Original Article

Predictive Value Of Placental Growth Factor In Preeclampsia

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Abstract

Background Preeclampsia is a common obstetric complication which causes both a maternal and fetal morbidity and mortality. The exact etiology is still unknown. Development of a test for preeclampsia with the use of a pathophysiologically relevant biomarker, such as Placental Growth Factor (PlGF), may have advantages over blood pressure and urinary protein, which are the consequences of established disease. **Aim** The purpose of our study was to evaluate the diagnostic accuracy of plasma PlGF concentrations in women presenting with suspected preeclampsia. **Methods** This was a prospective observational study; that was carried out on a total sample of 80 women. The study was conducted between September 2021 and September 2022 at obstetrics and gynecology department of Damanhur Medical National Institute. We investigated and followed up all first trimester pregnant women who were at risk of pre-eclampsia. Women with confirmed diagnosis of pre-eclampsia development were included in case group. Enzyme-linked immunosorbent assay (ELISA) kits were used according to manufacturer principles to detect concentration of PLGF in the patient sample. Also, soluble fms-like tyrosine kinase 1 (sFlt -1) was measured according to manufacturer principles to detect sFlt-1/PlGF ration. **Results** Mean PLGF concentration in patients who developed pre-eclampsia was significantly decreased compared to others. So, sFlt-1/PlGF in patients who developed pre-eclampsia was significantly increased compared to others. **Conclusion** PLGF concentration showed good specificity in the prediction of the development of pre-eclampsia with statistical significance. sFlt-1 and sFlt-1/PLGF showed high sensitivity in the prediction of the development of pre-eclampsia with statistical significance.

Keywords: Placental Growth Factor, Preeclampsia, Diagnosis, Pregnancy.

INTRODUCTION

Preeclampsia is a common obstetric complication which causes both maternal and fetal morbidity and mortality. Preeclampsia also increases the risk of developing long-term cardiovascular and cerebrovascular diseases. The exact aetiology is still unknown but associated with a failure of the trophoblastic invasion of the spiral arteries, which may be associated with increased vascular resistance of the uterine artery and a decreased perfusion of the placenta **(1).**

The placenta is a key point of fetal development which transfers oxygen and nutrition to the fetus; therefore, abnormal placentation in the first trimester of pregnancy may play a crucial role in determining the risk of subsequent late pregnancy complications. Impaired placentation leads to the development of preeclampsia. In addition, the placental size and shape at delivery are strongly correlated to birth weight **(2).**

Although multiple mechanisms and factors have long been recognized, including increased oxidative stress; abnormal placentation; cardiovascular maladaptation to pregnancy; malfunction in genetic, immunological, nutritional, hormonal, and angiogenic mechanisms; and inflammation the understanding of the exact pathophysiology of preeclampsia has been elusive **(3).**

Recent advances in understanding preeclampsia and fetal growth restriction have elucidated important biological roles for placentally derived angiogenic factors. In normal pregnancy, placental growth factor (PlGF), synthesized by the syncytiotrophoblast, increases with gestation in maternal circulation, with concentrations peaking at 26 to 30 weeks and declining toward term. PlGF is abnormally low in women with preeclampsia in comparison with gestational age-matched controls and is reduced further in severe preeclampsia **(4).**

Development of a test for preeclampsia with the use of a pathophysiologically relevant biomarker, such as PlGF, may have advantages over blood pressure and urinary protein, which are the consequences of established disease. Because earlier gestation of preeclampsia onset is associated with greater maternal and perinatal risks, and the difference in PlGF concentrations between normal and preeclamptic pregnancies is most marked before 35 weeks, PlGF has the potential to aid the diagnosis of hypertensive disorders of pregnancy at gestations critical to the clinical outcome **(5).**

The most clinically relevant test for health professionals would identify women with preeclampsia associated with a deteriorating disease requiring iatrogenic delivery. Because women with suspected hypertensive disease are routinely monitored every 2 weeks, a test should be applicable for a subsequent 14-day window to impact management strategies **(6).**

The purpose of our study was to evaluate the diagnostic accuracy of plasma PlGF concentrations in women presenting with suspected preeclampsia. The study was approved by review and research ethics committee at Damanhour Medical National Institute (Approval number HD000161).

Material and Methods

This was a prospective observational study; that was carried out on a total sample of 80 women. The study was conducted between September 2021 and September 2022 at the obstetrics and gynaecology department of Damanhur Medical National Institute.

Inclusion criteria 1St-trimester pregnancy, Singleton pregnancy, presence of at least one of the following risk factors: primiparity; history of PE in previous pregnancies; family history of PE; chronic arterial hypertension; renal diseases; diabetes mellitus; systemic lupus erythematosus; antiphospholipid syndrome; thrombophilia; history of obstetric disorders (fetal hypotrophy, oligohydramnios, perinatal mortality, premature separation of the normally implanted placenta); obesity (BMI > 30 kg/m2); maternal age (40 years).

Exclusion criteria Infections, recent treatment with non-steroidal anti-inflammatory drugs and corticosteroids (14 days prior to inclusion), chronic inflammatory diseases, multiple pregnancies and fetal abnormalities.

We investigated and followed up on all first-trimester pregnant women who were at risk of pre-eclampsia. Women with a confirmed diagnosis of pre-eclampsia development were included in the case group. All patients were subjected to complete history taking and a complete physical examination.

The diagnosis of preeclampsia was based on a systolic blood pressure of ≥140 mmHg or diastolic blood pressure ≥90 mmHg, measured twice in four-hour intervals while resting, after the 20th gestational week, as well as 300 mg/dL proteinuria detected in a 24-hour urine sample, or in the absence of proteinuria, hypertension together with evidence of systemic disease, including thrombocytopenia, increased levels of liver transaminases, renal failure, pulmonary oedema, and visual or cerebral disturbances **(7).**

The diagnosis of severe preeclampsia was based on the presence of any of the following criteria: systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥110 mmHg on two separate measurements, performed at six-hour intervals at the least, elevated serum creatinine level (>1.1 mg/dL), headache, visual impairment, epigastric pain or pain in the right upper quadrant, elevated hepatic transaminases (≥ 40 IU/ml), thrombocytopenia (PLT < 1 00,000/µL), or pulmonary oedema **(8).**

Gestational age was determined based on the first day of the last menstrual period (LMP) and first-trimester ultrasonographic measurement of the crown–rump length (CRL). If ultrasound dating differed from LMP dating by more than seven days, the estimated due date was changed to correspond with the ultrasound dating. If the patient was unsure of her LMP, dating was based on ultrasound estimates by using the earliest CRL measurement during the first trimester **(9).**

Fifteen milliliters of blood (additional to routine blood samples) were drawn into ethylenediamine tetra-acetic acid and transported to the laboratory within 1 hour, and plasma was stored until analysis (−80°C).

Test Principle the ELISA kit used is a solid-phase ELISA based on the sandwich principle. The microtiter wells are coated with a monoclonal antibody directed towards a unique antigenic site on a PLGF molecule. To perform the test, 25 µl serum, controls and standards plus 250 µl dilution buffer were incubated in the coated wells for 30 min at room temperature to allow the binding of the antigen by the capture antibody. After a washing cycle, 100 µl of a biotin-linked polyclonal antibody specific for PLGF was added to the wells for 60 min. After a second washing cycle to remove any unbound antibody, the amount of detector antibody bound to antigen was measured by binding with a

streptavidin/horseradish peroxidase conjugate (100 µl/well for 30 min). Subsequently, the unbound enzyme complex was removed by washing, and 100 µl substrate solution was added for 30 min. The reaction was stopped by the addition of 100 µl stopping solution, and the coloured product was quantitated by spectrophotometry at 450 nm with a microplate reader. The intensity of the colour developed was proportional to the concentration of PLGF in the patient sample.
Also sFlt -1 was measured according to manufacturer principles to detect sFlt-1/PlGF ratio.

Pregnancy Outcome the outcome of the pregnancies was monitored in all women included in this study. Preeclampsia was defined as gestational hypertension (systolic pressure of >140 mm Hg or diastolic blood pressure of >90 mm Hg on at least 2 occasions after 20 weeks of gestation) with proteinuria (>300 mg) according to the classification of the International Society for the Study of Hypertension in Pregnancy **(10).** Furthermore, clinical data of the patients were collected.

Statistical Analysis

IBM SPSS version 22.0 was used to analyses computer-generated data. To express quantitative data, percentages and numbers were employed. Before utilizing the median in nonparametric analysis or the interquartile range in parametric analysis, it was required to perform Kolmogorov-Smirnov tests to ensure that the data were normal. We used the (0.05) significance threshold to establish the significance of the findings. The Chi-Square test is used to compare two or more groups. The Monte Carlo test may be used to adjust for any number of cells with a count less than 5. Fischer Chi-Square adjustment was applied to tables demonstrating non continuous data.

Results

The clinical data of patients who participated in this study is outlined in table 1. Overall, there was no significant difference between patients who did not develop pre-eclampsia and those who developed pre-eclampsia regarding maternal age and BMI. Nulliparous patients number was significantly higher in the group who developed pre-eclampsia **(Table 1).**

As expected, the blood pressure was significantly higher in patients who developed pre-eclampsia **(Table 2).**
On the other hand, gestational age and birth weight, both were significantly decreased in patients developed pre-eclampsia compared with others **(Table 3).**

Mean PLGF concentration in patients developed pre-eclampsia was significantly decreased compared to others. So, sFlt-1/PlGF in patients developed pre-eclampsia was significantly increased compared to others **(Table 4).**

Correlation analysis showed that PLGF concentration was negatively correlated with developing of pre-eclampsia. Both sFlt-1 and sFlt-1/PLGF were positively correlated with pre-eclampsia **(Table 5).**

Besides, risk analysis revealed that highest specificity in prediction of developing of pre-eclampsia was with PLGF concentration 44.78 Pg/ml. It reached 94.7% with P value of <0.0001. sFlt-1 of 1831.29 Pg/ml and sFlt-1/PLGF of 18.85, both showed sensitivity of 95.7% and P value of <0.0001 **(Table 6, Figure 1).**

Discussion

This study suggests that PLGF testing presents a realistic and innovative adjunct to the management of women with suspected preeclampsia, especially those presenting preterm. Low PLGF concentration (<5th centile or ≤100 pg/mL) has high sensitivity and negative predictive value in determining which women presenting with suspected disease at <35 weeks' gestation are likely to need delivery for preeclampsia within 14 days. A previous review by Ghosh et al. **(11)** has highlighted the need for a test with high sensitivity in this setting, because there is greater preference for minimizing false negatives when considering overall benefits and harms and in ensuring appropriate resource use. Time to delivery is markedly different for women with very low, low, and normal PLGF values, facilitating stratified management strategies with appropriate surveillance. PLGF was more predictive of the need for delivery than other commonly used signs and tests, either singly or in combination, in current clinical practice. Sensitivity and negative predictive values were also high for delivery of a small for gestational age infant <1st centile; this indicator is most likely to equate to fetal growth restriction of placental origin and to be associated with adverse perinatal outcomes. Although diagnostic accuracy is greatest for women presenting before 35 weeks' gestation, the test may still benefit those presenting up to 37 weeks' gestation (using a threshold of <100 pg/mL) for whom stratified surveillance is also advantageous and the risks/benefits of delivery remain uncertain.

An imbalance between the factors promoting angiogenesis such as vascular endothelial growth factor or PLGF and factors antagonizing angiogenesis such as sFLT1 plays a fundamental role in the pathogenesis of preeclampsia. Decreased concentrations of circulating free PLGF and free vascular endothelial growth factor have been noted during clinical preeclampsia **(12).** Some studies have demonstrated that PLGF concentrations begin to decrease from 11 to 9 weeks before the onset of preeclampsia, with substantial reductions during the 5 weeks before the onset of hypertension or proteinuria. These alterations in the PLGF level are more pronounced in women with early-onset preeclampsia, especially before the 26th week of pregnancy **(13).** The mean serum sFLT1 levels and the sFLT1/ PLGF ratio are higher in women who developed earlyonset preeclampsia at less than 34 weeks of gestation when compared with the subjects without preeclampsia from 22 weeks of gestation onwards **(14).** Other studies have combined the use of uterine artery Doppler ultrasound and the measurement of angiogenic factors for the identification of patients with a high risk for early-onset and/or severe preeclampsia. **(15)** have recently demonstrated that the combination of an abnormal uterine artery Doppler velocimetry and a maternal plasma PLGF concentration of less than 280 pg/ml between 22 and 26 weeks of pregnancy is associated with a high risk for preeclampsia. Using the combination of measurement of sFLT1 and PLGF and Doppler ultrasound of the uterine arteries around 20 weeks of pregnancy, early-onset preeclampsia can be predicted with 83% sensitivity and 95% specificity **(16).**

Schmidt et al. **(17)** demonstrated that the women of this group who will develop preeclampsia in the course of pregnancy already have a significantly lower expression of PLGF between 15 and 18 weeks of pregnancy than the women who will not develop preeclampsia. These results lead to the assumption that an increase in PLGF serum concentration from 15 weeks onwards is not seen in patients who will develop preeclampsia. As the test has a sensitivity of 0.87 and a specificity of 0.83, it might contribute to an early prediction of preeclampsia.

Nikuei et al. **(18)** reported that mean Level of sFlt-1/PlGF was 91.33 ng/ml in PE patients and 17.62 in controls which were increased significantly ($P<0.001$). Also, The ROC curve analysis was applied to differentiate PE patients from normal controls and also for differentiating severe and early-onset forms of PE using sFlt-1/PlGF ratio. The results for differentiation of PE patients from normal pregnancies showed an AUC of 0.90 (95% CI =0.83–0.98). The best cut-off value was 24.96 ng/ml with sensitivity of 84.2% (95% CI =68.7–94) and specificity 85% (95% CI = 62.1–96.8).

Rana et. al. **(19)** reported sFlt1/PlGF ratio of more than 85 had an association with harmful pregnancy complications and termination of pregnancy in 2 weeks. Moreover, they reported sFlt1/PlGF ratio along with systolic blood pressure (SBP) and proteinuria were a better predictive tool rather than SBP, proteinuria, and uric acid levels. Ohkuchi et al. showed the best diagnostic power of sFlt1/PlGF ratio for both early and late onset PE. They reported a cut-off value of 45 with 97 and 95% sensitivity and specificity respectively for diagnosis of all preeclampsia and for diagnosis of earlyonset PE (100 and 95%) **(20).**

PLGF concentration as a predictive factor for early-onset, but not for late-onset preeclampsia **(21,22).** A possible explanation for this might be that the PLGF concentration in pregnancies which will be complicated by late-onset preeclampsia starts to increase later in pregnancy. This might explain why there is a significant difference between 15 and 18 weeks of gestation compared to nonpreeclamptic pregnancies which is no more significant later in pregnancy in contrast to pregnancies complicated by early-onset preeclampsia.

Conclusion

PLGF concentration showed good specificity in prediction of developing of pre-eclampsia with statistical significance. sFlt-1 and sFlt-1/PLGF showed high sensitivity in prediction of developing of pre-eclampsia with statistical significance.

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Table (1) Clinical data of the patients

	Patients without development of preeclamptic symptoms (N = 57)	**Patients developing preeclamptic symptoms (N = 23)**	**P. Value**
Maternal age (Years)	34.57 ± 5.27	33.37 ± 4.83	0.32985
BMI (Kg/m^2)	25.7 ± 3.61	26.15 ± 3.88	0.63312
Nulliparous, %	17 (29.8%)	14 (60.9%)	0.0099*

There was no significant difference between patients who did not develop pre-eclampsia and those who developed pre-eclampsia regarding maternal age and BMI. Nulliparous patients number was significantly higher in the group who developed pre-eclampsia.

Table (2) Blood pressure of the patients

	Patients without development of preeclamptic symptoms (N = 57)	**Patients developing preeclamptic symptoms (N = 23)**	**P. Value**
Systolic blood pressure (mm Hg)	122.51 ± 18.09	171.68 ± 20.87	<0.0001*
Diastolic blood pressure (mm Hg)	74.22 ± 12.05	112.55 ± 17.96	<0.0001*

Blood pressure was significantly higher in patients developed pre-eclampsia.

Table (3) Delivery outcomes in study groups.

	Patients without development of	**Patients developing**	**P. Value**

	preeclamptic symptoms (N = 57)	preeclamptic symptoms (N = 23)	
Time of delivery, weeks			
Median	40	37	
Range	31-42	24-41	<0.0001*
Birth weight (g)	3440.65 ± 642.07	2075.14 ± 1066.72	<0.0001*

Gestational age and birth weight, both were significantly decreased in patients developed pre-eclampsia compared with others.

Table (4) PLGF concentration and sFlt-1/PlGF ratio.

	Patients without development of preeclamptic symptoms (N = 57)	Patients developing preeclamptic symptoms (N = 23)	P. Value
PLGF concentration (Pg/ml)	80.89 ± 31.38	42.87 ± 22.19	<0.0001*
sFlt-1 (Pg/ml)	1853.47 ± 75.85	3760.37 ± 278.82	<0.0001*
sFlt-1/PlGF	23.07 ± 2.4	88.15 ± 12.58	<0.0001*

Mean PLGF concentration in patients developed pre-eclampsia was significantly decreased compared to others. So, sFlt-1/PlGF in patients developed pre-eclampsia was significantly increased compared to others.

Table (5) Correlation between different parameters and risk of developing of pre-eclampsia

Parameter	r	P. Value
PLGF concentration	-.533**	<0.0001
sFlt-1	.990**	<0.0001
sFlt-1/PLGF	.732**	<0.0001

PLGF concentration was negatively correlated with developing of pre-eclampsia. Both sFlt-1 and sFlt-1/PLGF were positively correlated with pre-eclampsia.

Table (6) Association between different parameters level and risk of developing of pre-eclampsia

Parameter	Cutoff Value	AUC	Sensitivity	Specificity	P. Value
PLGF concentration	44.78	0.161	56.5	94.7	<0.0001
sFlt-1	1831.29	0.926	95.7	66.7	<0.0001
sFlt-1/PLGF	18.85	0.892	95.7	77.2	<0.0001

Highest specificity in prediction of developing of pre-eclampsia was with PLGF concentration 44.78 Pg/ml. It reached 94.7% with P value of <0.0001. sFlt-1 of 1831.29 Pg/ml and sFlt-1/PLGF of 18.85, both showed sensitivity of 95.7% and P value of <0.0001.

Figure (1)

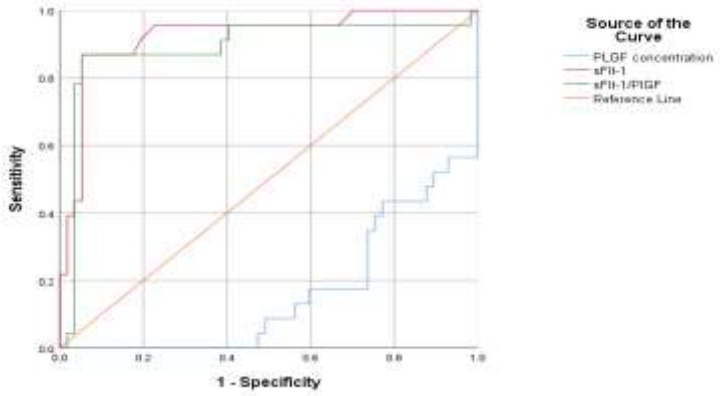

Figure (1): ROC curve analysis of association between different parameters level and risk of developing of pre-eclampsia