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Redefining probability of preeclampsia in high risk women using PlGF later in pregnancy

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Abstract

Objective: To determine the effectiveness and gestational age-specific cut-off of Placental growth factor (PlGF) in the second half of pregnancy for the prediction of adverse materno-fetal outcome among high-risk women. **Methods**: This secondary analysis explored associations between placental growth factor (PlGF) among women at high risk of PE at 20-22, 28-30, and 34-36 weeks of gestation. Women were divided into two groups based on PlGF levels cut-off derived after applying area under the receiver operating curve. **Results:** Of the 287 high risk women, 116(40.4%) had preeclampsia (PE). The cut off of PlGF was 224pg/ml, 211pg/ml and 176 pg/ml at 20-22, 28-30 and 34-36 weeks respectively, nearly 30% of the high risk women had PlGF below cut-off. The sensitivity and specificity of PE prediction using PlGF at 20-22 weeks was 81.0% and 72.2% respectively. For PlGF done at 28-30 weeks, the sensitivity and specificity of PE prediction till 32 weeks were 91.7% and 78.5% respectively. For PlGF done at 34-36 weeks, the sensitivity and specificity of PE prediction till 37 weeks was 95.8% and 73.3%, respectively. The negative predictive value of the PlGF at any gestation was nearly 90% or above for PE prediction till delivery. The accuracy of the test was highest at 28-30 weeks and for prediction before 37 weeks. **Conclusion:** The PlGF is a good marker to be done at 28-30 weeks for prediction of PE especially early onset and its adverse outcome; it can also be done at 34-36 weeks for preterm PE prediction.

Introduction

Preeclampsia (PE) affects 2-3 % of all gestations globally; although mortality due to PE is uncommon in high-resourced countries, morbidity is high[1]. The overall burden of adverse outcomes associated with preeclampsia is considerable; close antenatal surveillance and timely interventions can prevent these adverse outcomes.

Angiogenesis is essential for embryonic development and growth and is regulated by a complex interplay of a numerous factors. Placental growth factor (PlGF) is a glycoprotein synthesized in villous and extra-villous cytotrophoblasts, and is the most validated and studied biomarker of PE screening. Its function is angiogenesis and assistance in trophoblastic invasion of the maternal spiral arteries, thus maintaining the placental oxygenation[2]. The strategy of early pregnancy universal screening of all women with PlGF, mean arterial pressure and uterine artery Doppler for the detection of PE has been accepted now. Those who are found to be at high risk need to be started on aspirin, but although the prevention rate of early onset PE is close to 90%, the late onset preeclampsia can be prevented in just over half of the women on aspirin, hence vigilance in the latter half of pregnancy is needed even if the women are on aspirin [3].

In the high-risk women who are booked late in pregnancy, screening and risk stratification can modify their antenatal surveillance, consequently, avoiding long term hospitalization and frequent hospital visits if they are deemed low risk. The use of sFLT-1/PlGF ratio has also proved to be a very effective marker [4,5,6] ,but

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using both sFLT-1 and PlGF for the assessment of risk, doubles the cost of the test. PlGF levels have been seen to decrease many weeks before the onset of PE, with a substantial decrease five weeks before its onset[5].

Though the usefulness of PlGF alone as a biomarker in early pregnancy is established [4], its use in the latter half of pregnancy has not been fully explored, especially with respect to the timing of the test and its cut-offs at particular gestation. Hence, the study was designed to evaluate the predictive value of the angiogenic biomarker PlGF for likelihood of adverse perinatal and maternal outcomes among high-risk women. We also wanted to find out the gestational age-specific cut-off of PlGF in the second half of pregnancy.

Material and method

In this study the secondary analysis of the data from analytical prospective study conducted from September 2019 to April 2022 after approval from the institutional ethical committee was done. All antenatal high risk women with gestational age between 20-22 weeks were included; the gestational age was calculated from the first-trimester ultrasound. The antenatal women were adjudged as high risk for preeclampsia based on the presence of one or more risk factors, namely, nulliparity; pre-pregnancy or first-trimester body mass index (BMI) of 30 Kg/M^2 or more; maternal age either 35 years or older; use of assisted reproductive technology for conception or family history of hypertension; previous pregnancy more than ten years ago or the presence of one or more major risk factors such as preeclampsia in previous pregnancy; chronic hypertension; diabetes mellites; or chronic kidney disease [7]. Those with multiple pregnancies were excluded from the study. The blood pressure was measured in one arm, and two recordings were made at the one-minute interval. The final BP measurement (average of the two measurements) was used to calculate mean arterial pressure (MAP). The women underwent transabdominal ultrasonography (Aloka Prosound alpha 6) for the uterine artery Doppler measurement. It was identified as an aliasing vessel perpendicular to the internal iliac vessel, atleast four even waveforms were considered good image; both right and left uterine vessels were measured and the mean value was taken.

For the measurement of serum sFLT-1 and PlGF, three ml of venous blood was drawn by venepuncture into non-heparinized tubes. The blood samples were allowed to clot for 15–20 min and centrifuged at 1500 rpm for 5 min. The serum was removed, and aliquots were stored at -20°C. The biomarkers were measured by fully automated equipment using electro-chemiluminescence technology on the Roche platform (cobas e 411). the biomarkers were repeated at 28-30 weeks, and 34-36 weeks of gestation.

The antenatal check-up was done regularly at four-week intervals till 28 weeks, then two weekly till 36 weeks, and weekly thereafter. Investigations such as liver function tests, kidney function tests, fundus examination, peripheral smear, and complete blood count were done as and when required. Intergrowth 21 growth charts were used for the estimation of fetal weight centiles [8]. FGR was defined as an estimated fetal weight (EFW) less than the 3rd centile, or EFW less than 10th centile plus abnormal fetal Doppler (PI more than 95th centile in the umbilical artery, PI less than 5thcentile in the middle cerebral artery, or cerebroplacental ratio less than 5thcentile) on antenatal ultrasound [9]. The delivery details, the newborn's condition at delivery, and that of the mother were noted. The women and babies were followed for one week following delivery.

The data entry was done in the Microsoft EXCEL spreadsheet, and the final analysis was done using Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 21.0. For statistical significance, the p value of less than 0.05 was considered statistically significant. The association of the variables which were quantitative and not normally distributed in nature was analyzed using the Mann-Whitney test. The Receiver operating characteristic curve (ROC) was used to find the cut-off of PlGF. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Results

Total of 292 women were recruited, and 287/292 were fully followed. Among the high risk factors based on history, 95/287 (33.1%) cases were primigravida, and family history of hypertension was present in 65/287(22.6%). After clinical evaluation, MAP was more than 95 mmHg in 102/287(35.5%) and blood sugars were deranged in 64/287(22.3%) women. While 287 women were assessed at 20-22 weeks, by 28 weeks

three of them delivered and the assessment of 284 women was done, subsequently, 15 cases were delivered by 34 weeks; hence, PlGF was assessed in 269 only at 34-36 weeks of gestation.

The PlGF values were significantly low in women with PE or early onset PE at 20-22, 28-30 and 34-36 weeks (Figure 1) and its cut-off at the above three time points was found to be 224pg/ml, 211pg/ml and 172pg/ml respectively. The PlGF values were below the assigned cut-off in 83/287(28.9%), 74/284 (26.1%) and 94/269(34.9%) cases at 20-22, 28-30 and 34-36 weeks of gestation respectively. When we divided the women based on their PlGF levels above or below the cut-off at 20-22 weeks, the uterine artery Doppler more than 95th centile (OR-4.63, p<0.001) and the history of hypertension (OR-2.95, p<0.001) were significantly associated with low PlGF levels. There was no significant difference in the PlGF levels with respect to the maternal age above 35 years, primigravidity, family history of hypertension, BMI more than 30 kg/M^2 and MAP (Table 1).

Table 2 shows the maternal outcome in the study cohort. Hypertensive disorders of pregnancy (HDP) was observed in 116/287 (40.4%) cases, preeclampsia in 46/287(16.0%), PE was early onset in 21/287(7.3%), severe in 31/ 287(10.8%). Total 67/287 (23.3%) had preterm delivery, and 103/287 (35.9%) underwent Caesarean section. When HDP was analysed with respect to PlGF levels, it was found that women with HDP had significantly low PlGF level at all-time points (p<0.001). At 20-22 weeks the highest odds ratio was observed for the presence of complications such as HELLP syndrome (hemolysis, elevated liver enzymes and low platelets) (OR-15.81). At 28-30 weeks, low PlGF levels had highest odds ratio for PE before 32 weeks' gestation. At 34-36 weeks, the PlGF levels below cut-off had the highest Odds for severe high blood pressure (OR -90.65) and preterm PE (OR- 56.36).

Significantly more women with PlGF below cut off had preterm delivery compared to those above cut-off at all gestational time points (p<0.001), with the highest odds ratio at 28-30 weeks' gestation (OR-3.9). Regarding adverse fetal outcomes, early onset fetal growth restriction (EO FGR) was seen in 51/287(17.8%) cases, absent or reverse umbilical artery Doppler pulsatility index (PI) was present in 11/287 (3.8%), and perinatal death occurred in 9/287 (3.1%). The PlGF levels were significantly below cutoff in cases with early onset FGR (p<0.001) at all time points, there was no significant difference in PlGF levels among cases with late onset FGR. Total 21/25 (84%) cases with NICU stay more than 7 days had PlGF below cut off at 28-30 weeks (p<0.001, OR 20.4). At 20-22 weeks, the PlGF levels were below cut-off in significantly more number of cases having perinatal death (7/287, 4% OR - 9.3) (Table 3).

The bar diagram in figure 3 shows the comparison of factors like deranged LFT, severe high blood pressure more than 150/100 mmHg, FGR, sFLT-1/PlGF ratio above cut-off along with PlGF below cut-off in predicting PE, preterm PE and PE till 30 weeks. PlGF was found to be below cut-off in all cases of PE before 28 weeks (5/5, 100%), 18/21 (85.7%) cases of early onset PE and 38/46 (82.6%) total cases of PE.

The AUROC levels, sensitivity, specificity, PPV and NPV are given in table 4. The AUROC for PE prediction was highest at 34-36 weeks (0.818) with detection rate of 78.4% at 20% false positive rate (specificity 80%). For preterm PE the predictive accuracy was higher than PE at all gestations and at 34-36 weeks, the AUC for Preterm PE was at excellent level of 0.934, with 100% sensitivity and 80% specificity (Figure 2). For prediction of complication, the PlGF levels had good negative predictive value above 89% at all gestations. Accuracy was best at 20-22 weeks (79.5%), whereas the detection rate was best at 34-36 weeks (86.5%).

When we evaluated the PE prediction based on the timing of the test vis a vis the occurrence of PE till particular gestation, we found that the sensitivity and specificity of PE prediction for the PlGF at 20-22 weeks was 81.0% and 72.2% respectively. For PlGF done at 28-30 weeks, the sensitivity and specificity of PE prediction till 32 weeks were 91.7% and 78.5% respectively. For PlGF done at 34-36 weeks, the sensitivity and specificity of PE prediction till 37 weeks was 95.8% and 73.3%, respectively. The negative predictive value of the PlGF at any gestation was nearly 90% or above for PE prediction till delivery. The accuracy of the test was highest at 28-30 weeks and for prediction before 37 weeks (Table 5).

Discussion

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Although PlGF is a well-recognized first trimester PE screening tool and the sFLT-1/PlGF ratio is gradually gaining ground as a marker to identify PE and its complications later in pregnancy, the role of PlGF alone in the second trimester and beyond, for the prediction of adverse pregnancy outcome is still under evaluation. In the present study by serial evaluation of its levels at three time intervals in the second half of pregnancy, the cut-offs and the best timing of test for the PE prediction was determined. PE occurred in one out of every six high risk women included in the study, it was early onset in one out of fourteen of them. PlGF proved to be a reliable prognostic and diagnostic marker in the study cohort. Early onset PE could be predicted in 9 out of 10 cases by testing at 28-30 weeks and in all cases of preterm PE by PlGF estimation at 34-36 weeks of gestation.

In the present study, nearly 30% of the high risk women had PlGF below cut-off, in the study by Mclaughlin et al on the similar cohort PlGF was below cut -off of 100pg/ml in 29.5% cases [10] . Other previous studies have also taken 100 pg/ml as PlGF cut-off and estimated it only once any time between 20- 36 weeks [10,11], however, in the present study it was done successively thrice and the gestation specific cut-offs were derived (224pg/ml, 211pg/ml and 176 pg/ml at 20-22, 28-30 and 34-36 weeks respectively). In the study by Omsher et al a low PlGF (<12 pg/ml) was associated with a shorter test-birth interval and universally (100% PPV)[12] , in our study women with values less than 12pg/ml constituted only 1.4% (4/287) cases and already had severe clinical features. As the PlGF levels differ with gestation using the different cut-offs deemed more appropriate and is a subject for further research.

PlGF was effective in the prediction of severe maternal and fetal complications. Its values were below cut off at all time points in significantly high number of women who delivered preterm, with the highest odds at 28-30 weeks. All women with hypertension and its complications such as preeclampsia, early onset preeclampsia or severe preeclampsia had significantly low PlGF in second as well as third trimester. In the study done by Mc Laughlin et al, low PlGF was similarly found to significantly increase the risk of preterm delivery and early-onset preeclampsia (adjusted odds ratio, 58.2 [95% CI, 32.1–105.4] [10]. In the multi-centric randomized controlled trial by Duhig et al (PARROT study), PlGF estimation in the intervention group resulted in substantially fast clinical confirmation of preeclampsia, and a lower incidence of maternal adverse outcome[11]. A meta-analysis by Lim et al, demonstrated that PlGF had moderate sensitivity and specificity for predicting adverse maternal or perinatal outcomes (sensitivity ranged from 46–87%, specificity from 78–90% and area under the receiver operating characteristic curve ranged from 0.63–0.96) [13, 14, 15, 16].· But in most of the earlier studies, the cohort consisted of suspected cases of PE, in our study we included women who were clinically at high risk of PE , which is more commonly observed and poses a management dilemma with respect to the degree of surveillance needed [12, 13, 14]. In the present study, a significant number of early onset FGR cases and those who had more than one week nursery stay had significantly low PlGF but there was no marked difference in its levels between late onset FGR and normal outcome. Sharp et al , reported that revealing the PlGF values in women with suspected PE was associated with lower perinatal mortality but lead to earlier delivery with more neonatal respiratory morbidity[15]. Hence, there is need for more robust data for better clinical management of cases at high risk of PE.

In our study, the performance of PlGF was similar or slightly better than sFlt-1/PlGF ratio in predicting adverse outcome, and performed better in women with severe PE and early onset preeclampsia compared to those with late onset PE. Doing sFLT-1/PlGF ratio doubles the cost of the test; hence use of PlGF alone as a marker of preeclampsia in the second half of pregnancy is certainly more cost effective. The inclusion of PlGF levels in routine biochemical testing would enable individualized treatment of patients, hence avoiding severe morbidity and ensuring timely delivery. There is also a double benefit of appropriately reassuring women who do not need intensive investigation and minimizing excessive health service use by avoiding unnecessary admission and follow up[17]. In a commentary by Stephan et al, it was proposed that the American College of Obstetricians and Gynecologists definition of preeclampsia should may also include new-onset of altered angiogenic factors (sFlt-1/PlGF ratio or PlGF alone) [18].

The strength of the study was that serial evaluation of PlGF and determination of the gestational age specific cut-off in clinically high risk women was done, and the time to delivery interval for guidance in management

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could be provided. The weakness could be that early pregnancy assessment was not done, and only high risk women were included.

Conclusion :

The PlGF is a good marker to be done at 28-30 weeks for prediction of PE especially early onset and its adverse outcome; it can also be done at 34-36 weeks for prediction of preterm PE. The new cut-offs derived in the study need further validation and research.

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Disclosure of interests

there are no conflict of interest among authors to declare

Contribution to authorship

KB: Carrying out, and co-writing the manuscript

BH: Carrying out, preparing the draft of manuscript

BM: Carrying out and planning the work

SS: Carrying out and planning the work

AR: Carrying out, analysing the work

MK: Conception, planning, carrying out, analysing, and writing up of the manuscript

Details of patient's consent:

We Confirm that patient's informed consent to participate in the study and permission for publication was obtained.

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Details of ethics approval :

the study was approved by ethics committee for human research (ECHR), Lady Hardinge Medical College, New Delhi, ref no LHMC/ECHR/126

Legends to figures

Figure 1: the PlGF levels among cases with PE (A) and severe PE (B) compared to normal outcome

Figure 2: ROC curve of PlGF estimation at gestational age of 20-22, 28-30, 34-36 weeks of gestation

Figure 3: The bar diagram showing the comparison of factors deranged LFT, severe high blood pressure more than 150/100 mmHg, FGR, sFLT-1/PlGF ratio above cut-off along with PlGF below cut-off

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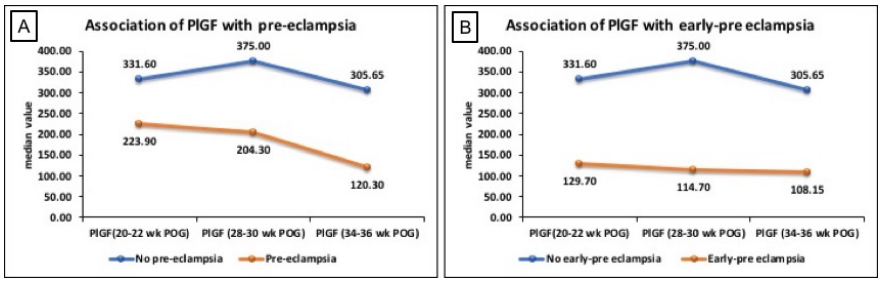

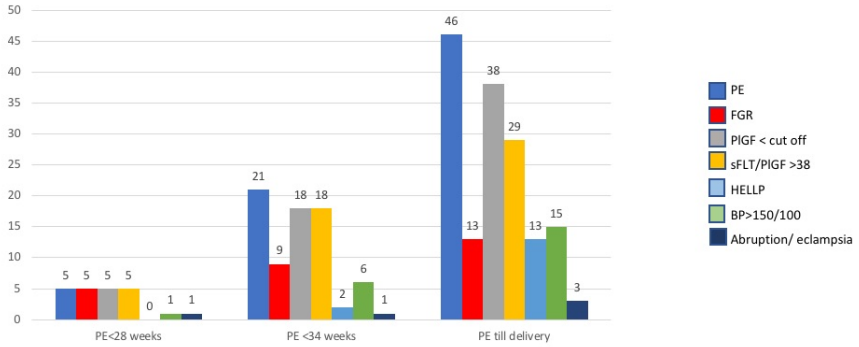

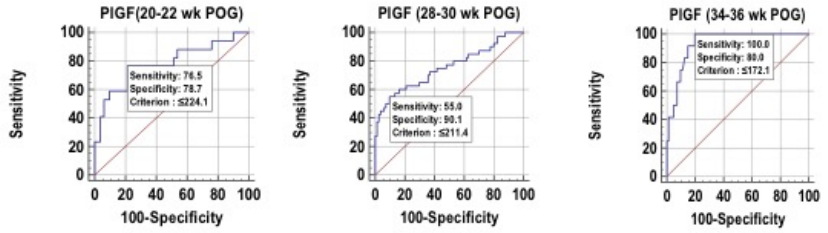

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