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ROLE OF SFLT-1 & PLGF RATIO IN WOMEN WITH SUSPECTED PREECLAMPSIA - A CROSS SECTIONAL STUDY

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AIM- To evaluate the role of SFLT-1/PLGF ratio in early prediction of preeclampsia in hypertensive pregnant women.

INTRODUCTION- In preeclampsia maternal blood levels of soluble FMS -like tyrosine kinase (SFLT-1) are increased and the placental growth factor is reduced (PLGF) . SFLT-1, an antagonist to placental growth factor and vascular endothelial growth factor, causes vasoconstriction and endothelial damage characteristic of preeclampsia . A high SFLT-1 to PLGF ratio is found to be associated with a higher risk of preeclampsia and can be measured in peripheral blood that serves as a better predictor of risk than either biomarker alone.

MATERIAL AND METHOD- It was a hospital-based cross-sectional study conducted in the period of 6 months (March 2021 to September 2021) with 50 high risk hypertensive pregnant women at Department of Obstetrics and Gynecology, Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun.
RESULT- The relation between SFLT-1 /PLGF ratio in early onset and late onset PE was statistically significant (p value<0.001). 83.3% women with risk of early onset PE had value >85, and 20.0% women with late onset PE had ratio >110. This shows the associations between level of ratios and risk of PE were statistically significant (p value<0.001).
CONCLUSION- This study concluded SFLT- 1/PLGF ratio can be used as a surrogate marker for prediction of PE in high-risk women and is a good screening tool for exclusion of PE in already hypertensive women.

Introduction

Hypertensive disorders in pregnancy encompass a wide spectrum of illness to include, preeclampsia, eclampsia syndrome, chronic hypertension, chronic hypertension superimposed with preeclampsia and gestational hypertension. These are associated with high risk of adverse outcome both for mother and fetus. Preeclampsia (PE) is a pregnancy specific multiorgan, multisystem disorder characterised by new onset hypertension with or without proteinuria, usually after twenty weeks of gestation, that complicates 2-5% of pregnancies worldwide (1,2) . Eclampsia, HELLP syndrome, acute renal failure and cerebral complications in the mother, add to a major proportion of maternal morbidity and mortality. It is responsible for 15% of preterm births , 5.6-11.8% of perinatal deaths and 9-26% of maternal deaths globally(3,4,5). From the fetal viewpoint it is responsible for iatrogenic prematurity, fetal growth restriction, placental abruption and even demise. Even with modern modalities of management, preeclampsia remains a leading cause of maternal and perinatal mortality and morbidity. It is the third most important cause of maternal mortality after haemorrhage and sepsis. In spite of extensive research preeclampsia still remains a mysterious, interesting complication of pregnancy. Due to multifactorial nature of pathogenesis of preeclampsia, its prevention and prediction remains a challenge leaving the main emphasis of preeclampsia management on early detection, symptomatic clinical treatment, surveillance, prevention of complications and timely and judicious delivery to procure a favourable outcome. (6)

The widely accepted “two stage theory” was first put forward by Redman in 1991, who describes two connected events : the first placental stage caused by shallow spiral artery remodelling in first trimester-which he called the ‘structural defects in spiral arteries supplying the intervillous spaces’ leading to placental ischemia.

This placental insufficiency create an imbalance between release of angiogenesis regulatory factors and those that promote anti- angiogenesis in maternal circulation. A decreased concentration of proangiogenic factors like placental growth factor (PLGF) and elevated levels of prohypertensive and antiangiogenic factors like soluble FMS- like tyrosine kinase-1(SFLT1) is characteristic of the process (7) . PLGF is a member of VEGF family and promotes angiogenesis
,increases vascular permeability and increase trophoblastic activity, conversely, SFLT-1 can decrease PLGF concentrations and inhibit biological function of PLGF leading to impaired vascular permeability and integrity of vessel wall resulting in generalized edema, urinary protein excretion and haemoconcentration typically seen in PE (8). This leads to development of the second and important stage of PE, the clinical stage 2 (new-onset hypertension and proteinuria or other signs of end-organ dysfunction), but the causes and timing of placental mal- perfusion may differ [9]. This could explain the difference between early and late onset PE. In preeclampsia maternal blood levels of soluble FMS -like tyrosine kinase (SFLT-1) are increased and the placental growth factor is reduced (PLGF) (10,11,12) . SFLT-1, an antagonist to placental growth factor and vascular endothelial growth factor, causes vasoconstriction and endothelial damage characteristic of preeclampsia (13) . A high SFLT-1 to PLGF ratio is found to be associated with a higher risk of preeclampsia and can be measured in peripheral blood that serves as a better predictor of risk than either biomarker alone and is also associated with poor pregnancy and neonatal outcomes.(12,14) Therefore, the monitoring of SFLT1/PLGF ratio in pregnant women with fetal growth restriction may assist in timely management for individual improved outcome.

In this study we tried to estimate two analytes SFLT-1 and PLGF and their ratio in pregnant women with hypertension, with an aim to test its utility in predicting/identifying PE.

AIM :

To evaluate role of SFLT-1/PLGF ratio in early prediction of preeclampsia in hypertensive pregnant women.

OBJECTIVE :

To identify early onset (<34 weeks) and late onset preeclampsia (>34 weeks).

MATERIAL AND METHOD-

Study Design : A hospital-based cross-sectional study .

Study Setting : Department of Obstetrics and Gynecology, Shri Guru Ram Rai Institute of Medical and Health Sciences, Dehradun

Study period:

Study was conducted for the period of 6 months (March 2021 to September 2021)

Sample size : About 50 sample size were taken

Inclusion criteria :

- All singleton pregnant women with hypertension in third trimester.

Exclusion criteria:

- Women with no obvious clinical features of preeclampsia
- Women with twin & triplet pregnancy.
- Women with Intra uterine fetal demise
- Hypertensive women with complications attributable to preeclampsia (HELLP syndrome,eclampsia,DIC)
- Known cases of hypertension with chronic diseases (Kidney disease Heart diseases , Hyperthyroidism etc)

Statistical Analysis:

Data were described in terms of range; mean ±standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) as appropriate . Comparison of quantitative variables between the study groups was done using ANOVA. For comparing categorical data, Chi square ($\chi 2$) test was performed and fisher exact test was used when the expected frequency is less than 5. Receiver operator characteristics (ROC) curve was done, and criterion value was estimated depending on the specificity and sensitivity. Area under curve (AUC) was measured. A probability value (p value) less than
0.05 was considered statistically significant. All statistical calculations were done using (Statistical 46 Package for the Social Science) SPSS 21version (SPSS Inc., Chicago, IL, USA)statistical program for Microsoft Windows.

OBSERVATION & RESULTS :

Total 50 antenatal hypertensive women were screened in third trimeseter of pregnancy for prediction of early and late onset preeclampsia by measurement of SFLT-1/PLGF ratio. Results were tabulated and analysed by tabular representation of data.

Table 1: Distribution of women according to onset of pre- eclampsia:

EARLY ONSET / LATE ONSET PE	No. of cases	Percentage
EARLY ONSET (<34 weeks)	24	48.0%
LATE ONSET (>34 weeks)	26	52.0%
TOTAL	50	100.0%

In our study we found that out of 50 pregnant hypertensive women 24 women (48.0%) had early onset preeclampsia (<34weeks) and 26 women(52.0%) had late onset preeclampsia (>34weeks).

Table 2 : Mean SFLT-1 /PLGF ratio

SFLT-1/PLGF ratio	No. of cases	Percentage
< 38	8	16.0 %
>85 (early onset PE)	21	42.0%
>110(late onset PE)	4	8.0%
38-85(early onset)	2	4%
38-110(late onset PE)	15	30.0%

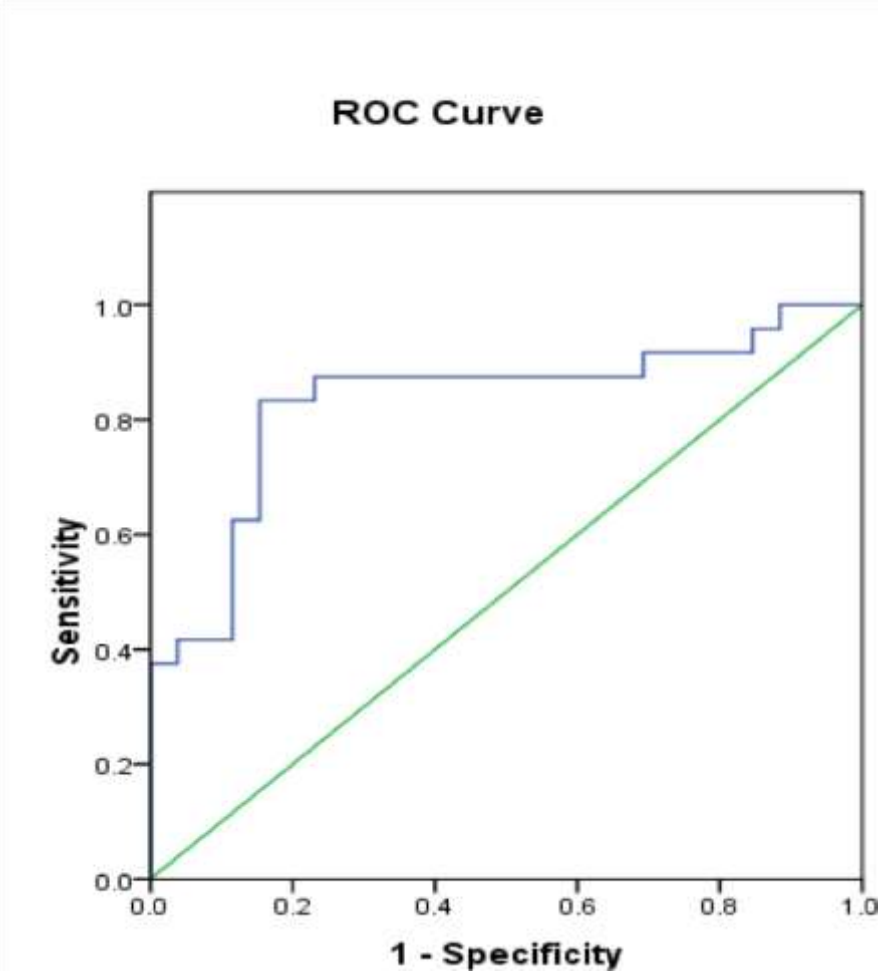
Out of 50 women 16% women had a SFLT-1 /PLGF ratio of less than 38 and were not predicted to develop preeclampsia. 42% women had SFLT -1/PLGF ratio of more than 85 and were the candidates who would develop early onset preeclampsia (<34 weeks) and 8% women had SFLT -1/PLGF ratio more than 110 were destined to develop late onset preeclampsia.

Table 3: Correlation of SFLT-1/PLGF ratio to development of early vs late onset preeclampsia :

	SFLT-1/PLGF RATIO								Total	Chisquare	pvalue
Onset	< 38		39-85		86-110		> 110				
early onset	1	12.5%	2	12.5%	5	83.3%	16	80.0%	24	19.053	0.001
late onset	7	87.5%	14	87.5%	1	16.7%	4	20.0%	26		
Total	8	100.0%	16	100.0%	6	100.0%	20	100.0%	50		

On applying statstics the relation between SFLT-1 /PLGF ratio in early onset and late onset PE was statistically significant (p value<0.001) and 83.3% women with a risk of early onset PE had value >85, and 20.0% women with late onset PE had ratio >110. This shows the associations between level of ratios and risk of PE were statistically significant (p value<0.001).

Figure 1 : ROC curve



Sensitivity and specificity of the SFLT-1/PLGF ratio was calculated and ROC curve was constructed, showing area under curve of 0.83 with CI (95% to 71%) with significant p- value. The test showed a sensitivity of 64.52% and a specificity of 72.73% with 95 % confidence interval. Suggesting that the test had more specificity in ruling out PE and a lower sensitivity of predicting PE. The positive predictive value of 86.96% and a negative predictive value of 42.11 %.

Table 4: Predictive efficiency of SLFT-1/PLGF Ratios :

		PE				Total
		Developed		Not Developed		
	early onset	20	64.5%	3	27.3%	23

Early onset/late onset PE	late onset	11	35.5%	8	72.7%	19
Total		31	100.0%	11	100.0%	42

Out of 50 participants, 8 women had SFLT-1/PLGF ratios of less than 38 and did not develop PE on follow up. Of remaining 42 women, 20 out of 23 with ratio >38 (early onset) developed PE and 11 out of 19 women with ratio >110 (late onset) developed PE later on.

DISCUSSION :

Preeclampsia and its consequences are the leading cause of maternal and fetal morbidity and mortality**.** SFLT-1 and PLGF are angiogenic
/antiangiogenic factors that are released into maternal circulation as a result of first trimester defective trophoblastic invasion of the placenta in women who are destined to develop PE. Higher SFLT-1/PLGF ratio has been shown to have prognostic significance not only in prediction of PE but also in prognosticating perinatal outcome like fetal growth restriction and still birth. In this present study an evaluation of SFLT-1/PLGF ratios in 50 hypertensive women in third trimester of pregnancies was undertaken in order to understand utility of this test as a tool for prediction of PE. This study evaluated these factors , the mean SFLT- 1 was found to be 12376.03 (±12705.911) pg/ml and mean PLGF was 136.15 (± 94.679) pg/ml and the mean SFLIT-1 /PLGF ratio was 110.10±101.338 .When categorised by levels of SFLT-1/PLGF ratio 8 women (16%) had a ratio of less than 38 signifying no or a low risk of PE, 21 women (42%) had ratios between >85 (denoting a risk of early onset PE) and 4 (8%) women had ratios greater than 110 (suggesting a risk of late onset PE), 15 (30%) women had ratio between 38-110 and 2 (4%) women had between 38-85.

Similar study done by H. Stepan et al.[15] who also took the cut-off values as <38 but divided the women into following three categories based on SFLT-1/PLGF ratios;SFlt-1/PLGF ratio < 38: Women unlikely to develop PE for at least 1 week ;SFlt-1/PLGF ratio > 85 (early-onset PE) or > 110 (late-onset PE): these women were very likely to have PE or another form of placental insufficiency and SFLT-1/PLGF ratio 38–85 (early-onset PE) or 38–110 (late-onset PE): These women do not have a definitve diagnosis of PE but are highly likely to develop PE within the next 4 weeks. Nine women in this study with ratios lower than 38 did not develop PE when followed and therefore the predictive accuracy of the ratio in ruling out PE in these cases was 100%.

Another study done on 67 women by Hélène Caillon,[16] and co-workers used SFLT-1/PLGF ratios to improve clinical care in PE and they found that 53 of them had a SFLT-1/PLGF ratio lower than 38 and None developed PE subsequently leading to a negative predictive value of 100%. Therefore, A standard cut-off value of 38 works better to exclude PE and values between 39-85 and 85-110 may be regarded as predictive values for diagnosis and prognosis of early and late onset PE respectively .

Conclusion :

Our study proves that evaluation of these biomarkers in maternal blood of already hypertensive pregnant women may be feasible for exclusion of PE and the value of the ratios so obtained

correspond well with actual development of PE within a week of testing. We found that the SFLT-1/PLGF ratios less than 38 were good for ruling out preeclampsia with a predictive accuracy of 100 %. Ratios higher than 38 were correlated well with occurrence of PE, and ratios higher than 85 were commensurate with early onset PE and ratios greater than 110 were correlated with late onset PE. Although the SFLT- 1/PLGF ratios were not 100% accurate in predicting early or late onset PE, they were more efficient in ruling out presence or development of PE. Therefore this study concluded that SFLT- 1/PLGF ratio can be used as a surrogate marker for prediction of PE in high-risk women and is a good screening tool for exclusion of PE in already hypertensive women.

Limitations : small sample size and further follow up is also needed.

Conflicts of interest- nil

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