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Original Research Article

A COMPARATIVE STUDY OF ANGIOGENIC MARKERS (SFLT-1/PIGF RATIO) WITH UTERINE ARTERY DOPPLER INDICES IN PREDICTION OF PREECLAMPSIA AT 22-24 WEEKS PERIOD OF GESTATION AT TERTIARY CARE CENTRE: AN OBSERVATIONAL STUDY

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ABSTRACT

Background: Preeclampsia is a condition that happens during pregnancy and can harm both the mother and the baby. Various pro and antiangiogenic factors like sFlt-1 and Plgf have been linked to the etiopathogenesis of placental vascular disease and their combination with uterine artery doppler studies may improve the prediction accuracy. Present study was conducted to analyze sFlt-1/Plgf ratio and uterine artery doppler indices among high risk patients and to compare these in prediction of preeclampsia. **Materials and Methods:** This was a hospital based prospective study done on fifty pregnant women at risk of PE at the department of obstetrics and gynaecology in SSIMS & RC, Davangere, Karnataka, India during one-year period. They giving consent and satisfying inclusion criteria were evaluated for various risk factors and were subjected to sFlt-1/Plgf ratio test and uterine artery doppler study at 22-24 weeks period of gestation. They were followed up and maternal outcome was analysed. **Result:** Majority (52%) of study participants had late onset of pre- eclampsia and about 48% of them had early onset of pre-eclampsia. Uterine artery mean PI was significantly higher in the early-onset PE as compare to late-onset PE, which was statistically non-significant ($p>0.05$). However, the difference in PlGF levels was much more pronounced in late-onset cases than in early-onset PE. There were significant differences in mean (IQR) PlGF levels. Maternal serum sFlt1 levels were insignificantly higher in the early-onset PE than in late-onset group. Finally, although the sFlt1/PlGF ratio was significantly increased in the early-onset PE compared to late-onset group. The sFlt-1/Plgf was found to be a good predictor tool with a sensitivity of 91.4% and specificity of 87.7%. Uterine artery RI, PI and SD had their sensitivities as 71.4%, 74.3% and 60.5% respectively, while their specificities were 76.9%, 73.8% and 50.8% respectively. It was observed that sFlt-1/Plgf had highest positive predictive value (PPV) of 80% as well as best negative predictive value (NPV) of 95% amongst all. **Conclusion:** The sFlt-1/Plgf ratio was found to be a better indicator than uterine artery Doppler measurements for predicting pre-eclampsia between 22-24 weeks pregnancy. So, the sFlt-1/Plgf ratio could be a useful tool for predicting pre-eclampsia and might help in managing the condition to improve outcomes for both the mother and the baby.

INTRODUCTION

Preeclampsia is a condition that happens during pregnancy and can harm both the mother and the baby. It occurs in 2%–8% of all pregnancies.[1] In clinical practice, preeclampsia is diagnosed when after the 20th gestational week, hypertension (systolic blood pressure 140 mmHg or more and diastolic blood pressure 90 mmHg or more, when measured twice in a period of not less than 6 h) and proteinuria (more than 300 mg/L in a 24-h period) commence. In more serious cases, symptoms like headache, impaired vision, epigastric pain, thrombocytopenia, hemolysis or abnormal liver and

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renal function can occur. Early- onset preeclampsia is associated with a higher incidence of adverse perinatal outcomes, including oligohydramnios, Apgar score < 7, stillbirth and early neonatal death, compared with late- onset PE.[2,3] Early treatment is important to improve maternal and foetal outcomes,[4] and the classical clinical markers of PE (hypertension and proteinuria) are poorly predictive of those who will develop the condition, markers of angiogenesis have been examined as aids to PE prediction.

A variety of pro and antiangiogenic factors involved in placental vascular development have been studied. The families of vascular endothelial growth factor (VEGF) and angiopoietin (Ang) are most extensively studied among other factors.

Soluble Fms-like tyrosine kinase 1 (sFlt-1) is a variant of the Flt-1 receptor for placental growth factor (Plgf) and for VEGF. When the placenta produces more sFlt-1, it can cause preeclampsia.[5] Soluble fms-like tyrosine kinase-1 (sFlt-1) binds vascular endothelial growth factor- A (VEGF-A) and placental growth factor (Plgf) which are the main angiogenic factors, responsible for placental vascular development and maternal endothelial function, and in this way prevents their interaction with endogenous receptors in the vessels.[6] Because of that, circulating Plgf levels are decreased and sFlt-1 levels are elevated.[7] Ratio of these two factors has proven to be more accurate for prediction of preeclampsia than any of these factors alone.[8-11] Combining Plgf concentrations with other biochemical markers, uterine artery doppler studies, or both, substantially improves the predictive value.[12]

Uterine artery doppler ultrasound is also useful in predicting preeclampsia, especially between 22-26 weeks of pregnancy.[13] Resistance to blood flow within uteroplacental circulation is transmitted upstream to the uterine arteries.[14] Faulty trophoblastic invasion of the spiral arteries results in diminished placental perfusion and upstream increased uterine artery resistance; leading to higher pulsatility or resistance index and a lasting early diastolic notch in the blood flow pattern.[1]

Because not much research has been done on using the sFlt-1/Plgf ratio to predict preeclampsia. We planned a study to compare this ratio with uterine artery doppler results for predicting preeclampsia between 22 and 24 weeks of pregnancy.

MATERIALS AND METHODS

This was a hospital based prospective study done on fifty pregnant women at risk of PE at the department of obstetrics and gynaecology in SSIMS & RC, Davangere, Karnataka, India during one-year period. Antenatal patients at 22-24 weeks period of gestation with essential hypertension, overt diabetes, renal disease, autoimmune diseases, history of abruption, foetal growth restriction, unexplained IUFD, preterm delivery, elderly primigravida and bad obstetrics history were included in the study. Patients who had gestational diabetes mellitus, prelabour rupture of membranes, molar pregnancy, multifetal pregnancy and those who did not consent were excluded from the study.

sFlt-1/Plgf ratio estimation

Maternal serum levels of sFlt-1 and Plgf (both levels measured in picograms per milliliter) were determined by means of the fully automated Elecsys assays on an electrochemiluminescence immunoassay platform and were used to calculate the sFlt-1: Plgf ratio.

Uterine artery doppler ultrasonography

At 22-24 weeks period of gestation, a transabdominal doppler ultrasound (with 3.5 MHz curvilinear probe) of uterine artery velocity waveforms were performed on a woman using an ultrasound machine. Pulsed wave doppler was then used with a sampling gate set of 2 mm to cover the whole uterine artery of both sides. When three similar consecutive waveforms were obtained, the uterine artery PI (Pulsatality index), RI (Resistance index), S/D ratio was calculated, and the mean doppler values of the uterine arteries were calculated.

All the females were followed up at 2 weekly intervals to detect preeclampsia or any other adverse maternal outcome at the earliest. The early onset and late onset preeclampsia were recorded and managed as per local institutional protocol.

Statistical analysis: All the data was entered in MS-Excel and statistical analysis was done on SPSS 20.0. Sensitivity analysis was done for various screening tools and ROC curves were plotted for each of them.

RESULTS

Out of 50 participants enrolled in the study, 17 patients (34%) developed preeclampsia [Table 1]. Majority (52%) of study participants had late onset of pre- eclampsia and about 48% of them had early onset of pre-eclampsia. 22% of participants developed non-severe preeclampsia and 12% developed severe preeclampsia.

All study participants were tested with sFlt-1/Plgf ratio and uterine artery doppler study at 22-24 weeks period of gestation. It was observed that 20 participants were screened positive for pre-eclampsia by sFlt-1/Plgf ratio (cut off > 25) and among them 17 developed preeclampsia. This number of screened positive was similar in participants screened positive by resistance index (20) (cut off > 0.7) and 12 among them developed preeclampsia. Using PI 22 participants were screened positive for pre-eclampsia (cut off > 1.1) and among them 13 participants developed preeclampsia as compared to 27 participants who were screened positive (cut off > 2.6) when SD (systolic to diastolic) ratio among them only 10 patients developed preeclampsia.

Uterine artery mean PI was significantly higher in the early-onset PE as compare to late-onset PE, which

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was statistically non-significant (p>0.05). However, the difference in PlGF levels was much more pronounced in late-onset cases than in early-onset PE. There were significant differences in mean (IQR) PlGF levels.

Maternal serum sFlt1 levels were insignificantly higher in the early-onset PE than in late-onset group. Finally, although the sFlt1/PlGF ratio was significantly increased in the early-onset PE compared to late-onset group [Table 2].

sFlt-1/Plgf was found to be a good predictor tool with a sensitivity of 91.4% and specificity of 87.7%. Uterine artery RI, PI and SD had their sensitivities as 71.4%, 74.3% and 60.5% respectively, while their specificities were 76.9%, 73.8% and 50.8% respectively. It was observed that sFlt-1/Plgf had highest positive predictive value (PPV) of 80% as well as best negative predictive value (NPV) of 95% amongst all.

Table 1: Distribution of study participants according to blood pressure, urine analysis, blood sugar status, liver enzyme values at the time of diagnosis of preeclampsia (N = 50).

Parameters	Frequency	%
Normotensive	33	66%
Non severe preeclampsia	11	22%
Severe preeclampsia	6	12%
Urine albumin 1+	13	26%
Urine albumin 2+	5	10%
Deranged GTT (140-200 mg/dl)	1	2%
Deranged LFT (SGOT > 50, SGPT > 50)	10	20%

Table 2: Uterine artery pulsatility index (PI) and maternal serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase(sFlt1) in early-onset PE & Late-onset PE.

Variable	Early-onset PE	Late-onset PE	P-value
Uterine artery mean PI	1.72±1.23	1.56±0.72	>0.05
PlGF (pg/mL)	98±27	262±154	<0.05*
sFlt1 (pg/mL)	1062±573	680±361	>0.05
sFlt1/PlGF ratio	10.83±21.24	2.59±2.34	<0.05*

DISCUSSION

PE is a pregnancy-specific multisystem disorder, affecting 2-7% of all pregnancies.[16,17] Our study observed that 34% of the study participants enrolled in the study developed pre-eclampsia. Lijie Li et al, studied sFlt-1/Plgf ratio for prediction of preeclampsia and found the incidence of preeclampsia to be 5.1%, high incidence of preeclampsia in our study was because the study population enrolled was a cohort with risk factors or with history of maternal adverse event.[14] Perales A et al, in their study using the same ratio found that 19.64% developed preeclampsia.[18] They also reported that 35.5% study participants with history of preeclampsia in previous pregnancy developed early onset preeclampsia. These results differ from that of the current study, where 48% had early onset preeclampsia.

The findings of our study are consistent with previously reported data.[19-21] In a prospective study conducted in 122 high-risk pregnancies with a PE prevalence of 11%, second-trimester PlGF had the highest predictive value for PE whereas uterine artery Doppler was slightly less effective.[19] In another study, Parra et al. prospectively evaluated PlGF and sFlt1 together with other biochemical markers in the first and second trimester in 170 low-risk pregnancies.[20] Second-trimester PlGF levels were independently associated with PE, although PlGF did not improve the predictive value of uterine artery Doppler results alone. Savvidou et al. evaluated sFlt1 but not PlGF at 23–25 weeks. In agreement with our results, these authors found considerable overlap with controls and a relatively poor predictive value.[21] However, although the sample size was too small to allow definitive conclusions to be drawn, their findings suggest higher levels in early-onset PE. Finally, Muller et al. found no correlation between uterine artery Doppler velocimetry and circulating angiogenic factor levels, and suggested a potential improvement in the prediction of PE/IUGR by combining both markers.[22]

In our study sensitivity and specificity of sFlt-1/Plgf ratio was found to be 91.4% and 87.7% respectively. The sensitivity and specificity of PI is 74.3% and 73.8% respectively. While in a similar study conducted by Perales A et al, found that sFlt-1/Plgf ratio was better predictor for preeclampsia than uterine artery doppler pulsatility index with sensitivity and specificity of 91.1% and 82% respectively similar to our study.18 Taraseviciene V et al in the study on prediction of preeclampsia found that sensitivity and specificity of sFlt-1/Plgf was 95.8% and 96.2% respectively.[23] Gomez A et al did a study using sFlt-1/Plgf ratio and found a sensitivity of 64% and 95% specificity to predict preeclampsia.[24]

CONCLUSION

The sFlt-1/Plgf ratio was found to be a better indicator than uterine artery Doppler measurements for predicting pre-eclampsia between 22-24 weeks pregnancy. So, the sFlt-1/Plgf ratio could be a useful tool for predicting pre-eclampsia and might help in

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managing the condition to improve outcomes for both the mother and the baby.

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