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Placental Growth Factor for the Prediction of Adverse Feto-Maternal Outcome in Patients with Pre-eclampsia

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Abstract

Background: Placental Growth Factor (PlGF) level is reported to be low in preeclampsia. Recent research suggested that it can be a promising tool for predicting adverse fetomaternal outcomes compared to nonspecific biomarkers. This study evaluated the predictive accuracy of maternal serum PlGF level for adverse fetomaternal outcomes in pre-eclamptic women.

Materials and methods: Seventy women with preeclampsia from the Department of Obstetrics and Gynecology of Chittagong Medical College Hospital from January 2021 to December 2021. PIGF level at admission was measured by ELISA method, and value >100 and ≤100 pg/ml was defined as normal and low, respectively. Patients were prospectively followed till delivery to observe fetomaternal outcomes.

Results: Out of 70 women, 28 (40%) developed adverse fetomaternal outcomes. The median level of PlGF was significantly lower among women with adverse fetomaternal outcomes than their counterparts [37.0 (18.9 - 61.5) pg/ml versus 122.7 (91.3-156.3) pg/ml, p <0.001)]. From the ROC curve, the best cutoff PlGF value for prediction of adverse fetomaternal outcome was 68.9 pg/ml [Area Under Receiver Operating Characteristic (AUROC) curve = 0.934, 95% Confidence Intervals (CI): 0.862-1.0] with the sensitivity, specificity, accuracy, positive predictive value and negative predictive value of 89.29%, 92.86%, 91.43%, 89.29% and 92.86%, respectively. Low PlGF level was independently associated with adverse fetomaternal outcome [Odds Ratio (OR):16.11, 95% CI: 1.94-133.18, p<0.010].

Conclusion: This study showed that the PlGF is a good predictor of adverse fetomaternal outcomes among women with preeclampsia.

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Introduction

Hypertensive disorders of pregnancy, especially, pre-eclampsia is a significant cause of maternal morbidity and mortality.[1] Despite advances in reducing child and infant mortality, preeclampsia and eclampsia-related mortality constitute a significant concern in Bangladesh.[2]

Several pre-clinical diagnoses and prognostic evaluation methods have been studied for early detection of adverse fetomaternal outcomes in preeclampsia, with various degrees of predictive accuracy such as biochemical markers (Urinary protein, uric acid).[3-6] These findings demand advanced evaluation of biomarkers for early diagnosis and prompt treatment for women who developed the condition and thus help in providing proper prenatal care.

PlGF, secreted by the syncytiotrophoblast that promotes placental angiogenesis, is a promising tool. PlGF concentrations increase as gestation advances in a healthy pregnancy, reaching a peak at 26–30 weeks' gestation before decreasing towards the term.[7,8] Recent observations support the hypothesis that defective placentation with consequently reduced concentrations of angiogenic growth factors (Free PlGF) and increased concentration of anti-angiogenic factor Soluble Fms-Like Tyrosine kinase-1 (SFLT-1) are associated with the onset of pre-eclampsia.[9,10] The NICE (National Institute for Health and Care Excellence) has recommended using PlGF to rule out PE in women between 20 and 34^{+6} weeks of pregnancy.[11] Few studies reported that the measurement of PlGF levels could be helpful in clinically predicting adverse pregnancy outcomes in women with suspected pre-eclampsia[12,13] or in predicting Small for Gestational Age (SGA) in the absence of clinically recognized pre-eclampsia.[14] Considering the contribution of pre-eclampsia to adverse fetomaternal outcomes in the study site

(Chittagong Medical College Hospital, CMCH) and poor predictive accuracy of available biochemical markers on adverse pregnancy outcomes among pre-eclamptic women, this study aimed to investigate the role of PlGF in predicting adverse fetomaternal outcome in patients with pre-eclampsia based on a single assay at the time of admission.

Materials and methods

This prospective observational study was conducted at CMCH, Chattogram, Bangladesh, from January 2021 to December 2021. The study was conducted after getting ethical clearance from the Ethical and Review Committee of Chittagong Medical College. Informed consent was taken from the patients or the patient's relatives after an explanation of the study procedure and purpose.

Preeclampticwomen admitted to the Department of Obstetrics and Gynecology with a gestational age of over 28 weeks up to 35 weeks were included. Pre-eclampsia patients with a medical disorder such as diabetes mellitus, gestational diabetes mellitus, chronic kidney disease, heart disease, systemic lupus erythematosus and women with multiple pregnancies were excluded.

Demographic, clinical, and obstetrical data on admission were collected using a pretested case record form. About 2ml blood specimens were drawn from the antecubital vein and collected in vacutainers (Blood-collecting tubes) with no additives, following standard hospital guidelines for venipuncture and sample collection. Maternal serum PlGF level was analyzed by Stat Fax 4200 Microplate Reader using Demeditec PLGF DE4529 ELISA kit, an enzyme immunoassay for the quantitative in vitro diagnostic measurement of PlGF in serum.PlGF levels>100 pg/ml and ≤100 pg/ml were taken as normal and low, respectively.[15] Test expenses bear by the patients and authors equally.

All patients were monitored until delivery. Maternal and fetal outcomes were recorded. Maternal outcome measures were preterm delivery, eclampsia, HELLP syndrome, abruptio placentae, cerebrovascular accident, acute renal failure, and maternal death. Adverse fetal outcome measures were Intrauterine Fetal Death (IUFD) Intrauterine Growth Restriction (IUGR) Low Birth Weight (LBW) prematurity and still birth.

Quantitative or categorical variables were expressed as mean [± Standard Deviation (SD)] and median and 25%–75% Interquartile Range (IQR), according to their spread. Count and proportion were used to present qualitative variables. Between groups, a comparison of quantitative variables was done by independent sample t-test for data with normal distribution and Mann–Whitney U-test for data with skewed distribution. The chi-square test determines the association between two qualitative variables. If an expected value was less than 5 in any cell, Fisher's exact test was used instead of the Chi-square test. Independent predictive variables for adverse fetomaternal outcomes were identified by regression analysis. Variables that had $p < 0.05$ at univariate analysis were included in the multivariate analysis. The results were described as OR and 95% CIs. The discriminatory values of serum PlGF and other related variables for predicting adverse fetomaternal outcomes were studied using AUROC. The optimal cutoff value of PlGF for predicting adverse fetomaternal outcomes was defined by calculating Youden's index. Based on the optimal cutoff value, different diagnostic accuracy parameters of PlGF were calculated with 95% CI. $p < 0.05$ was considered statistically significant.

Results

Table I shows the distribution of sociodemographic and clinical characteristics, laboratory parameters at enrollment and treatment modalities used for the studied patients. The mean age was 28.6±4.4 years. The majority of the pre-eclamptic women (61.4%) were 20-29 years old. About half of the patients were nulliparous (47.1%). Gestational age at enrollment was between 33-34 weeks in 74.3% of the cases. The majority (64.3%) of the women had pre-eclampsia without severe features.

Table I Baseline demographic, clinical and biochemical characteristics (n=70)

Variables	Frequency	Percentage
Age in years (Mean ±SD)	28.6±4.4	
Gravidity		
Primigravida	33	47.1
Multigravida	37	52.9
Gestational age at Enrollment (Weeks)		
<34 weeks	39	55.7

Variables	Frequency	Percentage
≥ 34 weeks-35 weeks	31	44.3
PE in previous pregnancy	21	30.0
Systolic blood pressure, mm Hg	150.0 (140.0-160.0)	
Diastolic blood pressure, mm Hg	100.0 (90.0-100.0)	
Body mass index, kg/m^2	24.9 (24.1-26.2)	
Type of preeclampsia		
Without severe features	45	64.3
With severe features	25	35.7
Platelet count, 10^9 /L	230.0 (190.0-263.3)	
Serum uric acid, mg/dl	3.1 (2.7-4.3)	
Serum SGPT, IU/L	22.5 (20.0-26.3)	
Serum creatinine, mg/dl	0.7 (0.6-0.8)	
Serum PlGF, pg/mL		
Median (IQR)	90.5 (47.3-140.5)	
Normal (>100 pg/mL)	34	48.6
Low (≤100 pg/mL)	36	51.4
Magnesium sulfate use	21	30.0

Data were expressed as frequency (%) if not mentioned otherwise. IQR: Interquartile range, PE: Pre-eclampsia, SD: Standard deviation.

Pregnancy outcomes are presented in Table II. It depicted that, majority of the women was delivered by cesarean section and the median gestational age at delivery was 37 weeks. The most frequent maternal complication was preterm delivery and abruptio placentae followed by eclampsia. The common fetal complications were IUGR, prematurity, low birth weight and IUFD.

Table II Maternal and fetal outcomes (n=70)

Variables	Median (IQR)/Frequency (%)
Mode of delivery	
Vaginal	22 31.4
Cesarean	48 68.6
Gestational age at delivery (Weeks)	
Median (IQR)	37.0 (36.0-37.0)
Maternal complication	
No complication	53 75.7
Eclampsia	5 7.1
Abruptio placentae	6 8.6
Preterm delivery	6 8.6
Fetal complication	
No complication	42 60.0
IUGR	10 14.2
Low birth weight	7 10
Prematurity	10 14.2
IUFD	1 1.4

IQR: Interquartile Range, IUGR: Intrauterine Growth restriction, IUFD: Intrauterine Fetal Death, PE: Pre-eclampsia.

Out of 70 women, any of the adverse fetomaternal outcomes were observed in 28 cases, thus giving the prevalence of adverse fetomaternal outcomes of 40.0%. Table III shows that the median level of maternal serum PlGF level at admission was lower in preeclamptic women with adverse maternal, fetal or composite fetomaternal outcomes than their counterparts ($p<0.001$ in each case). The median maternal serum PlGF level was lower in women without adverse fetomaternal outcomes than in women with adverse fetomaternal outcomes.

Table III Maternal serum PlGF levels stratified by presence of adverse fetomaternal outcome

Outcome variables	Median (IQR) PlGF levels, pg/mL	p value*
Adverse maternal outcomes		
Absent (n=53)	110.0 (72.5-152.0)	<0.001
Present (n=17)	22.1 (17.1-45.6)	
Adverse fetal outcome		
Absent (n=42)	122.7 (91.3-156.3)	<0.001
Present (n=28)	37.0 (18.9-61.5)	
Composite feto-maternal outcome		
Absent (n=42)	122.7 (91.3-156.3)	<0.001
Present (n=28)	37.0 (18.9-61.5)	

*Mann-Whitney U test.

ROC curve was plotted for PIGF in the prediction of adverse fetomaternal outcomes was, and AUROC was 0.934 (95% CI: 0.862-1.0) for adverse outcomes (Figure 1). The best cutoff PlGF value for predicting adverse fetomaternal outcomes was 68.9 pg/ml. With this cutoff value, the sensitivity was 89.29% and specificity was 92.86%. The overall accuracy, PPV and NPV were 91.43%, 89.29%, and 92.86%, respectively.

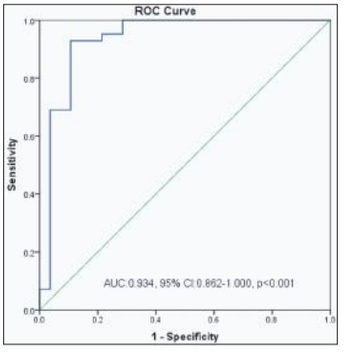

Figure 1 ROC areas for maternal serum PlGF level in predicting pre-eclampsia with adverse feto-maternal outcomes

ROC: Receiver Operating Characteristics, AUC: Area Under Curve, CI: Confidence Interval.

In univariate analysis, maternal age at enrollment, types of preeclampsia, blood pressure at enrollment, platelet count, serum uric acid level, serum PlGF level, administration of $MgSO_4$, and mode of delivery was significantly associated with adverse fetomaternal outcomes (Table IV).

Table IV Relation between adverse feto-maternal outcomes and different clinical and laboratory factors

	Adverse feto-maternal outcomes		
Characteristic	Yes (n=28)	No (n=42)	p value
Age, years	26.6±5.2	29.9±3.1	0.001*
Gravidity			
Primigravida	17 (60.7)	16 (38.1)	0.063†
Multigravida	11 (39.3)	26 (61.9)	
BMI at admission			
30.0kgm^2	20 (71.4)	36 (85.7)	0.063†
≥30.0 kg/m	8 (28.6)	6 (14.3	
Gestational age at delivery			
<34 weeks	5 (17.9)	0 (0)	0.143†
≥ 34 weeks	23 (82.1)	42 (100.0)	
Types of preeclampsia			
Without severe feature	8 (28.6)	37 (88.1)	<0.001†
With severe feature	20 (71.4)	5 (11.9)	
SBP, mmHg	160.0 (150.0-160.0)	150.0 (140.0-150.0)	<0.001‡
DBP, mmHg	100.0 (100.0-110.0)	100.0 (90.0-100.0)	0.001‡
Platelet count, 10^9 /L	195.0 (165.5-245.0)	242.5 (200.0-277.7)	0.003‡
Serum uric acid, mg/dl	4.5 (3.2-5.2)	3.0 (2.3-3.0)	<0.001‡
Serum SGPT, IU/L	25.0 (20.0-30.0)	22.0 (20.8-26.0)	0.847‡
Serum creatinine, mg/dl	0.7 (0.6-0.8)	0.7 (0.6-0.8)	0.117‡
Serum PlGF, pg/mL			
Normal (>100 pg/mL)	3 (10.7)	31 (73.8)	<0.001†
Low (≤100 pg/mL)	25 (89.3)	11 (26.2)	
Magnesium sulfate use			
No	11 (39.3)	26 (61.9)	<0.001†
Yes	17 (60.7)	16 (38.1)	
Mode of delivery			
Vaginal	3 (10.7)	19 (45.2)	
Cesarean	25 (89.3)	23 (54.8)	<0.001†

*Independent sample t test, ‡Mann-Whitney U test, †Chi-square test.

In multivariate analysis including maternal age at enrollment, systolic blood pressure, diastolic blood pressure, platelet count, serum uric acid level, type of pre-eclampsia, administration of magnesium sulfate and mode of delivery, low level of PlGF was revealed as an independent risk factors for adverse fetomaternal outcomes. Pre-eclamptic women with low PlGF were 16.11 times more likely to develop adverse fetomaternal outcomes compared to those with normal PlGF with a p-value of 0.010, (95% CI:1.94-133.18).

Table V Independent factors associated with adverse feto-maternal outcomes in pre-eclampsia

Variables	B	S.E.	Wald	OR	95% CI for OR		p value
Low PlGF	2.780	1.078	6.653	16.11	1.94	133.18	0.010
Age, years	-0.111	0.108	1.057	0.89	0.72	1.10	0.304
SBP, mmHg	0.001	0.045	0.000	1.00	0.91	1.09	0.990
DBP, mmHg	-0.065	0.086	0.563	0.93	0.79	1.11	0.453
Platelet, 10^9 /L	0.000	0.000	0.000	1.00	1.00	1.00	0.988
Uric acid, mg/dl	0.154	0.427	0.130	1.16	0.50	2.69	0.718
PE with severe features	1.001	1.476	0.460	2.72	0.15	49.06	0.497
Use of $MgSO_4$	-3.297	1.613	4.177	0.03	0.00	0.87	0.041
Cesarean delivery	0.978	1.089	0.808	2.66	0.31	22.46	0.369

OR: Odds Ratio, CI: Confidence Interval, SE: Standard Error, PE: Pre-eclampsia.

Discussion

The current study found an excellent accuracy and discriminatory performance of PlGF for predicting adverse feto-maternal outcomes in preeclamptic women admitted to a tertiary referral hospital in Bangladesh. Accurate prediction of adverse events could reduce unnecessary interventions for those at low risk for decompensation. Duhig et al. found fewer adverse maternal outcomes after implementing PlGF testing.[16]

The analysis of PLGF serum levels in the studied patients showed that the median PlGF serum level was 90.5 pg/ml and varied from 6.7 pg/ml to 354.0 pg/ml. In an Indian study, the average PlGF serum level in the mothers diagnosed with preeclampsia the average PlGF serum level was 71.51, which varies from 11.31 to 226.71.[17] In a study from Turkey, the mean PlGF level was 87.85±18.96 pg/ml.[18] As the maternal serum PlGF varied according to the gestational age, this might be responsible for the variation of the PlGF level among studies. In the present study, serum PlGF level was low in more than half (51.4%) of the preeclamptic women, which agreed with the analysis of Parchem et al., where plasma PlGF was low in 66.7% of women and very low in 31.7%.[19]

In the present study, the majority (68.6%) of the women were delivered by cesarean section. The most frequent maternal complication was preterm delivery, abruptio placentae, followed by eclampsia. The most frequent fetal complication was IUGR, prematurity, low birth weight and IUFD. Certain serious but rare events included in the composite outcome did not occur during the study (Maternal death, acute myocardial infarction, hypertensive encephalopathy, cortical

blindness and liver hematoma or rupture). The current study's adverse outcome profile of preeclamptic women was in agreement with previous reports.[19-21] The median level of PlGF was significantly lower among pre-eclamptic women with adverse feto-maternal outcomes, which agreed with previous reports.[20,22,23]

The present study revealed a significant prognostic value of serum PlGF, as evidenced by the AUC value, which was 0.934, indicating an excellent discriminatory role of PlGF for detecting pre-eclamptic women with adverse feto-maternal outcomes. Sibiude et al. performed an ROC analysis for predicting unfavorable outcomes and found that AUC was 0.76 for adverse outcomes and 0.92 for severe adverse consequences.[24] Regarding the utility of maternal serum PlGF in pre-eclampsia, most studies determine the cutoff value for detecting or diagnosing pre-eclampsia. A cutoff value of PlGF between 80 and 120 pg/mL has a very high specificity and is thus more helpful to rule in pre-eclampsia.[25] A previous review has highlighted the need for a high-sensitivity test in this setting because there is a need to minimize false negatives when considering overall benefits and harms and ensuring appropriate resource use.[26] In the present study, a cutoff value of 68.9 pg/ml showed good sensitivity and specificity for detecting adverse feto-maternal outcomes in the confirmed cases of pre-eclampsia. This cutoff value had good diagnostic accuracy, as evident by its high sensitivity and specificity (89.29% and 92.86%).

Moreover, positive and negative predictive values were also high in the current study. However, large confidence intervals were due to the low number of patients, so more extensive studies must confirm this finding. In Parchem et al.'s study, low PlGF had high sensitivity and NPV for neonatal and maternal composite outcomes but poor PPV.[19]

The current guideline suggests that treatment of pre-eclampsia should be based on signs and symptoms and not on test results.[27] However, the existing evidence11,25 and the current study results indicated that the PlGF test is clinically valuable in identifying women likely to develop pre-eclampsia and pre-eclamptic women likely to have adverse feto-maternal outcomes as pregnancy advances. In the current study, a low level of PlGF was an independent risk factor for adverse feto-maternal outcomes. The relatively high OR and the wide confidence interval of the OR might be due to the small sample size of the present study. Low PlGF levels were significantly associated with the composite adverse pregnancy outcome score for all parameters (OR 3.48, 95% CI:2.28-5.32) in the study of Ekelund et al.[21] Among preeclamptic patients who were included <34 weeks, the risk of severe adverse outcome was also higher in the lowest group of PlGF value (OR = 216, 95% CI 18–2571, p,0.001) when compared with the highest group in the study of Sibiude et al.[24]

Limitations

The study was performed in a relatively small sample. In addition, the blood samples were collected only at enrollment, at a particular gestational age. Another limitation of this study was that there was no long-term follow-up of participants after delivery, so complications that would occur after delivery could not be assessed.

Conclusion

In conclusion, the incidence of adverse feto-maternal outcomes was high in the present study, and low PlGF was associated with a significantly increased risk of adverse feto-maternal outcomes among women with pre-eclampsia. Serum PlGF level of pre-eclamptic women would help to guide clinical decision-making and thereby reduce feto-maternal morbidity and mortality associated with pre-eclampsia.

Recommendation

PlGF should be used for screening adverse pregnancy outcomes in early pregnancy. Pre-eclamptic patients with low PlGF levels warrant intensive monitoring, so prompt and early recognition would be possible and timely intervention could be ensured.

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Contribution of authors

FA-Conception, data collection and analysis, manuscript drafting and final approval.

LD-Design, drafting and final approval.

TT-Data analysis, revision of content and final approval.

DS-Design, drafting and final approval.

SB-Interpretation of data, critical revision and final approval.

SA-Conception, critical revision and final approval.

Disclosure

The authors declared no conflicts of interest.

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