Original Research Article

Comparative study of sFlt-1/Plgf ratio with uterine artery doppler indices in prediction of preeclampsia at 22-24 weeks period of gestation

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ABSTRACT

Background: Hypertensive disorders like pre-eclampsia along with hemorrhage and infection, contributes greatly to maternal morbidity and mortality. 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.

Methods: A prospective observational study was conducted from September 2017 to February 2019 in which 100 patients 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.

Results: Among the cohort of 100 women with high risk factors, 35% of the study participants developed pre-eclampsia. Using sFlt-1/Plgf ratio 40% of them were screened positive for pre-eclampsia. This percentage of screened positive was 40%, 43%, and 53% using uterine artery RI, PI, and SD respectively. sFlt-1/Plgf was found to have a sensitivity of 91.4% and specificity of 87.7%. ROC curve analysis showed highest area under curve (AUC) for sFlt-1/Plgf (0.858).

Conclusions: sFlt-1/Plgf ratio was found to be a better predictable biomarker than uterine artery Doppler indices in prediction of pre-eclampsia at 22-24 weeks period of gestation.

Keywords: High risk, Pre-eclampsia, Resistive index, Systolic to diastolic, sFlt-1/Plgf, Uterine artery

INTRODUCTION

Hypertensive disorders complicate 5 to 10 percent of all pregnancies, and together they are one of the deadly triad along with hemorrhage and infection, contributing greatly to maternal morbidity and mortality. Preeclampsia either alone or superimposed on chronic hypertension, is the most dangerous.[1]

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. Enhanced placental expression and secretion of sFlt-1 appear to play a major role in the development of preeclampsia.[2] 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.[3] Because of that, circulating Plgf levels are decreased and sFlt-1 levels are elevated.[4] Ratio of these two factors has proven to be more accurate for prediction of preeclampsia than any of these factors alone.[5-8]

Combining Plgf concentrations with other biochemical markers, uterine artery doppler studies, or both, substantially improves the predictive value.[9]

Uterine artery doppler waveform analysis also has the best predictability at 22-26 weeks period of gestation.[10] Resistance to blood flow within uteroplacental circulation is transmitted upstream to the uterine arteries.[11] Faulty trophoblastic invasion of the spiral arteries results in diminished placental perfusion and upstream increased uterine artery resistance; resulting in increased uterine artery pulsatility index (PI) or resistance index (RI) and persistence of early diastolic notch.[1]

As limited studies have been done for prediction of preeclampsia by sFlt-1/Plgf ratio. We planned to do comparative study between sFlt-1/Plgf ratio and uterine artery doppler indices for prediction of preeclampsia at 22-24 weeks period of gestation.

METHODS

A prospective observational study was conducted from September 2017 to February 2019 at the department of obstetrics and gynaecology and department of biochemistry ESIC-PGIMSR Basaidarapur, New Delhi. Antenatal patients at 22-24 weeks period of gestation with essential hypertension, overt diabetes, renal disease, autoimmune diseases, history of abruption, fetal 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.

The study protocol was approved from Institutional ethical Committee, ESIC-PGIMSR Basaidarapur, New Delhi. All patients were informed about the study procedure and confidentiality regarding data. Written consent was taken from each participant. Each patient had a right to withdraw at any stage from the study.

Sample size calculation

Previous studies conducted in the similar settings to ours for prediction of pre-eclampsia had the sensitivity of serum biomarkers combined with uterine artery doppler indices ranging from 70% to 90%. Considering the observational nature of present study, sample size was calculated using formula:

$N \geq Zpq/l2$

Assuming p = 85% and taking 7% margin of error, applying the above formula give sample size to be 100 patients.

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 (cobas e analyzers Roche diagnostics) 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 (Toshiba). 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 17.0. Sensitivity analysis was done for various screening tools and ROC curves were plotted for each of them.

RESULTS

At enrolment detailed history of study participants were asked about various clinical history variables and their responses were recorded. Following observations were seen. Study participants were assessed for various risk factors (essential hypertension, overt diabetes, renal disease, autoimmune diseases) based on history (abruption, fetal growth restriction, unexplained IUFD, preterm delivery, elderly primigravida and bad obstetrics history). Unexplained intra-uterine fetal death was found to be most common (24%) risk factor among all. This was followed by bad obstetric history (14%) (Figure 1).

Out of 100 participants enrolled in the study, 35 patients (35%) developed preeclampsia (Table 1). Majority (51.4%) of study participants had late onset of pre-eclampsia and about 48.6% of them had early onset of pre-eclampsia. 23% of participants developed non-severe preeclampsia and 12% developed severe preeclampsia.

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 = 100).

Parameters	Frequency	%
Normotensive	65	65
Non severe preeclampsia	23	23
Severe preeclampsia	12	12
Urine albumin 1+	25	25
Urine albumin 2+	10	10
Deranged GTT (140-200 mg/dl)	02	2
Deranged LFT (SGOT > 50, SGPT > 50)	20	20
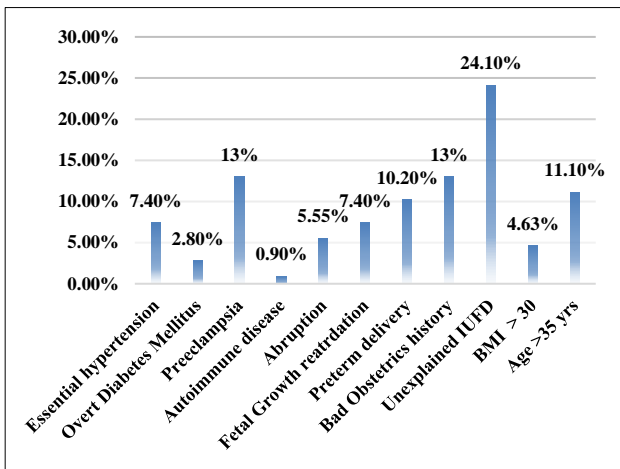
Figure 1: Risk factors observed, pre-disposing study participants to pre-eclampsia.
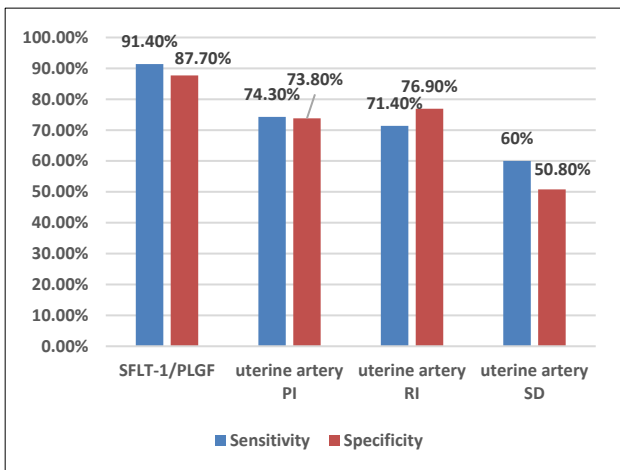
Figure 2: Comparing sensitivity and specificity of various predictor tools.

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 40 participants were screened positive for pre-eclampsia by sFlt-1/Plgf ratio (cut off > 25) and among them 32 developed preeclampsia. This number of screened positive was similar in participants screened positive by resistance index (40) (cut off > 0.7) and 25 among them developed preeclampsia. Using PI 43 participants were screened positive for pre-eclampsia (cut off > 1.1) and among them 26 participants developed preeclampsia as compared to 53 participants who were screened positive (cut off > 2.6) when SD (systolic to diastolic) ratio among them only 21 patients developed preeclampsia.

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 (Figure 2).

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.

ROC curve analysis depicted highest area under curve (AUC) for sFlt-1/Plgf [0.858 (95% CI: 0.777-0.939) (p value - 0.041)]. This was found to be significantly good in prediction of preeclampsia. AUC for PI was found to be significantly good [0.697 (95% CI: 0.581-0.809) (p value - 0.001)]. For RI and SD AUC values were poor [0.695 (95% CI: 0.586-0.608)] and failed [0.551 (95% CI: 0.435-0.666)] respectively (Figure 3).
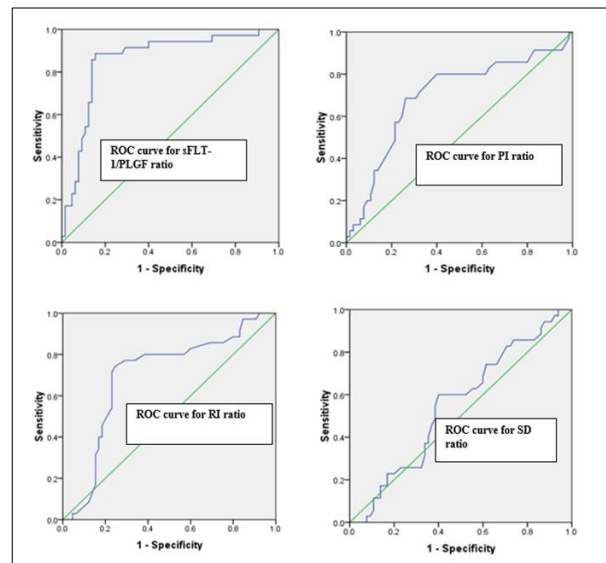
Figure 3: ROC Curve analysis of sFlt-1/Plgf ratio and uterine artery doppler indices.

DISCUSSION

It was observed that 35% 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.[11] Perales A et

al, in their study using the same ratio found that 19.64% developed preeclampsia.[12] 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 48.6% had early onset preeclampsia.

In the study 2% of the women had deranged blood sugar level. Vellamkondu A et al, conducted a study on risk assessment at 11-14 weeks gestation and observed that 8.63% of patient had deranged blood sugar levels.[10] Present study has reported 20% of the participants with raised liver enzyme values (SGOT > 50, U/L SGPT > 50 U/L). Elbishry GM et al, conducted a study in which they reported that 22% of the patients with preeclampsia had deranged LFT.[13]

In the current study, 40 patients were screened positive by sFlt-1/Plgf ratio and by RI and amongst them 32 patients and 25 patients were diagnosed as preeclampsia respectively. 43 patients were screened positive with uterine artery PI and of them 26 developed preeclampsia. 53 patients were screened positive with uterine artery SD and among them 21 patients developed preeclampsia.

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.[12] 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.[14] Gomez A et al did a study using sFlt-1/Plgf ratio and found a sensitivity of 64% and 95% specificity to predict preeclampsia.[15]

Narang S et al, conducted a study on prediction of pre-eclampsia at 11-14 weeks of pregnancy using uterine artery doppler indices found similar sensitivity (75.9%) and specificity (79.6%) of uterine artery doppler PI as reported in the present study.[16]

sFlt-1/Plgf had highest positive predictive value (PPV) of 80% as well as best negative predictive value (NPV) of 95%. Zeisler H et al did a study in which they found that NPV of sFlt-1/Plgf was 99.3% which is almost like our study.[17] In our study positive predictive value for PI was 60.46% and negative predictive value was 84.21%.

CONCLUSION

sFlt-1/Plgf ratio was found to be a better predictable biomarker than uterine artery doppler indices in prediction of pre-eclampsia at 22-24 weeks period of gestation. Hence sFlt-1/Plgf ratio may be a promising tool for prediction of preeclampsia and thus may aid in the management to improve maternal and fetal outcome.

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