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Original Article

Predictive Role of Placental Induced Growth Factor (PIGF) In Preeclampsia: A Case-Control Study

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Abstract-
Preeclampsia (PE) is a hypertensive condition that occurs during pregnancy and accounts for 2% to 8% of complications related to pregnancy globally. The diagnosis of preeclampsia is made when the blood pressure exceeds 140/90 mmHg after 20 weeks of pregnancy, occurring on two separate occasions with a minimum time gap of 4 hours, or exceeds 160/100 mmHg within a short period of time. Several biomarkers have been identified for prediction and diagnosis of preeclampsia. One of these biomarkers is Placental induced growth factor (PlGF), a factor that promotes angiogenesis, which belongs to the vascular endothelial growth factor family. Significantly reduced serum levels of placental growth factor (PIGF) have been observed in women diagnosed with preeclampsia compared to normotensive pregnancies. This study was designed to answer the question whether the measurement of PIGF at third trimester might be a predictive factor for the appearance of preeclampsia.
Method: A comparative study was made on 40 women with PE and 40 age-gestational-age matched women without preeclampsia, as case and control, respectively. Levels of serum PIGF were measured, compared and its role in prediction of preeclampsia was studied.
Results: The mean serum level of PIGF in cases was significantly lower (78.54±152.63pg/ml) than mean serum PIGF level of controls (553.73±263.27 pg./ml). When ROC analysis was done , PIGF ≤121.9pg/ml was found giving highest Youden index with sensitivity of 97.50%(95%CI-86.8 - 99.9) , specificity of 100% (95%CI-91.2-100) and AUC of 0.97 (95% CI =0.91–0.99).
Conclusion: Along with the hallmark symptoms of preeclampsia like high blood pressure and proteinuria, measurement of PIGF levels in late pregnant stage may be helpful in prediction of preeclampsia before actual onset of clinical symptoms which further assist in better diagnosis and management of disease.

Keywords: Preeclampsia, PIGF, Normotensive.

INTRODUCTION

Preeclampsia is a pregnancy specific multisystem disorder of unknown etiology and is characterized by development of hypertension to extent of 140/90 mmHG or more with proteinuria. It is characterized in a previously normotensive and non proteinuric woman. (1) According to ACOG (American College of Obstetrician and Gynecology), it is defined as maternal systolic blood pressure >140mmHG and diastolic >90 mmHG measured on two occasions separated by at least 6 hours and proteinuria > 300 mg in 24 hour or qualitative >1+, after 20 weeks of gestation. (2) A WHO report stated that in developing countries hypertensive disorders are responsible for 16.1% of maternal death. (3)

Preeclampsia has its clinical importance in its relation to maternal and neonatal mortality and morbidity. Pregnant females with pre-eclampsia may suffer a severe complication like eclampsia, HELLP (Hemolysis, elevated liver enzymes, and low platelet count) syndrome, pulmonary edema, even renal impairment, and failure (4). It is also associated to fetal growth restriction and premature delivery. A raised blood pressure can develop into kidney dysfunction, which leads to salt, and water retention, which further complicates hypertensive condition. This vicious cycle leads to severe preeclampsia and later poor obstetrics outcome. Infants born to preeclamptic mother may have a high risk of bronchopulmonary dysplasia and cerebral palsy due to preterm birth. (5,6)

Preeclampsia may cause prematurity, neonatal morbidity, and perinatal mortality. (7,8) hence, there has been increase interest for predictive biomarkers for its early diagnosis. Such biomarkers can predict high-risk female in early pregnancy (<16 weeks) and has clinical utility in preventing preterm delivery and premature birth. (9-13)

Out of many, Placental Induced Growth Factor (PIGF) is an important molecule in clinical management of preeclampsia. PIGF is a part of VEGF family and is mainly expressed in placenta and to some extent in other tissues like heart, lungs, thyroid, liver, skeletal mussels, and bone. (14) PIGF is a pro-angiogenetic factor because it helps in the process of angiogenesis by regulating the activity of Vascular Endothelial Growth Factor (VEGF) by competitively binding to VEGFR-1 receptor which allows VEGF to bind, and then VEGFR-2, which possess strong tyrosine kinase activity. (15) During pregnancy PIGF is mainly secreted by placenta where it promotes development and maturation of placental vascular system. (16) From the second trimester of the pregnancy, placental development and secretion of PIGF increases. At 16 to 18 weeks of gestation, remodeling of myometrial spinal arteries also speeds up. PIGF increases trophoblast proliferation and reduces apoptosis under starving condition (17). However, the phenomena do not occur during trophoblastic exposure to inflammatory cytokines. It is manifested as in pre-eclampsia there is increase circulating debris of trophoblast which reflects PIGF deficiency (18). Besides this, PIGF helps in differentiation of uterine Natural Killer (NK cells) cells, which may further mediate trophoblast invasion into decidua (19).

LEVELS OF PIGF IN NORMAL AND PRE-ECLAMPTIC PREGNANCIES.

In the first trimester of an uncomplicated pregnancy concentration of PIGF decreases and increases from week 11 to 12, continuously rises and is at peak at week 30. Later, it tends to decreases. However, normal PIGF concentration is a factor that depends on gestational age with the lower limit of normal (defined as the fifth centile) ranging from a peak of approximately 141pg./ ml at around 30 weeks of gestation to 23 pg./ml at the time of delivery (20).

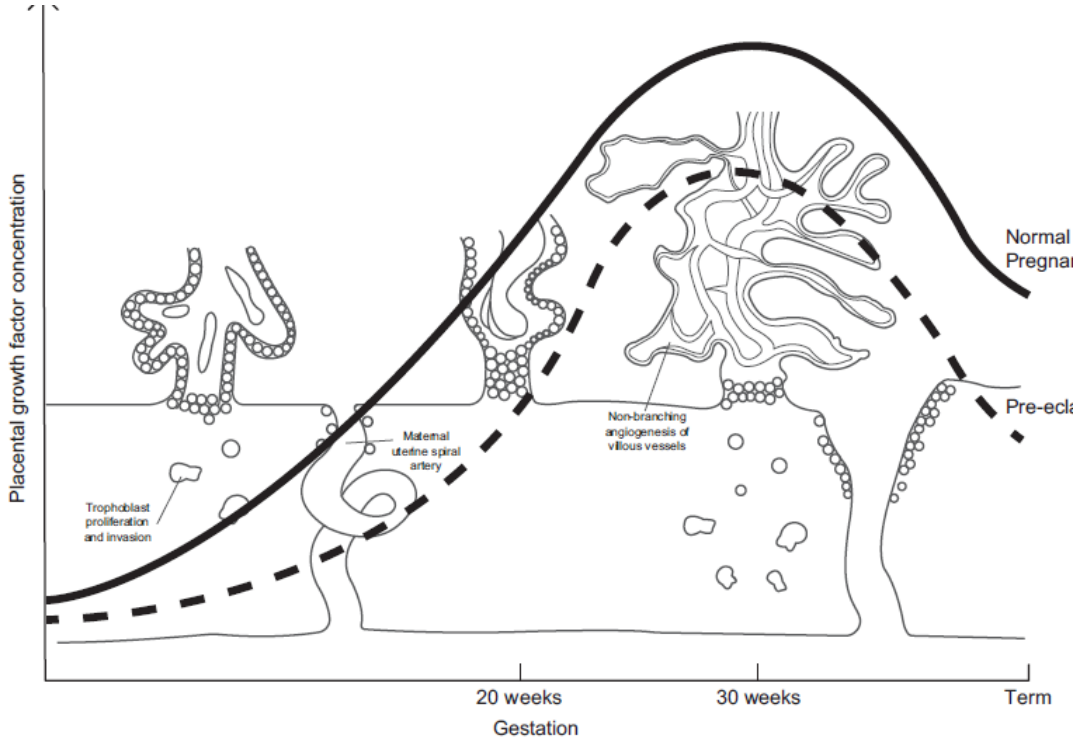

Figure 1. Circulating PlGF concentrations gradually increase during pregnancy to reach peak at ~ 30 weeks gestation. In pre-eclampsia PlGF concentrations are comparatively lower throughout pregnancy.

During the time of diagnosis and even in advance stage of the PE serum and urinary PIGF is found to increase. It occurs mainly due to reduced expression of PIGF and low free PIGF due to its binding with sFlt-1, which tends to increase in affected females (21).
In early pregnancy PIGF concentration is lower in suspected women, but soluble FMS Like Tyrosine kinase-1 (sFlt-1) level is no different, which suggest that expression of PIGF get decreased. However, towards term, there is a reciprocal relationship between sFlt-1 and PIGF with increased level of total (both free and bound to PIGF), sFlt-1 and lower free PIGF levels (22).
This picture depicts that in latter half of pregnancy, decreased level of PIGF occurs due to seclusion of the PIGF by sFlt-1. Probably, low-circulating levels of PIGF occurs as a consequence of abnormal early phenomena of placentation and is an important contributing factor to continued abnormal growth in later half of pregnancy (23).
Few studies have been conducted to find out predictive role of PIGF for PE, but there is huge variation in finding of these studies, therefore, this study is one another step to assess predictive role of PIGF in early diagnosis of PE.

Material and method

This comparative study was carried out in the Department of Biochemistry of SMS Medical College & Hospital, Jaipur (Rajasthan) from April 2023 to August 2023. During the study period, pregnant women with viable singleton fetus in their third trimester, diagonosed with preeclampsia were taken as case group and non-preeclamptic pregnant female who were matched for gestational and biological age were taken as controls. Patients were recruited from antenatal clinic, wards, and emergency unit by purposive sampling. The study was approved by the Institutes Ethics Committee (Reference No147MC/EC/2023 Dated 01/04/2023), and informed written consent was obtained from all the participants.

Inclusion Criteria:
1. Pregnant females with gestation >28 weeks.
2. All pregnant subjects with singleton pregnancy who were willing to participate.
3. All pregnant women who gave informed consent.

Exclusion Criteria:
1. Pregnant females with previous history of hypertension.
2. Severely ill patients.
3. Pre-existing diagnosed preeclampsia or haemolysis.
4. Pregnant women with renal diseases.
5. Pregnant females with multiple fetuses.
6. Pregnant women with gestational diabetes.
7. Pregnant women with chronic hypertension.
8. Pregnant women who did not give informed consent.

SAMPLE SIZE: Sample size was calculated at 80% study power and alpha error of 0.05 assuming standard deviation of 51.03pg/ml of serum PIGF level in preeclampsia group as found in reference study.(Abidoye Gbadegesin et al., (DOI: 10.4236/ojog.2021.116070 June 18,2021 Open Journal of Obstetrics and Gynaecology).
For minimum detectable mean difference of 32.0pg/ml in serum PIGF level,40 patients in each group were required as sample size for present study.

Formula used for the calculation of sample size,

$$n = \frac{2(Z_{1-\alpha\div 2}+Z_{1-\beta})^2\times\sigma^2}{(M_1-M_2)^2}$$

n = sample size

$Z_{1-\alpha\div 2}$ = 1.96 (corresponding 'Z' value for α error of 0.05)

$Z_{1-\beta}$ = 0.84 (corresponding 'Z' value for % study power)

σ =assumed standard deviation^2

Matching: Preeclamptic(cases) and non-preeclamptic group(controls) were matched for their gestational and biological age to eliminate confounding effect.
The blood pressure of control group was monitored to make sure they remained normotensive during pregnancy otherwise were excluded.

Methodology-

All eligible patients who visited Mahila Chikitsalya, SMS Medical College, Jaipur, during study period were screened through inclusion and exclusion criteria were approached by the investigator herself and explained about nature and purpose of study through participant information sheet (PIS). After taking detailed history of participants general and obstetrics examination was done by co-guide of study and required investigations was done.
Blood samples were drawn at recruitment for each participant. 5ml of venous blood was collected from the patients into plain bottles that were well labelled for prior identification, left for two hours to clot, and retract, and then centrifuged at 2500RPM for 5 minutes. The serum was decanted into vials and stored at -80 ◦C until analysis. Maternal serum PIGF assayed using ELISA (sandwich principle) according to manufacturer's instructions. For serum, PIGF assay kit provided by Elabscience Research and Diagnostics products was used. All tests assayed on Bio-Tek ELISA machine provided by Department of Biochemistry, SMS Medical College and Hospital, Jaipur.

Patients with blood pressure >140/90 mmHg with proteinuria ≥2 considered as preeclamptic patients and they constitute group A as case group.
Gestational and biological age matched pregnant women were taken as control group and constituted group B.

Data Analysis-

All information/data/ finding thus collected was recorded on a pre design study performa and entered in MS-Excel sheet to prepare master chart. This master chart was subjected to stastical analysis. Qualitative variables were summarised as mean and SD whereas quantitative variables were presented as proportional (%).
Unpaired T-test was used for analysis of quantitative variable while Chi-square test was applied for analysis of qualitative variables. P value= <0.05 was taken as significant. The Receiver Operating Characteristics(ROC) curve analysis was done to calculate the Area Under the Curve (AUC) and to find the best cut-off point, sensitivity, specificity, and likelihood ratios.
Medcale 16.4 version software was used for all statistical calculations.

RESULTS-

Participants Characteristics-
In present study, mean age of cases was (27.05±34.35years) while that in control group was (26.80±32.22years).47.50 % of cases and 32.50 % of controls were second gravida while 20 % & 25% of participants were primigravida among cases and controls respectively. Both the groups were found comparable with respect to age, gravida and parity.

PIGF Levels in Normal and Preeclamptic pregnancies-

Parameters	Group	N	Mean	SD	Median	Min.	Max.	'p' Value*
PIGF	A	40	78.54	152.63	53.7	0	1000	<0.001
	B	40	553.73	263.27	583	139	1000	

Table No : 1

The mean PIGF levels in cases were 78.54±152.63pg/ml while mean PIGF of controls were 553.73±263.27 pg/ml.
When independent sample t-test was applied, the difference in mean PIGF between cases and controls were found statically significant. (p=<0.01).
However, median serum PIGF levels were 53.7pg/ml and 583.0pg/ml in cases and controls respectively.

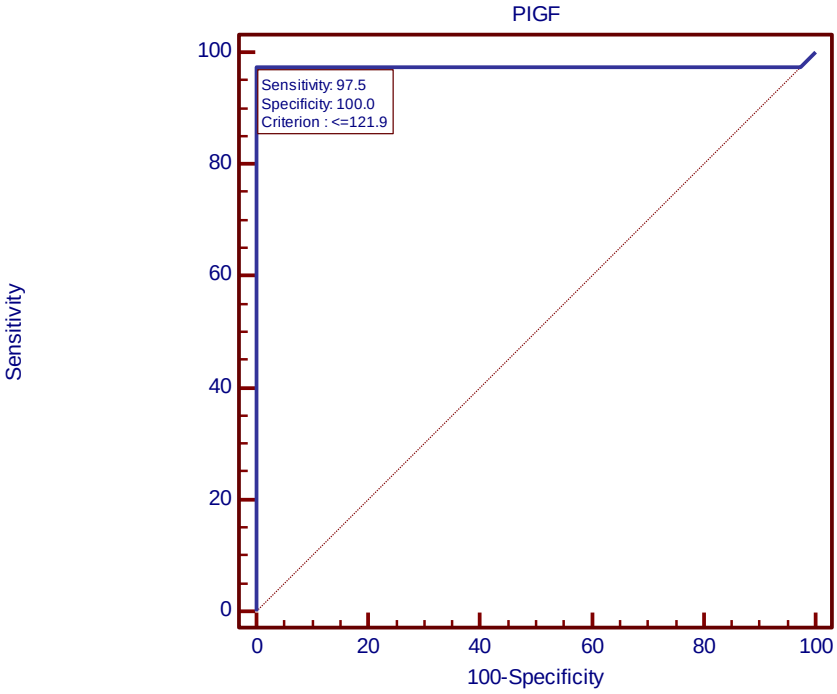

Figure.2

Table No.2

Area under the ROC curve (AUC)	0.975
Standard Error	0.0247
95% Confidence interval	0.913 to 0.997
z statistic	19.252
Significance level P (Area=0.5)	<0.0001

ROC Curve Analysis- When ROC curve analysis was done to find out optimum cut-off value of serum PIGF level to discriminate cases from controls, it was found that PIGF level>121.9pg/ml was showing 97.50% sensitivity (95% CI-86.8-99.9) and 100% specificity (95%CI-91.2-100) with AUC of 0.975(Table.2)

DISCUSSION-

The present study attempts to investigate the predictive value of PIGF in preeclampsia in third trimester pregnancy (>28weeks of gestation). The serum levels of PIGF were estimated in cases and compared with controls. The mean value of serum PIGF level in present study was significantly lower in cases as compared to controls, which is consistent with the study of Ghosh et al.(24) and Abidoye et al.(25), where also mean value of serum PIGF was significantly lower in PE group as compared to non-preeclamptic group. In a similar study done by Shuyuan Xue et al.,(26)mean value of serum PIGF was lower in preeclamptic females as compared to non-preeclamptic females but the stastical difference was non-significant.

Present study finds a good predictive role of serum PIGF level (AUC=0.975) in early diagnosis of PE similar to the study of Stefan Velhoren et al.(27) and Maha Basuni et al., (28)where they also found positive predictive role of PIGF(AUC=0.92 & AUC=0.87 respectively) for PE. However, sensitivity and specificity for corresponding cut-off value were not coherent with the present study.

CONCLUSION

It can be concluded from our study that the level of PIGF is low in preeclamptic females in comparison to non-preeclamptic pregnant females in their third trimester of pregnancy. Serum PIGF levels can be used in early prediction of PE along with other markers like sFlt-1 and sFlt-1: PIGF for better prediction of preeclampsia.

Conflict of Interest: None.

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