Original Research Article

Predictive and prognostic significance of placental growth factor in pregnant women at high-risk for development of preeclampsia

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ABSTRACT

Background: The study aimed to assess the predictive and prognostic role of placental growth factor (PlGF) in high-risk antenatal women for development of preeclampsia (PE).
Methods: In this observational cohort study, antenatal women with gestation age from 20 to 32 weeks with high risk for development of PE were included. Serum PlGF was estimated by sandwich ELISA technique. A p-value of less than .05 was considered significant.
Results: A total of 286 high-risk women were analysed for development of PE and obstetric outcomes. Of these 97/286 (34%) developed PE and 62/286 (21.7%) had abnormal PlGF value (<100 pg/ml). Among the women with abnormal PIGF, 48 (77.4%) developed PE and out of 224 women with normal PIGF level, 49 (21.9%) developed PE resulting in a significant (p<0.001) odds ratio of 12.2 (95% CI: 6.0-25.9). For prediction of PE, a sensitivity and specificity of more than 75% at a cut-off value of <204.5 pg/ml was observed by ROC curve analysis. For prediction of preterm delivery (<34 weeks), a sensitivity and specificity of 65% was observed at a cut-off value of PlGF 191.7 pg/ml. Obstetric complications like eclampsia, preterm births (<34 weeks), neonate with low 5-minute APGAR score, low birth weight, fetal growth restriction, still-births and neonatal intensive care unit admissions all were significantly higher in abnormal PlGF group compared with normal PlGF group (p<0.05).
Conclusions: Serum PlGF levels can provide valuable information for the prediction of PE and preterm births and abnormal PlGF values showed a significant association with adverse obstetrical outcomes.

Key Words: Placental growth factor, Preeclampsia, Preterm birth, Fetal growth restriction, Adverse obstetrical outcomes

INTRODUCTION

Preeclampsia (PE), is a significant contributor to maternal and perinatal morbidity and mortality (7%), and one of the most common complications during pregnancy affecting approximately 3-10% of cases.[1,2] PE can be diagnosed with clinical and biochemical measures but the variable presentation and unpredictable progression pose a significant difficulty for the treating obstetricians to reliably identify pregnant women who are at high risk of development of adverse outcomes. The patient's and physician's apprehension can lead to prolonged hospitalization and unnecessary interventions, on the other hand, some patients can be missed. Hence, the need of the hour is the availability of such a marker which can guide us in predicting the disease itself and the adverse maternal and foetal outcomes so that timely management can be done for high-risk patients.

The clinical features used to recognise PE are neither specific nor precise. Blood pressure alone has a poor predictive value for the diagnosis of PE as well as for the prediction of adverse obstetrical outcomes.[3] Various studies have shown that defective placentation, which itself is caused by malfunctioning of syncytiotrophoblasts is the root cause of the development of PE.[4] Studies had also demonstrated that altered expression of angiogenic and anti-angiogenic factors produces an anti-angiogenic environment, that leads to widespread endothelial dysfunction and disease manifestation.[5-7]

Recently, Placental growth factor (PlGF) and soluble-fms-like-tyrosine kinase-1 (sFlt-1) were extensively studied regarding their significance in the diagnosis and prediction of the development of PE.[8,9] PlGF is a member of the vascular endothelial growth factor (VEGF) family, which is expressed in the villous trophoblasts during pregnancy. It binds with the Flt-1 receptor (VEGFR-1) and leads to normal angiogenesis. Recently some studies also reported that along with the prediction and diagnosis of PE, PlGF also has the potential to predict the maternal and fetal outcome weeks before the development of the disease.[10] In the present research, the use of maternal serum PlGF levels in predicting PE in high-risk cases as well as the prognostic performance of PlGF in these cases was investigated.

METHODS

This was an observational prospective cohort study done in the Department of Obstetrics and Gynaecology in collaboration with the Department of Biochemistry at All India Institute of Medical Sciences, New Delhi from September 2015-2017. The inclusion criteria for enrolment were antenatal women with a period of gestation from 20 to 32 weeks with high-risk factors including gestational hypertension without proteinuria (G.HTN), isolated proteinuria, chronic hypertension (Ch. HTN), chronic kidney disease (CKD) and previous history of PE or eclampsia. Antenatal women who had a fetus with a major congenital anomaly were excluded from the study.

The participants were enrolled after taking written and informed consent. The study protocol was approved by the institute's ethics committee (IEC/NP-142/10.04.2015, RP-36/2015). Baseline characteristics of the patients along with pregnancy-specific details, high-risk factors, and history of previous pregnancy were noted. A blood sample for detection of serum PlGF was withdrawn at the time of enrolment only. The pregnant women were followed regularly and were clinically evaluated for the development of PE at each antenatal visit until delivery and during the postpartum period. The maternal and foetal outcomes were noted for all.

The final diagnosis of PE, G.HTN and Ch. HTN along with superimposed preeclampsia was made based on the American College of Obstetricians and Gynecologists (ACOG) 2013 criteria.[11] PE was defined as a systolic blood pressure (SBP) of 140 mmHg or more or diastolic blood pressure (DBP) of 90 mm Hg or more on two occasions at least four hours apart in a normotensive woman after 20 weeks of gestation along with a 24-hour urinary protein 300 mg or more or protein creatinine ratio of 0.3 or more or dipstick reading of +2. In the absence of proteinuria, new-onset hypertension with the new onset of any of the following thrombocytopenia (platelet count less than 100×10^9/l), renal insufficiency (serum creatinine more than 1.1 mg/dl or a doubling of serum creatinine concentration in the absence of another renal disease), impaired liver function (transaminases elevation to twice to normal concentration), pulmonary oedema, new-onset headache unresponsive to medication were included. The severe features also include SBP of 160 mmHg or more or DBP of 110 mmHg or more. G.HTN was defined as SBP of 140 mmHg or more or DBP of 90 mm Hg or more, or both on two occasions at least four hours apart without proteinuria after 20 weeks of gestation in previously normotensive women. Ch HTN was defined as the presence of hypertension before 20 weeks or the presence of high blood pressure before pregnancy. Isolated proteinuria was defined as the presence of protein 300 mg or more in 24 hours without hypertension. The blood sample was drawn once at the time of enrolment and PlGF was estimated quantitatively by colourimetric detection assay using the principle of sandwich ELISA. The range of the assay was 1.372 pg/ml to 1000 pg/ml and the detection limit was less than 2 pg/ml. Results were expressed in pg/ml and the analysts were blinded to clinical diagnosis. The main exposure variable was abnormal PlGF. A PlGF Value of <100 pg/ml was considered abnormal. A value of less than 12 pg/ml was considered highly abnormal. The primary outcome of the study was to assess the predictive ability of PlGF for the development of PE and preterm delivery. Among Secondary outcome measures, adverse maternal outcomes including, maternal death; eclampsia; hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome; placental abruption; requirement of magnesium sulfate, presence or absence of retinal changes, doppler changes, oligohydramnios, antihypertensive therapy, duration between enrolment to development of preeclampsia, duration between the development of preeclampsia to delivery, lower segment caesarean section (LSCS), preterm delivery and Intensive Care Unit (ICU) stay along with adverse fetal outcomes including, fetal death; neonatal death; APGAR score less than 7 at 5 minutes; prematurity (less than 34 weeks); neonatal intensive care unit (NICU) admission; and birth weight less than 2500 gm were compared between the abnormal and normal PlGF group.

Statistical analysis

Descriptive statistics such as mean, standard deviation (SD) and median values were calculated for continuous variables. For qualitative variables, percent values were computed. Student's independent t-test was used to compare the mean values of normally distributed data between two groups. For non-normality variables, median

values were compared between the two groups using Mann-Whitney U-test. Frequency variables were compared using Chi-square/Fisher's Exact test as appropriate. Univariate analysis like crude odds ratio was carried out to identify risk variables that might contribute to preeclampsia. The ROC curve was drawn to find out the accuracy of the predictive cut-off of PlGF at an optimum level of sensitivity and specificity level. A p value of less than 0.05 was considered significant.

RESULTS

In total, 291 women were enrolled in the study; the final analysis was done for 286 women as three patients were lost to follow-up and two were delivered elsewhere. Out of 286 high-risk women, 97 (34%) developed PE and 189 (66%) women did not develop PE (No PE). The baseline characteristics of the patients in PE and no PE group were shown in (Table 1) and it was found comparable between the two groups (Table 1). On comparing the PlGF values between the PE and No PE groups, we found that the median PlGF value in the PE group was substantially lower (104.76 pg/ml; IQR: 37.6-254.5 pg/ml) than the no PE group (400.48 pg/ml; IQR:186.9-577.2 pg/ml) (p=0.001). In addition, the patients in the PE group, who developed severe features showed a significantly lower value of the median PlGF (72 pg/ml; IQR: 20.4-131.0 pg/ml) compared with those who did not develop severe features (155.7 pg/ml; IQR: 79.4-350.3 pg/ml) (p=0.019).

Table 1: Comparison of Baseline variables between PE and No PE groups.

Variables	PE group (N=97)	No PE (N=189)	P value
Age (years) (mean±SD)	29.39±4.67	29.29 ±4.36	0.857
BMI (kg/m^2) (mean±SD)	24.04±2.33	24.41±3.14	0.300
MAP at enrolment (mmHg) (mean±SD)	88.7±10.4	87.5±8.8	0.532
Parity, N (%)			
0	25 (25.8%)	62 (32.8%)	
1	32 (33.0%)	50 (26.5%)	0.473
2	18 (18.6%)	40 (21.2%)	
≥3	22 (22.7%)	37 (19.6%)	
POG at enrolment (weeks) (mean±SD)	26.12±3.57	25.97±3.33	0.720

To find out the predictive performance of PlGF for the development of PE, we used Receiver Operating Characteristic Curve (ROC) analysis. The (Figure 1) illustrates the ROC curve for PlGF, and PlGF showed a sensitivity and specificity of more than 75% at a cut-off value of 204.5 pg/dl for the prediction of PE with an area under the curve (AUC) of 0.804 (95% CI: 0.748-0.860) with a p<0.001. The false positive and false negative rate of PlGF at this cut-off value was estimated to be 25% (Figure 1).
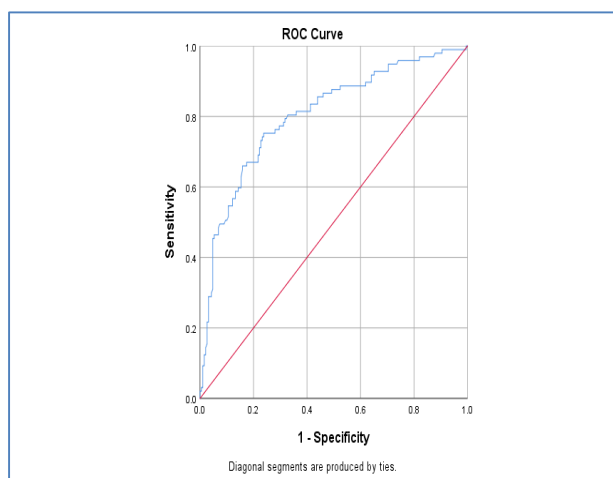
Figure 1: ROC curve for the prediction of preeclampsia.

To find out the association of PlGF with maternal and fetal outcomes, we again divided the participants into two categories based on serum PlGF value, abnormal PlGF category (<100 pg/ml) and normal PlGF category (≥100 pg/ml). Out of 286 patients, 62 (21.7%) had abnormal PlGF values (<100 pg/ml) and 224 (78.3%) patients had normal PlGF (≥100 pg/ml) values. Out of 62 patients with abnormal PlGF value, 48 (77.4%) developed PE while among 224 patients with normal PlGF value, only 49 (21.9%) developed PE resulting in an odds ratio of 12.2 (95% CI: 6.0-25.9), which was statistically significant (p<0.001). In our study, 11 patients had highly abnormal PlGF values <12 pg/ml; out of which nine developed PE, 8/11 had a preterm delivery, all of them belonged to the PE group, and all the newborns required neonatal NICU care due to prematurity. For early vs. late-onset PE, a total of 48/97 (49.5%) patients developed early-onset PE (<34 weeks POG), out of which, 29/48 (60.4%) had abnormal PlGF value, and 19/48 (39.6%) had normal value of PlGF. This finding was also statistically significant (p=0.014).

A comparison of the maternal outcomes between abnormal versus normal PlGF groups is shown in (Table 2). The patients in the abnormal PlGF group had a significantly increased risk of development of complications such as eclampsia (p=.009), retinal changes (p=0.033), abnormal Doppler (p<0.001) and requirement of antihypertensive (p<0.001), and magnesium sulfate therapy (p<0.001). The difference was found to be statistically significant for these complications between abnormal and normal PlGF groups.

Table 2: Association of PlGF with maternal outcome.

Outcome variables	PlGF<100pg/ml (Test-Positive/ Abnormal) (N=62), Frequency (%)	PlGF≥100pg/ml (Test-Negative/ Normal) (N=224), Frequency (%)	P value
Eclampsia	3 (4.8)	0 (0.0)	0.009[a]
HELLP	1 (1.6)	1 (0.4)	0.383
Abruption	1 (1.6)	1 (0.4)	0.387
Need of Magnesium sulphate	9 (14.5)	5 (2.2)	<0.001[a]
Need of Antihypertensive therapy	49 (79.0)	79 (35.2)	<0.001[a]
Retinal Changes	3 (4.8)	1 (0.4)	0.033[a]
Oligohydramnios	7 (11.3)	11 (4.9)	0.112
Abnormal doppler	12 (19.4)	17 (7.6)	0.001[a]
Gestational age at PE development (weeks)	31.58±4.28	33.62±3.21	0.010[a]
Duration from enrolment to PE development (weeks) (mean±SD)	5.28±3.77	7.68±3.11	0.001[a]
Duration between PE development to delivery (days) (mean±SD)	10.85±15.47	29.53±14.62	<0.001[a]
Gestational age at delivery (weeks) (mean±SD)	33.76±4.11	36.89±2.15	<0.001[a]
Mode of delivery			
LSCS	40 (64.5)	134 (59.8)	0.503
VD	22 (35.5)	90 (40.2)	
Preterm delivery	44 (71.0)	76 (33.9)	
Early PT (<34 weeks)	24 (38.7)	22 (9.8)	
Late PT (<37 weeks)	20 (32.3)	54 (24.1)	<0.001[a]
Term (≥37 weeks)	18 (29.0)	148 (66.1)	
ICU stay	1 (1.6)	4 (1.8)	0.995

'a' indicates statistically significant parameters, HELLP- hemolysis, elevated liver enzymes, and low platelet count; PE- Preeclampsia; LSCS- Lower Segment Caesarean Section; VD- Vaginal Delivery, PT- Preterm, ICU- Intensive Care Unit

The mean gestational age at which PE developed was significantly earlier in the abnormal PlGF group (31.58±4.28 weeks) than in the normal PlGF group (33.62±3.21 weeks) (p=0.010).
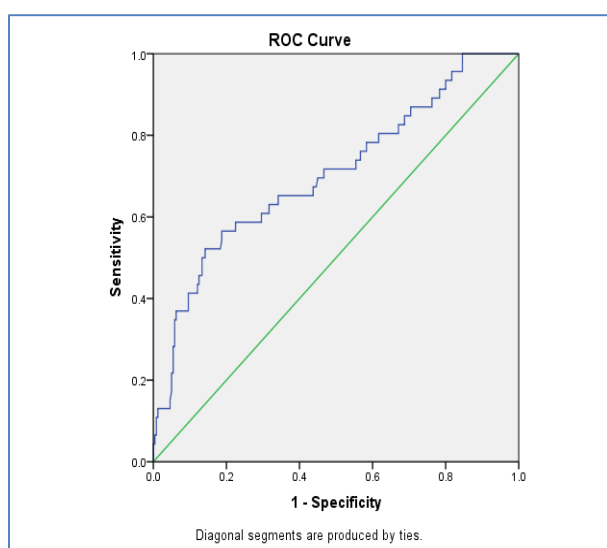
Figure 2: The ROC curve for an early preterm delivery (<34 weeks) with a median PlGF value.

Similarly, when we compared the mean duration from enrolment to development of PE between the abnormal and normal PlGF groups, it was 5.28±3.77 weeks and 7.68±3.11 weeks respectively, with a statistically significant difference (p=0.001). Gestational age at delivery in patients with abnormal versus normal PlGF values was 33.76±4.11 weeks and 36.89±2.15 weeks respectively and the difference was statistically significant (p<0.001). There was a small but nonsignificant increase observed in the incidence of HELLP, abruption, oligohydramnios and caesarean section. ICU stay was more in the normal PlGF group. There was no maternal mortality noted in our study (Table 2).

The association of serum PlGF levels with fetal outcome is shown in (Table 3). When considering the fetal outcome, preterm delivery was significantly higher in the abnormal PlGF group in comparison to the normal PlGF group (71% vs. 33.9%; p<0.001). The abnormal PlGF group had a significantly higher number of neonates with low APGAR scores (22.6% vs. 4.0%; p<0.001), FGR (45.2% vs. 20.5%; p<0.001), NICU admission (56.1% vs. 13.1%; p<0.001) in comparison to the patients in the normal PlGF group. The mean birth weight in the abnormal PlGF group was significantly lower than the normal PlGF group (1884.45±760.18 vs. 2611.61±579.82; p<0.001).

Table 3: Association of PlGF with fetal outcome.

Outcome variables	PlGF<100pg/ml (Test Positive) (N=62)	PlGF≥100pg/ml (Test Negative) (N=224)	P value
Prematurity (<37 weeks)	44 (71.0)	76 (33.9)	<0.001[a]
APGAR-1 minutes (mean±SD)	6.71±3.16	8.34±1.38	<0.001[a]
APGAR- 5 minutes (mean±SD)	7.35±2.84	8.71±1.20	<0.001[a]
Low APGAR Score	14 (22.6)	9 (4.0)	<0.001[a]
Birth Weight (mean±SD)	1884.45±760.18	2611.61±579.82	<0.001[a]
Birth Weight Category			
<1000 g	9 (14.5)	3 (1.3)	
<1500 g	11 (17.7)	7 (3.1)	<0.001[a]
<2500 g	28 (45.2)	76 (33.9)	
<4000 g	14 (22.6)	138 (61.6)	
FGR	28 (45.2)	46 (20.5)	<0.001[a]
IUD	4 (6.5)	3 (1.3)	0.042[a]
NICU Admission	32 (56.1)	29 (13.1)	<0.001[a]
Neonatal Mortality	3 (4.8)	3 (1.3)	0.176

a' indicates statistically significant parameters, FGR- Fetal Growth Restriction, IUD- Intra Uterine Demise, NICU- Neonatal Intensive Care Unit

Table 4: Comparison of preterm and full-term births using PlGF.

PT	N (PE)	PE group (N=97) Median PlGF value (IQR)	N (no PE)	No PE group (N=189) Median PlGF value (IQR)	P value
Early PT	31	34.1 (19.1-125.0)	15	278.6 (169.7-551.9)	<0.001
Late PT	35	98 (44.8-196.0)	39	426.4 (194.3-633.0)	<0.001
Term	31	145.6 (98.5-332.2)	135	403.1 (217.6-578.0)	<0.001

PlGF- Placental Growth Factor, IQR- Inter Quartile Range, PT- Preterm

The number of stillbirths in the abnormal PlGF group was also more than the normal PlGF group (6.5% vs. 1.3%) and the difference was statistically significant (p=0.042), while there was no difference found in neonatal mortality between the two groups (Table 3). When we compared the median values of serum PlGF between the PE and No PE groups concerning gestational age at delivery (early preterm, late preterm and term deliveries), it was observed that the median value of serum PlGF in all three groups was considerably lower in women with PE compared to those without PE (Table 4). To find out the predictive ability of serum PlGF for the development of preterm birth, ROC was plotted. Serum PlGF showed a sensitivity and specificity of 65%, at a cut-off value of 191.7 pg/ml with an AUC of 0.704 (SE: 0.045) at a 95% confidence interval (0.616-0.792) for predicting preterm delivery at less than 34 weeks period of gestation (p<0.001) (Figure 2).

DISCUSSION

Despite being studied extensively about pathophysiology, prevention, and diagnosis of PE, it is very difficult to stratify the risk category of patients and to provide optimum and timely management. This study was focused on evaluating the predictive performance of maternal serum PlGF with the development of PE and its association with adverse maternal and fetal outcomes in antenatal women who are at high risk for the development of PE. In our study, it has been observed that PlGF has an

important role in the prediction of PE, as well as, abnormal PlGF levels were associated with an increased risk of adverse maternal and fetal outcomes. In our study, the overall incidence of PE was 34%, which was lower than observed in other major studies (71.4%).[12] The difference in the ethnicity and background characteristics of the study population might be the reason for this discrepancy.

The predictive performance of PlGF for the diagnosis of PE is of great importance in patient management. In contrast to Agarwal et al.,[13] who found that serum PlGF had the best predictive performance at a cut-off of 80-120 pg/ml with a sensitivity of 0.78 (95% CI, 0.67-0.86) and a specificity of 0.88 (95% CI, 0.75-0.95), our study's revealed a cut-off value of <204.5 pg/ml with a sensitivity and specificity of >75% (95% CI, 0.748-0.860). Our results are in line with those of Varughese et al who researched a population that was similar to our study and discovered that maternal serum PlGF levels were considerably lower in PE patients than in controls (mean 236.77 pg/ml vs 744.98 pg/ml, p<0.0001).[14] Because of the varied methodologies used to quantify serum PlGF, variations in ethnicity, and different periods of gestation (POG), different absolute cut-off values have been observed in different studies.[15]

On considering the normal and abnormal test values of PlGF, we found that 62/286 (21.7%) patients had normal PlGF<100 pg/ml which was higher than the 13.6% in the study of Ukah et al and lower than the observations of

Parchem et al (66.7%).[16,17] For risk stratification, triaging and deciding the need for transfer of the patient to a higher facility, the enrolment to delivery interval is an important criterion. We observed a shorter enrolment to the delivery interval in participants with abnormal PlGF levels compared with those who had normal values of PlGF. These findings were in corroboration with the Ukah et al and PETRA trial, where abnormal PlGF levels (<100 pg/ml) were strongly correlated with time to delivery.[12,16] Adverse maternal and fetal outcomes including eclampsia, HELLP, placental abruption, FGR, neonatal death, stillbirth, low 5-minute APGAR score and preterm delivery, all were significantly increased in the abnormal PlGF group compared with those with normal values of PlGF. Our observations were similar to the results of Ukah et al and Perchem et al which confirmed the association of abnormal PlGF with increased incidence of adverse obstetrical outcomes.[16,17]

Preterm birth, which is a leading cause of neonatal death, a risk factor for short and long-term adverse health outcomes, and a major contributor to the financial burden on the health sector, was observed in 33.9% of women with normal PlGF compared to 71% in the abnormal PlGF group. This finding was in correspondence to the results of Parchem et al where preterm delivery in the abnormal PlGF group was 83.3% and in the normal PlGF group, it was 33.0%.[17] Along with that, for the prediction of preterm delivery at <34 weeks, we observed a cut-off value of 191.7 pg/mL with 65% sensitivity and specificity at a CI of 95% (0.616-0.792). However, in the study by Barton, et al. PlGF had 82% sensitivity and 85% specificity for the prediction of preterm delivery at 37 weeks POG with 93.5% PPV at a cut-off value of 100 pg/ml.[12] The PELICAN study, a multicenter prospective study, demonstrated that low maternal serum levels of PlGF (<5th centile for POG) had a high sensitivity (0.96; 95% CI 0.89-0.99) and negative predictive value (NPV 0.98; 0.93 0.995) for the diagnosis of PE and the requirement for delivery within 14 days in cases of suspected PE before 35 weeks POG.[18] To emphasize more about the role of serum PlGF in risk stratification, the PARROT trial was conducted, where they observed that when PlGF is implemented in diagnosis-making, the mean time to diagnose was significantly reduced and there was a lower incidence of adverse maternal outcomes, but no significant difference in adverse perinatal outcomes was noted.[19] Here, in our study, we also observed significantly increased adverse maternal and perinatal outcomes as shown by some other similar studies.[17,20] Cost is an important factor which needs consideration before the implementation of PlGF as a routine test. For the same, a cost-effective analysis of the PARROT trial was conducted by Duhig and colleagues and they concluded that each year around £2,891,196 can be saved by including PlGF which allows the appropriate redistribution of resources, rather than overall reduction.[21] Hence, triage of patients using PlGF testing can be a cost-effective measure, but more studies are needed to conclude this fact. An increase in the number of preterm deliveries was also

a matter of concern by various committees initially as the majority of studies had focussed on PlGF levels and preterm PE. However, many recent large trials and the NICE committee had concluded that the use of this test did not lead to unnecessary preterm births.[12,19,22,23]

Limitations and strengths

The strength of our study was, it was a prospective cohort study and addressed a significant need in the field of maternal and child health. We had chosen the high-risk patients, where establishing the diagnosis of PE is a challenging task and very few studies had addressed this issue in these patients. The observational nature of the study could be a limiting factor also the external validity of our study was less as we included only the high-risk population and gestation wise PlGF value could not be calculated due to variation in the number of women gestation-wise and thus the results could not apply to the general population.

CONCLUSION

Abnormal values of maternal serum PlGF had shown a positive association with adverse maternal and fetal outcomes in antenatal women who were at high risk of development of PE. Patients with a high risk of developing preterm PE could also be benefitted from serum PlGF levels for the prediction of the development of PE and preterm births. It might be of great benefit for maternal and child health as we can triage patients and provide them with optimal care. This can also help in the proper allocation of resources and can reduce the overall financial burden of the disease. Although significant research has been done to assess its utility, more randomized trials are required to analyze the impact of incorporating this marker as a routine for prediction of adverse obstetrical outcomes.

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