, 12 developed pre-eclampsia, while seven did not. The study calculated the PPV, NPV, sensitivity, and specificity of the sFLt1/PlGF ratio. The NPV was found to be 96.7%, indicating a high probability that a low sFLt1/PlGF ratio (<38) correctly predicts the absence of PE within a week. The PPV was 63.5%, reflecting the probability that a high sFLt1/PlGF ratio (>38) correctly predicts the presence of PE. The sensitivity was 92.3%, demonstrating its effectiveness in correctly identifying women who developed PE. The specificity was 81.08%, indicating the ratio's ability to accurately identify women who did not develop PE. The high NPV of 96.7% suggests that this ratio is a reliable predictor for the absence of PE within a week. This finding is crucial for clinicians as it helps identify patients who are unlikely to develop pre-eclampsia, thereby reducing unnecessary interventions and monitoring for those patients. Additionally, the good sensitivity (92.3%) and specificity (81.08%) values indicate that the ratio is highly capable of identifying patients who will develop pre-eclampsia and accurately identifying those who will not, respectively.

Several studies have shown results similar to our study and have collectively highlighted the significant role of the sFLt1/PlGF ratio in predicting PE, particularly in identifying those at high risk and those unlikely to develop the condition. The PROGNOSIS Asia (Prediction of short term Outcome in pregnant women with Suspected preeclampsia study using sFLt1/PlGF ratio in an Asian population), carried out by Bian X, Biswas A, et al, was a multicentric blinded noninterventional study. They concluded that sFLt1/PlGF ratio < 38 had an NPV of 98.6% (95% CI) for ruling out PE within a week, 76.5% sensitivity, 82.5% specificity, and a PPV of 30.3% The study validated the clinical performance of sFLt1/PlGF ratio cut off of 38 in Asian population to aid the short term prediction of PE in conjunction with the other diagnostic and clinical information [8].

Economical evaluation of the sFLt1/PlGF ratio for the short-term prediction of PE in the Japanese cohort of PROGNOSIS Asia study concluded that the sFLt1/PlGF ratio test is likely to reduce the unnecessary hospitalizations of women at low risk of developing PE in short-term, resulting in significant cost savings in the Japanese health care system [9].

The STEPS (Study of Early Pre eclampsia in Spain) concluded that the sFLt1/PlGF ratio can improve the prediction of early-onset Pre eclampsia for women at risk of developing this condition. This result validates the ratio's usage as a tool for diagnosis in healthcare facilities to firmly rule out pre-eclampsia [10].

Another study looked at the sFLt1/PlGF ratio's diagnostic accuracy as a PE marker. The findings further supported the efficacy of the sFLt1/PlGF ratio as a predictive biomarker by showing that it can distinguish PE individuals from non-PE patients with greater accuracy [11].

Generalizability

Applying the study's findings on the sFLT1/PLGF ratio to a larger population requires further research with diverse samples to confirm generalizability. The test's high sensitivity (92.3%), specificity (81.08%), and negative predictive value (96.7%) suggest it is reliable for early detection and ruling out pre-eclampsia in high-risk pregnancies. Implementing this test in routine prenatal care could enhance maternal and fetal outcomes. Evaluating cost-effectiveness and comparing it with other methods in broader settings will ensure practical application in varied healthcare environments.

CONCLUSION

The sFLt1/PlGF ratio serves as a valuable tool for predicting PE in high-risk pregnancies. Its high negative predictive value and good sensitivity and specificity make it an effective measure for early identification and management of PE, potentially improving maternal and fetal outcomes. The findings support the use of the sFLt1/PlGF ratio in clinical practice for better management of high-risk pregnancies and early intervention strategies.

Limitations

The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of a comparison group also poses a limitation for this study's findings.

Recommendation

Clinicians should consider incorporating the sF/P ratio in the routine assessment of high-risk pregnant women to enhance early detection and intervention strategies for pre-eclampsia.

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List of abbreviations

PE: Pre-eclampsia
PlGF: Placental Growth Factor
sFLT-1: Soluble fms-like Tyrosine Kinase-1
PPV: Positive Predictive Value
NPV: Negative Predictive Value
BMI: Body Mass Index
PAPPA: Pregnancy-associated plasma Protein A

MoM: Multiple of the Median
UtA PI: Uterine Artery Pulsatility Index
IVF: In Vitro Fertilization
FGR: Fetal Growth Restriction
OPD: Outpatient Department
ART: Assisted Reproductive Technology
ACOG: American College of Obstetricians and Gynecologists
FIGO: International Federation of Gynecology and Obstetrics
HELLP Syndrome: Hemolysis, Elevated Liver enzymes, and Low Platelets Syndrome

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Conflict of interest
The authors have no competing interests to declare.

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