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RESEARCH PAPER

Serum Placental Growth Factor and Uterine Artery Pulsatility Index as Predictor of Preeclampsia.

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Abstract

Background: Early identification of pregnant women at high risk for developing preeclampsia by measuring placental growth factor (PlGF) and uterine artery pulsatility index (UtA PI) levels could allow for earlier definite management and could potentially reduce the risk of complications of preeclampsia.

Objective: This study aimed to assess the efficacy of serum placental growth factor (PlGF) and uterine artery pulsatility index (UtA PI) as predictors for preeclampsia.

Methods: This prospective cohort study was conducted in the Department of Fetomaternal Medicine of Bangladesh Medical University (BMU) from November 2021 to October 2022. A total of 63 singleton pregnant women were enrolled purposively at 20-24 weeks of gestation. At enrolment UtA PI and serum PlGF were measured in each study subject. All the subject were then followed up till delivery for development of preeclampsia. The PI (pulsality index) was measured using uterine artery Doppler and the placental growth factor (PlGF) level was estimated from blood samples using ELISA. Uterine artery pulsatility index more than 95th percentile and serum placental growth factor less than 100 pg/mL were considered the baseline cut-off values using the Youden Index. In this study pregnant women having UtA PI above 95th percentile and PlGF below 100 pg/ml at enrolment were predicted to develop preeclampsia. The diagnostic efficacy of UtA PI and PlGF alone and in combination were determined for prediction of preeclampsia.

Results: Among the study subject 46% were estimated to have low serum PlGF levels and 26.9% had an increase in UtA-PI at 20-24 weeks of pregnancy. Subsequent follow-ups revealed the development of pre-eclampsia (PE) in 12(19%) patients. Patients with preeclampsia had significantly lower serum PlGF levels (80.8±58.8 pg/mL) compared to those without PE (206.2±162 pg/mL, p=0.011). UtA-PI was higher in patients with preeclampsia compared to those without PE (1.5±0.4 vs. 0.9±0.18, p<0.001). Low PlGF levels increased the risk of preeclampsia 12.9 times (p<0.001), while elevated UtA-PI raised the risk 29.8 times (p<0.001). Above four fifths (83.3%) of PE group of patients had combination of low PlGF and elevated UTA-PI while it was absent in majority (90.2%) of the women with no preeclampsia. The elevated UtA-PI with combination of low PlGF strengthens the predictive values for preeclampsia with reported sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate of 83.3%, 90.2%, 66.7%, 95.8%, and 88.9% respectively.

Conclusion: The combination of PlGF and UtA-PI is a good tool for predicting the development of preeclampsia.

Keywords: Placental growth factor (PlGF), uterine artery pulsatility index (UtA-PI), Preeclampsia

Introduction

Preeclampsia (PE) is a pregnancy-specific multisystem disorder, pertinent to immense maternal and perinatal morbidity and mortality worldwide.[1] Women with a history of preeclampsia is also at high risk for developing chronic hypertension, type 2 diabetes mellitus, renal failure, coronary heart disease, and various forms of arrhythmias in the long term.[2] Preeclampsia complicates 0.5 to 15% of all pregnancies globally, and symptoms are most likely to appear during the last part of the second or at the beginning of the third trimester.[3] Preeclampsia with severe features

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results in almost a third of a million maternal deaths and more than six million perinatal deaths in low- and middle-income countries (LMICs).[4]

There are two distinct phases to the pathophysiologic mechanisms that lead to preeclampsia. The first stage is characterized by reduced placental perfusion, possibly related to abnormal placentation, with impaired trophoblast invasion and inadequate remodelling of the uterine spiral arteries. This model can be evaluated by uterine artery Doppler. The second stage refers to the systemic manifestations characterized by inflammatory, metabolic, and thrombotic responses that converge to alter vascular function, which can result in multiorgan damage. The placental growth factor (PlGF) is one of the circulating angiogenic proteins that is anticipated to play a significant biological role in the pathophysiology of preeclampsia.[5] PlGF is a pleiotropic angiogenic growth factor involved in vasculogenesis and angiogenesis. The placental trophoblast produces PlGF, which is greatly increased early in pregnancy following implantation.[5] Placental expression of PlGF increases in the second trimester corresponding to a second wave of spiral artery remodelling at 16 to 18 weeks' gestation. From 25 weeks, PlGF is believed to contribute to a change in branching to non-branching angiogenesis, controlling the expansion of a low-resistance placental capillary network. Concentrations of PlGF peak between 29 and 32 weeks of pregnancy and then gradually decline till term. Placental hypoxia, caused by uteroplacental ischemia, inhibits trophoblastic PlGF.[6] Consequently, PlGF are measurable manifestations of impaired placentation caused by insufficient trophoblastic invasion of the maternal spiral arteries and decreased placental perfusion, resulting in placental ischemia and the release of inflammatory factors, platelet activation, endothelial dysfunction, maternal renal dysfunction, or abnormal oxidative stress. [7] Immunohistochemical analysis has shown that PlGF was significantly lower in the placentas of women with preeclampsia compared to those with placentas of normotensive women. [8] Moreover, the Doppler ultrasound of the uterine artery (UtA) is a reliable non-invasive screening tool of the uteroplacental circulation by comparing systolic and diastolic waveforms in high-risk pregnancies, especially in healthcare systems where analysing other indicators is difficult. [9] The UtA pulsatility index (PI) can be defined as an objective assessment of uterine arterial waveform (Peak Systolic flow velocity – End diastolic velocity / Mean velocity). During normal pregnancy, the PI declines due to increased diastolic flow. Most researchers used a PI of >1.6 in the second trimester for the prediction of preeclampsia[10, 11] .Combining PlGF and UtA-PI measurements in the second trimester can help identify women at high risk for preeclampsia. Early identification of high-risk pregnancies can lead to closer monitoring and earlier interventions, potentially reducing the incidence and severity of preeclampsia and its associated complications. Several studies have observed raised uterine artery Doppler pulsatility index and low maternal serum PlGF as strong predictors of preeclampsia[12, 13] However, their diagnostic accuracy varied for different populations and ethnic groups. [14,15]Therefore, this study was conducted to evaluate the role of serum placental growth factor and uterine artery Doppler as a predictor of preeclampsia at a tertiary-level hospital in Bangladesh.

Materials and Methods

After obtaining ethical clearance from the Institutional Review Board, this prospective cohort study was conducted in the Department of Fetomaternal Medicine, Bangladesh Medical University (BMU), Shahbag, Dhaka, for a period of twelve months from November 2021 to October 2022.

The study population included 63 women with singleton pregnancy (20-24 weeks of gestation), aged 18-40 years attending the outpatient department of Fetomaternal Medicine and Department of Obstetrics and Gynaecology, BMU. Women with multifetal gestation, history of preeclampsia, chronic hypertension or diabetes mellitus, and chronic renal and cardiovascular disease were excluded from the study. The purposive sampling method was used according to the availability of the patients.

After obtaining consent, data were collected through face-to-face interviews using a semi-structured questionnaire. The uterine artery pulsatility index (UtA-PI) was measured through uterine artery Doppler study immediate after enrolment and at the same time 03ml blood samples from the participants were collected for the estimation of serum PlGF levels. All The subjects were then followed up till delivery and was observed for the development of preeclampsia. All the respondents were followed-up with regular monitoring of blood pressure till their delivery according to World Health Organization's ante-natal care protocol. Women who developed preeclampsia (Confirmed by

clinical examinations and laboratory investigations according to NICE Guideline) and who did not develop preeclampsia were evaluated in the study.[16]

An UtA pulsatility index score above the 95th percentile (≥1.18) and a PIGF level below 100 pg/mL were considered the baseline cut-off values in this study for prediction of preeclampsia. These thresholds were determined using the Youden Index and compared by the ROC curve. Mann-Whitney U test was done to find out the difference in mean serum PIGF levels and UtA-PI values between the two groups. Relative risk (RR) of serum PIGF level and UtA-PI were calculated to predict the risk of developing preeclampsia among pregnant women at 20- 24 weeks of gestation with low serum PIGF level (<100 pg/ml) and increased UtA-PI (≥1.8). The sensitivity and specificity of the combination of maternal serum PIGF level and UtA-PI were measured for prediction of preeclampsia. For every subject, a separate data sheet was used. The data were analyzed using the latest version of SPSS (v27.0) software.

Ethical approval was obtained from the Institutional Review Board of BMU. The study was conducted in accordance with the guidance and principles of the Declaration of Helsinki. The privacy of the participants and confidentiality of data were maintained strictly in the study.

Results

A total of sixty-three pregnant women fulfilling the selection criteria were enrolled for the study. Serum PIGF and UtA-PI were estimated within 20-24 weeks of gestation and each study subject was monitored and evaluated till delivery for the development of preeclampsia.

Table I: Comparison of serum PIGF and UtA-PI between preeclampsia and no preeclampsia group (n = 63)

Parameter Mean ± SD	Pre-eclampsia (*n* = 12)	No preeclampsia (*n* = 51)	P-value
Serum PIGF level	80.8 ± 58.8	206.2 ± 162	0.011
UtA-PI	1.5 ± 0.4	0.9 ± 0.18	<0.001

Mann –Whitney U test done

Table I shows that the mean (±SD) maternal serum PIGF level was relatively lower (80.8±58.76 pg/ml) in preeclamptic patients compared to the no-preeclampsia group. This difference was statistically significant. The mean (±SD) uterine artery PI was relatively higher (1.5±0.37) in patients who developed preeclampsia compared to those who did not, which was statistically highly significant.

Table II: Relative risk of preeclampsia in relation to maternal serum low PIGF level (n=63)

Serum PIGF	Pre-eclampsia (*n* = 12)	No preeclampsia (*n* = 51)	RR	P-value
<100 pg/ml	11	18	12.9	<0.001
≥100 pg/ml	1	33		

Table II shows that patients with serum PIGF level <100pg/ml had 12.9 times more risk of developing preeclampsia compared to those with the normal PIGF value of (≥100 pg/ml) (p=<0.001;).

Table III: Relative risk of preeclampsia in relation to high UtA-PI (n = 63)

UtA-PI	Pre-eclampsia (*n* = 12)	No preeclampsia (*n* = 51)	RR	P-value
>1.18	11	6	29.8	
≤1.18	1	45		<0.001

Table III shows the risk of developing preeclampsia was significantly higher in women with uterine artery PI was >1.18, with a RR of 29.765. This was statistically significant (p<0.001).

Table IV: Performance of Low (<100 pg/ml) maternal serum PIGF level as a predictor of preeclampsia (n=63)

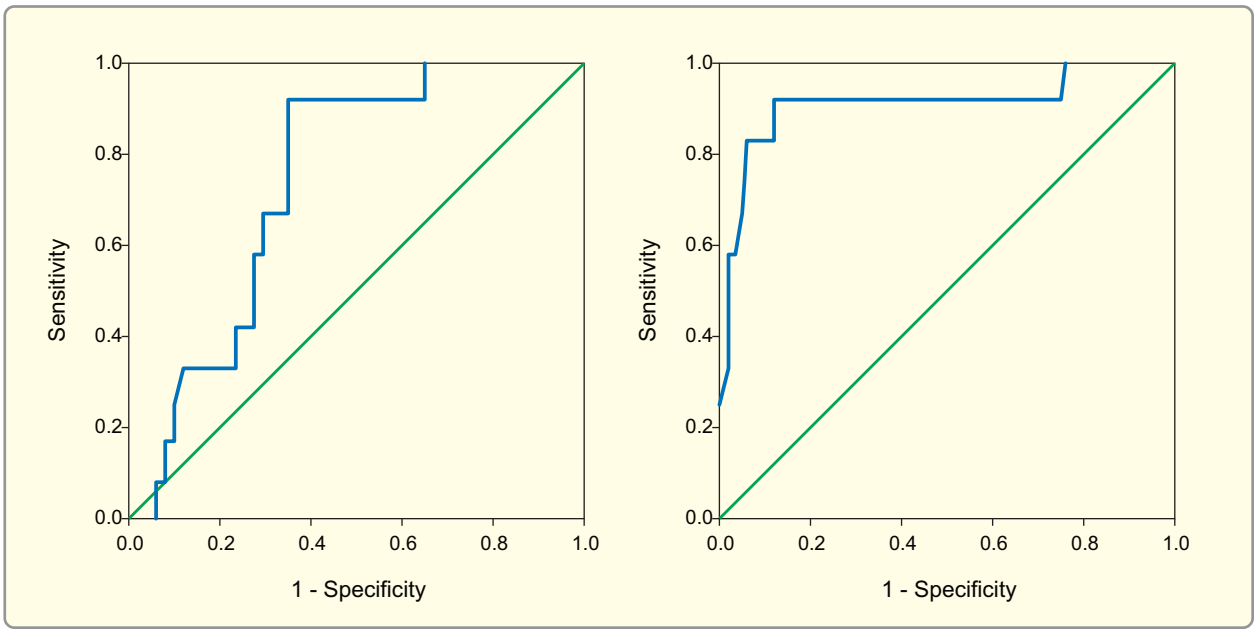
Statistics	PIGF <100 pg/ml	95% CI
Sensitivity	91.7%	61.5% to 99.8%
Specificity	64.7%	50% to 77.6%
PPV	37.9%	28.9% to 47.9%
NPV	97%	83.3% to 99.5%
Accuracy	69.8%	56.9% to 80.8%

Table IV illustrates, the maternal serum placental growth factor level <100pg/ml showed the highest sensitivity (91.67%) and NPV (97.06%) for the prediction of preeclampsia.

Table V: Performance of high (>1.8) maternal UtA-PI level as a predictor of preeclampsia (n=63)

Statistics	UtA-PI (>1.18)	95% CI
Sensitivity	91.7%	61.5% to 99.8%
Specificity	88%	76% to 95.6%
PPV	64.7%	45.9% to 79.8%
NPV	97.8%	87.3% to 99.7%
Accuracy	88.9%	78.4% to 95.4%

Table V shows, UtA-PI >1.18 has sensitivity 91.67 % and while the negative predictive value was (97.83%) for the prediction of preeclampsia.



(A) AUC (B) AUC

Figure 1: Receiver operating characteristic (ROC) curves of maternal serum PlGF level (A) and UtA-PI (B) for prediction of preeclampsia

Figure 1 shows, The ROC for the uterine artery pulsatility index (PI) and maternal serum PlGF score for the prediction of preeclampsia. The area under the curve for PlGF was 0.909 (0.790 -1.000), with a standard error of 0.061 and 0.739 with a standard error of 0.066, categorizing as an excellent test for the prediction of preeclampsia.

Table VI: Combined uterine artery PI and serum PlGF levels for prediction of preeclampsia (n = 63)

Parameters	Women with preeclampsia (n = 12)	Normal pregnant women (n = 51)
UtA PI >1.18 & PlGF <100.0 pg/ml	10	5
UtA PI ≤1.18 & PlGF ≥100.0 pg/ml	2	46

Table VI shows, the distribution of the respondents according to raised uterine artery PI (>1.18) and low serum PlGF (<100.0 pg/ml) for prediction of preeclampsia. Above four-fifths (83.3%) of the PE group of patient's uterine artery PI was >1.18 and serum PlGF level <100.0 pg/ml, while it was absent in majority (90.2%) of the women with no preeclampsia, (P <0.001).

Table VII: Performance of combined uterine artery PI (>1.18) and serum PlGF (<100 pg/ml) for prediction of preeclampsia (n = 63)

Statistics	Value	95% CI
Sensitivity	83.3%	51.6% to 97.9%
Specificity	90.2%	78.6% to 96.7%
PPV	66.7%	45.6% to 82.7%
NPV	95.8%	86.6% to 98.8%
Accuracy	88.9%	78.4% to 95.4%

Table VII shows, the uterine artery pulsatility index >1.18 and maternal serum PlGF <100 pg/ml, when used in combination for the prediction of preeclampsia, exhibit high specificity (90.2%), PPV (66.67%), and accuracy (88.89%).

Discussion

This study involved sixty-three pregnant women aged between 18 and 40 years with an aim to predict preeclampsia by low serum placental growth factor (PlGF) level (<100 pg/ml) and high uterine artery pulsatility index (UtA-PI).

Among the participants, 12(19.05%) developed preeclampsia during follow-up. The mean (±SD) maternal serum PlGF level was found relatively lower (80.8±58.76 pg/ml) in preeclamptic patients compared to no preeclampsia group (206.2±162.06 pg/ml). This

difference in the distribution was statistically significant, P value =0.011. On the other hand, the mean (±SD) uterine artery PI (MUAI) in the present study was relatively higher in women who developed preeclampsia (1.5±0.37) compared to women who did not develop preeclampsia (0.9±0.18), which was statistically highly significant (p<0.001).

The patients with serum PlGF level <100pg/ml at 20-24 weeks had 12.9 times more risk to develop preeclampsia subsequently compared to those with the normal PlGF value of (≥100 pg/ml) (p=<0.001; RR=12.897;).

ROC curve was constructed & the cut-off value of 100.0 pg/mL for serum PlGF level and 1.18% for UtA-PI in predicting preeclampsia showed the highest Youden index. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate of combination of low maternal serum PlGF level (<100.0 pg/mL) and a raised UtA-PI (>1.18) in the prediction of preeclampsia was 83.33%, 90.20%, 66.67%, 95.83% and 88.89%, respectively.

The present study observation was similar to the findings reported by Espinoza et al. (2007), the combination of abnormal UADV and maternal plasma PlGF of <280 pg/mL was associated with an odds ratio (OR) of 8.6 (95% CI, 5.35-13.74) for the development of preeclampsia. The diagnostic utility of a combination of abnormal UADV and maternal plasma PlGF in the identification of patients destined to develop preeclampsia was determined as the sensitivity 27.3%, specificity 96.4%, PPV 21.4%, and NPV 97.3% .[12]

In a clinical article, Diab et al. (2008) revealed, Doppler PI at a cut-off value of 1.84 had a sensitivity of 64%, specificity 85%, PPV 66% and NPV 84% for the prediction of PE. The sensitivity, specificity, positive predictive value, and negative predictive value of serum PlGF level in prediction of preeclampsia for the cut-off point of 144 pg/mL was 88%, 81%, 67%, and 94%, respectively.[17]

Barati et al.(2014) observed, for predicting preeclampsia, the mean uterine artery PI had to be >1.45, had to have a specificity of 95.5%, sensitivity of 79%, NPV of 98.9%, and PPV of 88.2% .[14]

Ghosh et al. (2012) showed both abnormal UADV and serum PlGF <188 pg/ml are independent variables in the occurrence of pre-eclampsia. Multivariate logistic regression analysis showed that a combination of them had a very poor association (p = 0.938) with the occurrence of preeclampsia .This indicated that UADV and maternal serum PlGF estimation at 20–22 weeks of gestation are strong predictors of the occurrence of pre-eclampsia when used individually but not in combination [13].

Inversely, Chien et al. (2000) in their study clinched that uterine artery Doppler flow velocity has limited diagnostic accuracy in predicting preeclampsia [17].

Therefore, in this study, all the findings showed, that a combination of low serum PlGF level and increased UtA-PI at 20-24 weeks of gestation can predict subsequent development of preeclampsia.

Conclusions

Both low serum PlGF (<100 pg/ml) and elevated uterine artery PI (>1.18) showed high sensitivity and negative predictive value, while their combined use improved specificity and overall predictive accuracy. These findings suggest that combined assessment of serum PlGF and uterine artery PI may be useful for early identification of women at increased risk of preeclampsia.

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