Original Research Article

The predictive value of sFlt-1/PIGF ratio in high risk patients for the development of preeclampsia

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ABSTRACT

Background: Hypertensive disorders of pregnancy constitute a major cause of maternal morbidity and mortality. Pre-eclampsia/eclampsia ranks second only to haemorrhage as a specific, direct cause of maternal mortality. A number of markers have been under study for the early detection of this disease. The study aims to evaluate the predictive value of sFlt-1/PlGF ratio for preeclampsia.

Methods: This study was conducted in the Department of Gynaecology and Obstetrics of ASCOMS hospital, Jammu for a period of 6 months from Jan 2019 to June 2019. 50 antenatal patients attending the outpatient department with risk factors for developing preeclampsia were enrolled in the study. Their sFlT-1/PIGF ratio was determined at gestational age of 20 weeks to 37 weeks and its predictive value was evaluated.

Results: In the present study, 8 patients developed preeclampsia subsequently. The mean sFlt-1/PIGF ratio values were significantly higher in the patients who developed preeclampsia (73.5) than who did not develop the disease (26.07). The positive predictive value at 1 week was 41.66% and negative predictive value was 100%. At 4 weeks, positive predictive value was 66.66% and negative predictive value was 100%.

Conclusions: The present study suggests sFlt-1/PIGF ratio values are useful marker was a predictor of preeclampsia and values >38 were associated with preeclampsia. It is more useful in ruling out preeclampsia than ruling in the disease.

Keywords: Preeclampsia, Predictive marker, sFlt-1/PIGF ratio

INTRODUCTION

Hypertensive disorders of pregnancy constitute a group of disorders that constitute a major burden of illness on the developing as well as developed countries. These are classified into four categories: pre-eclampsia-eclampsia, chronic hypertension, chronic hypertension with superimposed pre-eclampsia and gestational hypertension. Preeclampsia is defined as a multi system disorder characterised by new onset hypertension and proteinuria after 20 weeks of pregnancy. The incidence of pre-eclampsia in hospital practice in India varies from 5% to 15% and that of eclampsia about 1.5%.[1,2] Pre-eclampsia / eclampsia ranks second only to haemorrhage

as a specific, direct cause of maternal mortality.[3] It is also a major cause of severe and life-threatening complications such as intrauterine growth restriction (IUGR), eclampsia, HELLP syndrome, placental abruption, intrauterine fetal demise, preterm labour and adverse perinatal outcome.[4] The pathogenesis of preeclampsia is multifactorial and not fully understood. Abnormal remodeling of maternal spiral arteries is one of the factors leading to placental hypoperfusion. Other theories proposed are endothelial dysfunction and abnormal placentation. Preeclampsia can also be perceived as impairment of maternal immune system that prevents it from recognizing the fetoplacental unit. High levels of soluble fms-like tyrosine kinase 1 (sFlt-1), an

antagonist of vascular endothelial growth factor and placental growth factor, have been found in women with pre-eclampsia.[5,6] Therefore, assays of sFlt-1, placental growth factor, endoglin, and vascular endothelial growth factor, all of which increase 4-8 weeks before onset of the disease, may be useful predictors of pre-eclampsia.

A number of predictive markers are used for the early prediction of preeclampsia especially in patients at risk of developing the disease. A combination of maternal risk factors, uterine artery Doppler, mean arterial pressure, maternal serum pregnancy-associated plasma protein-A, placental growth factor and a variety of biochemical markers are used as predictors for preeclampsia.

sFlt-1/PlGF has emerged as a recent marker for the same.The PROGNOSIS study (Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study) demonstrated that an sFlt-1/PlGF ratio of 38 or lower can be used to rule out the onset of PE within one week, independently of gestational age.[7] The negative predictive value was 99.3%.[7] Furthermore, a sFlt-1/PlGF ratio greater than 85 (for early-onset PE, <34 weeks of gestation) or 110 (for late-onset PE, ≥34 weeks) is indicative of a high risk of PE diagnosis or placenta-related disorders requiring close clinical and biological monitoring. For women with a sFlt-1/PlGF ratio between 38 and 85 or between 38 and 110, current PE can be ruled out; however, these women carry a high risk of developing PE within four weeks.

The aim of the study was to evaluate the predictive value of sFlt-1/PlGF ratio in patients at risk for developing preeclampsia for the development of the disease.

METHODS

This was an observational, prospective study conducted in the Department of Gynaecology and Obstetrics after obtaining ethical clearance from the concerned society of ASCOMS hospital, Jammu for a period of 6 months from Jan 2019 to June 2019. The antenatal patients attending the outpatient department with the risk factors for developing preeclampsia were enrolled in the study. Their regular antenatal checkups were done. Their sFlT-1/PlGF ratio was determined at gestational age of 20 weeks to 37 weeks. These cases were followed up till after delivery for the development of preeclampsia and other maternal and perinatal outcomes.

The data was analysed to calculate the predictive value of sFlT-1/PlGF ratio in suspected patients of preeclampsia and also its relation with maternal and perinatal outcomes using chi square and student t-test.

Risk factors

- Age > 40 years
- Family history of preeclampsia
- History of preeclampsia in previous pregnancy
- Nulliparity
- Multiple pregnancy
- Pregnancy after ART
- Preexisting hypertension
- Preexisting renal disease
- Insulin-dependent diabetes
- Antiphospholipid syndrome
- Obesity
- Severe anaemia (Hb<7g/L)

Inclusion criteria

- Age 18 years or older
- Gestation age 20-37 weeks
- Risk factor for preeclampsia.

Exclusion criteria

- Existing preeclampsia
- HELLP syndrome.

RESULTS

Table 1: Risk factors for preeclampsia.

Risk factor	Number of patients	Percentage
Age > 40 years	10	20%
Family history of preeclampsia	6	12%
History of preeclampsia in previous pregnancy	5	10%
Nulliparity	11	22%
Multiple pregnancy	5	10%
Pregnancy after ART	12	24%
Preexisting hypertension	6	12%
Antiphospholipid syndrome	1	2%
Obesity	6	12%
Severe anaemia (Hb<7g/L)	4	8%

As shown in Table 1, among the risk factors for preeclampsia, the major was pregnancy after ART (24%) followed by nulliparity (22%) and age >40 years (20%).

The other risk factors were family history of preeclampsia (12%), preexisting hypertension (12%), and obesity (12%) followed by history of preeclampsia in previous pregnancy (10%), multiple pregnancy(10%), severe anaemia (8%) and antiphospholipid syndrome (2%).

As shown in Table 2, the mean age of patients who developed preeclampsia was 36.87 and of those without preeclampsia was 27.45 which was statistically significant (p-value <0.0001). The mean BMI was 28.625 in patients who developed preeclampsia and 24.66 in those who did not develop preeclampsia (p-value

0.0002). The mean arterial pressure was also significantly higher in the patients who developed preeclampsia (p-

value <0.0001).

Table 2: Demographic data of the patients.

	Total	With preeclampsia	Without preeclampsia	P-value
Age (mean)	28.96	36.87	27.45	<0.0001
BMI (mean)	25.3	28.625	24.66	0.0002
Mean Arterial BP at inclusion	95.57	114.57	91.94	<0.0001

Table 3: sFlt-1/PIGF ratio values.

	With preeclampsia	Without preeclampsia	P-value
Mean sFlt-1/PIGF ratio values	73.5	26.07	<0.0001

Table 4: Details of patients who developed preeclampsia.

sFlt-1/PIGF ratio	Gestational age(weeks) of performing test	Preeclampsia developed at gestational age(weeks)	Delay of development of preeclampsia (days)
60	28	31	22
75	32	33	7
45	30	34	29
80	30	32	14
85	33	35	15
92	29	29	4
75	30	32	13
76	32	34	16

Table 5: Predictive value of sFlt-1/PIGF ratio for development of preeclampsia.

	Total	With preeclampsia	Without preeclampsia
At 1 week			
Value <38	38	0	38
value >38	12	5	7
PPV	41.66%		
NPV	100%		
At 4 weeks			
Value <38	38	0	38
value >38	12	8	4
PPV	25%		
NPV	100%		

Table 3 shows the mean sFlt-1/PIGF ratio values were significantly higher in the patients who developed preeclampsia (73.5) than who did not develop the disease (26.07) with a p-value of <0.0001. Table 4 shows the details of the eight patients who developed preeclampsia. All these patients had sFlt-1/PIGF ratio of >38. The gestational age of developing preeclampsia of each patient is mentioned in the table. The mean gestational age of development of preeclampsia was 32.5 weeks. The mean time delay for the development of preeclampsia

was 14.5 days shortest being 4 days and longest being 29 days.

Table 5 shows the predictive values of sFlt-1/PIGF ratio at 1 and weeks. In the study, 12 patients had ratio >38 at 1 week out of which 5 developed preeclampsia subsequently and none of the patients with ratio <38 developed the disease. The positive predictive value at 1 week was 41.66% and negative predictive value was 100%. At 4 weeks 3 more patients i.e. a total of 8 patients had developed preeclampsia. The positive predictive value at 4 weeks was thus 66.66% and negative predictive value was 100%.

DISCUSSION

In the study the value of sFlt-1/PIGF was established in ruling in and ruling out preeclampsia. The patients enrolled were those at high risk for the development of preeclampsia. Among the risk factors for preeclampsia, the highest was accounted by pregnancy after ART (24%), followed by nulliparity (22%) and advanced age >40 years of pregnancy (20%).

Among the demographic data, age was significantly higher in the patients who developed preeclampsia than those who did not. This is in accordance with the fact that increasing maternal age is associated with preeclampsia.[8]

Body Mass Index (BMI) was comparable in both groups i.e. with and without preeclampsia. Mrema D et al and Sohlberg S et al, in their studies showed that increasing BMI was a risk factor for preeclampsia but the presen/t study did not show any such correlation.[9,10]

On comparing the sFlt-1/PIGF values, it was found that they were significantly higher in the patients that developed preeclampsia. The PROGNOSIS study had validated a sFlt-1/PIGF ratio cut-off $\leq$ 38 to rule out the onset of preeclampsia within 1 week of testing in women with suspected disease.[11] The study showed the negative predictive value of sFlt-1/PIGF ratio to be 100% at 1 and at 4 weeks. The positive predictive value was found to be 41.66% at 1 week and 25% at 4 weeks.

Zeisier H et al in their study found that sFlt-1/PIGF ratio of $\leq$ 38 ruled out the onset of pre-eclampsia 2 and 3 weeks post-baseline with high negative predictive values (NPV) of 97.9% and 95.7%, respectively.[11] The onset of pre-eclampsia within 4 weeks was ruled out with a high NPV (94.3%) and high sensitivity and specificity (66.2% and 83.1%, respectively). In another study, the highest sensitivity and specificity for preeclampsia had SFlt-1/PlGF and PlGF with the cut-off values of $\geq$35 (sensitivity of 95.8% and specificity of 96.2%, respectively) and $\leq$138.6 pg/mL (sensitivity of 95.8% and specificity of 93.7%, respectively).[12]

Thus sFlt-1/PIGF has a high negative predictive value for ruling out preeclampsia in the patients who are at risk for the disease. This test is simple and easily reproducible. It can also be used in conjunction with uterine artery pulsatility index for the prediction of preeclampsia.[13,14]

The National Institute for Health and Care Excellence (NICE) guidance recommends sFlt-1/PlGF ratio testing to rule out PE in women presenting with suspected PE between 20 and 34+6 gestation weeks.

High cost of the test is one the limitations. However, it is especially useful for the patients at high risk for the disease, in whom negative test can help reassure the patient and prevent unnecessary hospitalisation and intervention. More frequent use of this test can help establish its role as a routine marker for the prediction of the disease.

CONCLUSION

The study suggests sFlt-1/PIGF ratio values are useful marker was a predictor of preeclampsia and values >38 were associated with preeclampsia. It is more useful in ruling out preeclampsia than ruling in the disease.

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