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Importance of Timing First-Trimester Placental Growth Factor and Use of Serial First-Trimester Placental Growth Factor Measurements in Screening for Preeclampsia

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Abstract
Objective: The aims of this study were to test whether the performance of first-trimester placental growth factor (PlGF) in screening for preterm preeclampsia (PE) is gestational age dependent and to assess the value of serial first-trimester PlGF measurements in discriminating women at risk for PE. ***Methods:*** PlGF was measured in women with singleton pregnancies at their first antenatal visit at 8+0 to 10+6 and additionally at 11+0 to 14+0 weeks of gestation. The difference in absolute values of serial PlGF measurements was expressed as Δ-PlGF. Values were compared between pregnancies with normal outcome and those complicated by PE. ***Results:*** A total of 814 pregnancies were included, 18 (2.19%) developed PE that required delivery before 37 weeks of gestation. PlGF increases significantly from 8 to 14 weeks of gestation ($\rho = 0.63$; $p < 0.0001$) in normal pregnancies, but not so in preterm PE ($\rho = 0.034$; $p = 0.893$). PlGF discriminates between PE and uneventful pregnancies only after 10 weeks of gestation. Δ-PlGF was significantly lower in PE 5.3 (–1.1 to 9.3) pg/mL compared to uneventful pregnancies 17.3 (9.8–26.0) pg/mL ($p = 0.0011$). ***Conclusion:*** The discriminatory accuracy of PlGF increases from 10 to 14 weeks of gestation, and serial PlGF measurements might be of particular interest in PE screening.

Introduction

Preeclampsia (PE) affects 2–3% of all pregnancies and is a major cause of maternal and fetal morbidity and mortality worldwide [1–3]. The only validated treatment today remains delivery, but prevention with low-dose aspirin (LDA) initiated before 16 weeks of gestation in women at risk has been shown to be effective [4]. Therefore it is important to identify women at increased risk to develop PE early in pregnancy to allow timely intervention with LDA. The National Institute of Clinical Excellence (NICE) and others propose screening by anamnestic and clinical risk factors alone [5]; however, about half of all women who develop PE have no classical risk factor [6]. To overcome this limitation, various biochemical, biophysical, and ultrasound markers have been identified as

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possible candidates for more objective screening purposes [7–10]. Algorithms to calculate the risk for early or late PE have been developed, combining some of these markers with the background risk defined by maternal history. The performance of such a screening is best for early PE requiring delivery before 34 weeks of gestation, but the detection of later PE is also possible [6, 11–13]. Placental growth factor (PlGF) is one of the most important first-trimester biochemical markers for PE. Compared to uneventful pregnancies, significantly lower maternal serum levels of PlGF have been reported in pregnancies complicated by PE, in particular early-onset forms [14].

In screening for aneuploidies, it has been shown that timing the assessment of the biochemical markers β-human chorionic gonadotropin and pregnancy-associated plasma protein A at 9–10 weeks of gestation substantially increases the test sensitivity and specificity [15]. Therefore, it was proposed to draw blood at this gestational age and combine it with nuchal translucency measurements performed at 11–14 weeks of gestation [15].

The aim of this study was to investigate the behavior of PlGF from 8 to 14 weeks of gestation in uneventful pregnancies and in those complicated by preterm PE and to explore whether the PE screening performance of PlGF is gestational age dependent. Additionally, we wanted to test the value of serial first-trimester PlGF measurements in discriminating women at risk for PE.

Material and Methods

This was a prospective cross-sectional and partly longitudinal study of consecutive pregnant women attending for their first routine antenatal visit between 8 and 14 weeks of gestation and who underwent PE screening between January 2014 and December 2015 at the outpatient clinic of our Department. We included consecutive patients with singleton pregnancy, who agreed to participate in the study and of whom outcome data were available. Exclusion criteria were: multiple pregnancies, pregnancies complicated by structural or chromosomal anomalies, and pregnancies resulting in fetal loss before 24+0 weeks of gestation. For the cross-sectional analysis of our results, pregnancies resulting in term PE were excluded.

PlGF was measured at the first antenatal visit between 8+0 and 10+6 weeks of gestation if the patient presented before 11 weeks and again at the time of first-trimester screening for PE at 11+0 to 14+0 weeks of gestation using the algorithm provided by the Fetal Medicine Foundation (FMF). Due to the low prevalence of PE in our cohort, we retrospectively analyzed also stored first-trimester serum samples of women who were referred to our service because of PE. PlGF was analyzed on Kryptor Compact Plus (Brahms GmbH) from mostly fresh or, in the case of retrospective analyses, frozen blood samples. The detection range for PlGF using this instrument is 0.03–7,000 pg/mL. For the cross-sectional analysis of our results, only the first PlGF measurement was used for statistical purposes. In patients with 2 samples, Δ-PlGF was calculated as the absolute values of the difference of both measurements. As the time interval between the 2 PlGF assessments is not standardized, and additionally, PlGF changes with gestational age in normal pregnancies, we decided for comparative purposes to calculate the Δ-PlGF per time interval in days between the 2 measurements (Δ-PlGF/d). For the analysis of Δ-PlGF, additionally a subgroup analysis was performed, matching each patient who later developed PE with 3 patients with uneventful pregnancies. The matching criteria were ethnicity, cigarette smoking, preexisting diabetes, method of conception, maternal age and weight. All these factors have been shown to affect the serum concentration of PlGF [16]. The outcome of the pregnancy was obtained from the clinical data system.

PE was defined according to the criteria established by the International Society for the Study of Hypertension in Pregnancy: systolic blood pressure of 140 mm Hg or more and/or diastolic blood pressure of 90 mm Hg or more preexisting or developing after 20 weeks of gestation in a previously normotensive woman occurring together with proteinuria defined as 300 mg or more in 24 h and/or other signs of maternal endothelial dysfunction and/or uteroplacental dysfunction with intrauterine growth restriction [17]. Small for gestational age was defined as birthweight below the 5th percentile for gestational age as provided by the software of the FMF for screening for PE [18]. The study was approved by the Ethics Committee of the University of Bern. Written informed consent was obtained from each woman agreeing to participate in the study.

Statistical analysis was performed with GraphPad version 5.0 for Windows (GraphPad Software, San Diego, CA, USA). Spearman rank correlation and linear regression were used to analyze the correlation between gestational age and absolute PlGF values in normal pregnancies and those complicated by PE. Continuous variables were analyzed using the Student *t* test or Mann-Whitney U test while proportions were evaluated utilizing the Fisher exact test. Statistical significance was considered achieved when p was less than 0.05.

Results

During the study period, 814 pregnancies were included; 342 women had a first PlGF measurement between 8+0 and 10+6 weeks of gestation, 302 of them also had a second measurement between 11+0 and 14+0 weeks of gestation. The remaining 473 women had a PlGF measurement between 11+0 and 14+0 weeks of gestation.

A total of 789 uneventful pregnancies were compared with 18 (2.19%) pregnancies that developed PE, which required delivery before 37 weeks of gestation. Patient characteristics and pregnancy outcomes are shown in Table 1. As expected, women who developed PE were more often nulliparous, had chronic hypertension, and delivery was at an earlier gestational age. Moreover, a higher incidence of small-for-gestational-age children was noted.

PlGF increases significantly from 8 to 14 weeks of gestation ($\rho = 0.63$; $p < 0.0001$) in normal pregnancies, while

Table 1. Patient characteristics and pregnancy outcome in the study population

	PE (*n* = 18)	No PE (*n* = 789)	*p*
Maternal age, years	29.6±4.5	30.8±5.4	ns
BMI at 12 weeks	26.4±5.4	24.0±4.8	0.032
Cigarette smoker	0	71 (9.1)	ns
Preexisting diabetes mellitus	0	6 (0.8)	ns
Chronic hypertension	3 (16.7)	11 (1.4)	0.003
SLE or APS	0	7 (0.9)	ns
Parity			
Nulliparous	14 (77.8)	373 (47.0)	0.015
Parous, previous PE	3 (16.7)	22 (2.8%)	0.016
Parous, previous SGA	0 (0)	23 (2.9)	ns
Parous, previous PE and SGA	1 (5.6)	5 (0.6)	ns
Parous, no PE or SGA	0 (0)	366 (46.7)	<0.001
Conception			
Spontaneous	18 (100%)	753 (95.5)	ns
ART	0	36 (4.3)	ns
Ethnicity			
White	14 (77.8)	575 (72.9)	ns
Black	4 (22.2)	118 (14.9)	ns
South Asian	0	41 (5.1)	ns
East Asian	0	36 (4.6)	ns
Mixed	0	19 (2.4)	ns
Delivery			
Vaginal	0	409 (51.3)	<0.001
Operative vaginal delivery	0	96 (12)	ns
Cesarean section	18 (100%)	284 (35.6)	<0.001
Gestational age at delivery	33.0 (25.4–35.0)	39.6 (25.9–42.1)	<0.001
Delivery before 37+0 weeks	18 (100%)	44 (5.6%)	<0.001
Birth weight, g	1,470 (530–2,745)	3,340 (730–4,670)	<0.001
Birth weight percentile	22.1±21.8	44.5±26.3	<0.001
<10 percentile	7 (38.9)	78 (9.9)	0.001
<5 percentile	3 (16.7)	33 (4.2)	0.042

Data are presented as *n* (%), mean ± SD, or median (range). ART, assisted reproductive technology; SLE, systemic lupus erythematous; APS, antiphospholipid antibody syndrome; ns, not significant. Comparisons between the normal and PE groups: Fisher exact test for categorical variables and Student *t* test for continuous variables.

in those complicated by preterm PE no such gestational age-dependent behavior can be demonstrated (ρ = 0.034; $p = 0.893$) (Fig. 1). The median (IQR) PlGF in preterm PE is 20.95 (17.08–24.43) pg/mL. Compared to the PlGF medians of normal pregnancies calculated for each gestational week, a significant and steadily increasing difference can be demonstrated from 10+0 weeks onwards, while before 10 weeks of gestation, PlGF does not discriminate between the 2 groups (Fig. 2).

Δ-PlGF values were available from 295 normal and 7 PE pregnancies, 4 requiring delivery before and 3 at term. Median (IQR) Δ-PlGF in the PE group is 5.3 (–1.1 to 9.3) pg/mL compared to 17.3 (9.8–26.0) pg/mL in pregnancies without PE ($p = 0.0011$). Δ-PlGF also shows a significant increase with increasing time interval between the 2 measurements in normal pregnancies (ρ = 0.346, $p < 0.0001$), but not in PE ($p = 0.302$). Mean gestational age at which blood was drawn was not statistically different between the groups for both measurements (9.8 ± 0.6 vs. 10.0 ± 1.1 weeks [$p = 0.34$] at the first and 12.7 ± 0.6 vs. 12.2 ± 0.6 weeks [$p = 0.171$] at the second measurement). The 7 PE pregnancies were matched with 21 normal pregnancies in the above-described manner. In this subgroup analysis, Δ-PlGF as well as Δ-PlGF/d were significantly higher in normal pregnancies compared to PE pregnancies (14.9 [8.8 to 24.4] vs. 5.3 [–1.1 to 9.3] pg/mL [$p = 0.0027$] and 0.69 [0.49 to 1.11] vs. 0.31 [–0.08 to 0.62) pg/mL/d [$p = 0.013$], respectively).

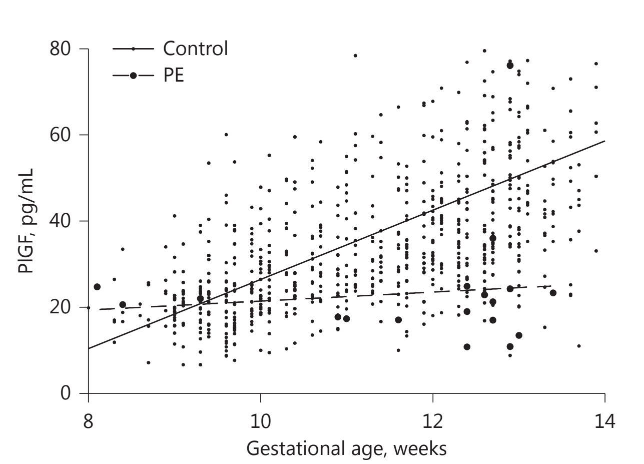
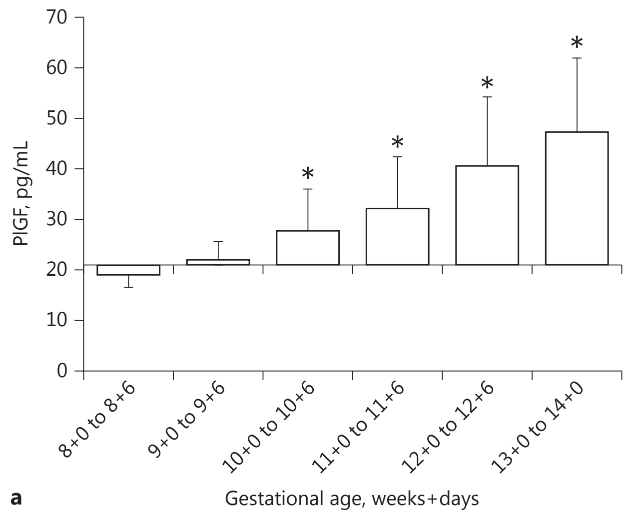


Fig. 1. The course of PlGF during the first trimester in patients who developed preterm PE compared to pregnancies without PE using linear regression analysis.

Discussion

Our results show that PlGF increases steadily from early to late first trimester in normal pregnancies, while in pregnancies complicated by preterm PE this gestational age-dependent first-trimester behavior of PlGF is not evident. Therefore, the capability of PlGF to discriminate between pregnant women at low and those at increased risk for PE is better when it is assessed late in the first trimester. Of note, before the 11th week of gestation, PlGF seems to be of no value for PE screening purposes. However, the combination of an early PlGF assessment (<11 weeks of gestation), with one performed between 11 and 14 weeks and expressed as Δ-PlGF, adds further discriminatory power to this angiogenic marker. Indeed, a low Δ-PlGF as well as a reduced increase in PlGF per day increases significantly the risk of developing PE later during pregnancy.

Most studies investigating the role of PlGF as screening parameter were conducted between 11 and 14 weeks [6, 14, 19]. Zhong et al. [20] summarized these results in a recently published meta-analysis and concluded that PlGF is a good predictive marker for PE, especially PE occurring before 34 weeks of gestation. Less information exists on the behavior of PlGF before 11 weeks of gestation. Wortelboer et al. [21] performed longitudinal measurements of several angiogenic and biochemical markers in 68 women with uneventful pregnancies between 6 and 13 weeks of gestation and, similar to our findings, they were also able to show a significant increase in PlGF, mainly from 10 weeks onwards. Pandya et al. [16] examined the performance of PlGF in first-trimester screening for Down syndrome and described a similar behavior of PlGF measured before 11 weeks and PlGF assessed between 11 and 14 weeks of gestation. However, in their study the number of patients with an assessment of PlGF before 11 weeks of gestation has not been provided, but mentioned to be low. Also, even if PlGF measured before 11 weeks is as good in distinguishing trisomy 21 from euploid pregnancies as PlGF assessed at 11 and 14 weeks, one cannot conclude that the same is true in screening for PE. Crovetto et al. [22, 23] performed the only other 2 studies that exist to our knowledge investigating early



a

Gestational age, weeks	Median PlGF, pg/mL (IQR)	*p*
8+0 to 8+6	19.2 (16.7–25.5)	0.855
9+0 to 9+6	21.7 (16.3–25.7)	0.577
10+0 to 10+6	27.8 (22.0–36.1)	0.0014
11+0 to 11+6	32.1 (26.2–42.3)	<0.0001
12+0 to 12+6	40.6 (31.5–54.2)	<0.0001
13+0 to 14+0	47.1 (37.0–62.0)	<0.0001

b

Fig. 2. Median PlGF according to the gestational age of normal pregnancies compared to pregnancies complicated by preterm PE (median 20.95 pg/mL) demonstrating a significant difference from 10+0 to 10+6 weeks onward. The included table shows the comparison for each gestational week of median (IQR) PlGF in uneventful pregnancies compared to the median PlGF of pregnancies complicated by preterm PE.

PlGF for PE screening. They analyzed different angiogenic markers from 8 to 11 weeks and demonstrated an improvement of the screening performance when PlGF was included in a screening algorithm. Of note, in their larger study, the median (range) first-trimester PlGF of pregnancies complicated by early PE (<34 weeks of gestation) was 21.9 pg/mL (14.8–31.6), which is very similar to the PlGF concentration we found in our cases with preterm PE. The median (range) gestational age in their study was 10.1 (9.1–10.6) weeks of gestation; just around this gestational age, we started to demonstrate a difference in PlGF in normal pregnancies compared to PE pregnancies also in our smaller cohort. However, our results demonstrate that the distinction of PE from normal pregnancies by PlGF is better at a later gestational age.

Others have studied serial measurements of PlGF before, mostly between the first and the second trimester of pregnancy, but also longitudinally throughout gestation in normal and high-risk pregnancies [24–28]. However, our study is so far the only one investigating serial PlGF assessments during the first trimester. Cumulatively, all these studies demonstrate significantly lower levels of PlGF throughout gestation in women who later develop PE and conclude that repeat measurements are likely to be better predictors of PE than a measurement at a single time point. The same conclusion could be drawn for other angiogenic and anti-angiogenic markers like soluble fms-like tyrosine kinase 1, soluble endoglin, or soluble VEGF receptor-1 [24, 25, 28]. Our results are therefore in line with previously described findings, but show, that serial measurements are already of use in the first trimester. So, while a single PlGF measurement early in the first trimester does not help to distinguish between PE and normal pregnancies, there is value in assessing PlGF between 8 and 11 weeks of gestation when combined with a second measurement towards the end of the first trimester. The optimal gestational ages for assessing serial measurements and the ideal time interval between the 2 measurements, however, must still be defined in larger studies. If serial assessments of PlGF prove to be better predictors for PE than a single measurement, first-trimester measurements are of particular interest, as LDA to prevent PE should be started early in pregnancy [4].

Screening for trisomies is shifting from combined screening to cell-free DNA screening, which makes optimal timing of measuring biomarkers for Down syndrome less important [15, 29, 30]. On the other hand, the FMF is carrying out an international multicenter trial (ASPRE project) to examine the use of LDA in preventing PE in women who screen positive in a combined first-trimester PE screening test [31]. The results are awaited within a year's time. If this randomized study confirms the promising results of Park et al. [32], who showed a very significant reduction in preterm PE after administrating LDA to pregnant women who screened positive in this test, the uptake of such PE screening will likely be important. According to our results, the assessment of a single PlGF value in combined PE screening should not be performed before the time of ultrasound and biophysical screening, and the whole test should best be performed only after 12 weeks of gestation. The same is true for early anomaly scanning, which also performs better late in the first trimester [15].

The strength of this study is that we have used a well-defined population at low risk and that all PlGF measurements were performed in the same laboratory using Kryptor Compact Plus (Brahms GmbH), which is sensitive in detecting PlGF also at low values. Indeed, we were able to obtain a result from all samples. Compared to other studies, this allowed us to analyze the course of PlGF at early gestational age.

The main limitation of our study is the low prevalence of cases in which Δ-PlGF could be compared between PE and uneventful pregnancies.

Conclusion

First-trimester screening is shifting from merely assessing the fetal risk for aneuploidies to a more complete exam including screening for placenta-associated maternal pregnancy complications. In screening for PE, PlGF has shown good discriminatory properties in large trials. Our results show that this distinction can be demonstrated from the 11th week of gestation onwards and is most significant at the end of the first trimester. Serial measurements of PlGF in the first trimester allowing to calculate Δ-PlGF seem to be of particular interest; however, larger studies are needed to test if integrating Δ-PlGF in a screening algorithm improves PE screening.

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Disclosure Statement

Analysis of PlGF was performed by a laboratory where co-authors are employees. No other conflicts of interest exist.

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