



Screening for pre-eclampsia with competing-risks model using placental growth factor measurement in blood samples collected before 11 weeks' gestation

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KEYWORDS: competing-risks model; Fetal Medicine Foundation; first trimester; placental growth factor; pre-eclampsia; screening

CONTRIBUTION

What are the novel findings of this work?

Placental growth factor (PIGF) in blood samples collected at 10 weeks' gestation had similar discriminatory value to PIGF collected at 11–14 weeks' gestation for prediction of preterm pre-eclampsia using the Fetal Medicine Foundation (FMF) screening algorithm. The discriminatory value of PIGF was relatively poor using samples collected earlier than 10 weeks' gestation.

What are the clinical implications of this work?

This study indicates that the gestational-age range for PIGF samples may be expanded from 11–14 to 10–14 weeks when assessing the risk of pre-eclampsia using the FMF first-trimester screening algorithm.

ABSTRACT

Objectives To describe the distributional properties and assess the performance of placental growth factor (PIGF) measured in blood samples collected before 11 weeks' gestation in the prediction of pre-eclampsia (PE).

Methods The study population consisted of pregnant women included in the Pre-eclampsia Screening in Denmark (PRESIDE) study with a PIGF measurement from the routine combined first-trimester screening (cFTS) blood sample collected at 8–14 weeks' gestation. PRESIDE was a prospective multicenter study investigating the predictive performance of the Fetal Medicine Foundation (FMF) first-trimester screening algorithm for PE in a Danish population. In the current study, serum concentration of PIGF in the cFTS blood samples was analyzed in batches between January and June 2021.

Results A total of 8386 pregnant women were included. The incidence of PE was 0.7% at <37 weeks' gestation and 3.0% at ≥37 weeks. In blood samples collected at 10 weeks' gestation, PIGF multiples of the median (MoM) were significantly lower in pregnancies with preterm PE <37 weeks compared to unaffected pregnancies. However, PIGF MoM did not differ significantly between pregnancies with PE and unaffected pregnancies in samples collected before 10 weeks' gestation.

Conclusions The gestational-age range for PIGF sampling may be expanded from 11–14 to 10–14 weeks when assessing the risk for PE using the FMF first-trimester

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screening model. There is little evidence to support the use of PlGF in blood samples collected before 10 weeks' gestation. © 2023 The Authors. *Ultrasound in Obstetrics & Gynecology* published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

Placental growth factor (PlGF) is a protein from the vascular endothelial growth factor family, which is involved in angiogenesis and trophoblastic invasion of the maternal spiral arteries^{1,2}. Adequate placental function is dependent on PlGF, and in pregnancies developing pre-eclampsia (PE), maternal plasma levels of PlGF are reduced^{3–5}. After 11 weeks' gestation, plasma PlGF is a reliable marker for discrimination between pregnancies with and without PE, whereas evidence of the predictive performance of PlGF at earlier gestational ages (GAs) is limited^{6–9}.

PlGF adds substantially to a first-trimester screening model for PE, which includes maternal characteristics, mean arterial pressure (MAP) and uterine artery pulsatility index (UtA-PI), developed by the Fetal Medicine Foundation (FMF)^{10–12}. At 11–14 weeks' gestation, this model detects approximately 75% of preterm (delivery < 37 weeks' gestation) PE cases at a screen-positive rate (SPR) of 10%, and it has been validated in several populations^{13–18}. In the FMF study, biomarkers (including PlGF and pregnancy-associated plasma protein-A (PAPP-A) in serum samples) were assessed between 11 and 14 weeks' gestation¹⁹, and this practice has been followed in subsequent validation studies. Although the FMF algorithm can accommodate PAPP-A, this biomarker has been shown not to add significant value to screening performance^{20–22}. Since PAPP-A could likely be omitted, PlGF is the primary biochemical marker of interest in first-trimester screening for PE.

Blood samples for combined first-trimester aneuploidy screening (cFTS) can be taken from as early as 8 weeks' gestation^{23–25}. While PAPP-A has been shown to perform better in relation to cFTS if measured before 11 weeks' gestation^{26–28}, performance of free beta-human chorionic gonadotropin (β -hCG) increases with increasing GA. However, the best overall performance of cFTS including both biochemical markers is obtained when blood sampling is done before 11 weeks' gestation^{27,29}. It is therefore relevant to also examine the possibility of measuring PlGF for PE screening in the cFTS routine blood samples from 8 to 10 weeks' gestation.

The aims of this study were to describe the distributional properties of PlGF and to assess screening performance for PE when measured in maternal blood samples collected before 11 weeks' gestation.

METHODS

In this study, we analyzed data from participants of the Pre-eclampsia Screening in Denmark (PRESIDE) study²².

The PRESIDE study was a prospective, non-interventional multicenter study investigating the predictive performance of the FMF first-trimester PE screening algorithm in a Danish population. The PRESIDE study was conducted between May 2019 and December 2020 at six Danish university hospitals: Copenhagen University Hospital Rigshospitalet, Copenhagen; Copenhagen University Hospital Herlev and Gentofte, Herlev; Copenhagen University Hospital Hvidovre, Hvidovre; Copenhagen University Hospital North Zealand, Hillerød; Odense University Hospital, Odense; and Aarhus University Hospital, Aarhus. Women with a singleton pregnancy were included at the time of cFTS. Exclusion criteria were age < 18 years, multiple pregnancy or inability to understand Danish or English. Written informed consent was obtained from the women agreeing to participate in the PRESIDE study, which was approved by the Danish Data Protection Agency (P-2020-598) and the research ethics committee (H-19001203).

Blood samples and biochemical analysis

In this study, the population consisted of pregnant women included in the PRESIDE study who had a PlGF measurement from the routine cFTS blood sample collected at 8–14 weeks' gestation. Blood samples were routinely centrifuged within 8 h after collection and serum analyzed in the cFTS double test (PAPP-A and free β -hCG). Excess serum was stored at -80°C at the participating hospitals between April 2019 and December 2020. Serum concentration of PlGF was quantified in the thawed samples in batches between January and June 2021 using the BRAHMS PlGF plus KRYPTOR automated immunofluorescent homogeneous assay (ThermoFisher Scientific GmbH, Hennigsdorf, Germany) on BRAHMS KRYPTOR compact PLUS or KRYPTOR GOLD platforms (ThermoFisher Scientific GmbH) in the Department of Clinical Biochemistry at each of the recruiting hospitals. The PlGF analysis was validated by all participating laboratories using a common set of 40 patient samples. The BRAHMS PlGF plus KRYPTOR assay is calibrated against an internal reference standard prepared from recombinant human PlGF. The assay has a limit of detection of 3.6 pg/mL, limit of quantification of 6.9 pg/mL and the measuring range is 3.6–7000 pg/mL. Interassay coefficients of variation (CVs) were < 10.1% (BRAHMS PlGF plus KRYPTOR Control 1; ~ 28 pg/mL), < 7.8% (BRAHMS PlGF plus KRYPTOR Control 2; ~ 100 pg/mL) and < 6.1% (BRAHMS PlGF plus KRYPTOR Control 3; ~ 410 pg/mL). For SeroNorm™ Immunoassay Liq-1 (Sero, Billingstad, Norway), CVs were < 19.8% (QC Level 1; ~ 10 pg/mL) and < 6.3% (QC Level 2; ~ 130 pg/mL).

PRESIDE study measures

In the PRESIDE study, maternal characteristics and information on acetylsalicylic acid (ASA) use among participants were obtained via patient questionnaires

and stored in the local fetal medicine databases (Astraia Software; Nexus Astraia GmbH, Ismaning, Germany). Blood pressure and UtA-PI were measured at the time of the nuchal translucency scan at 11–14 weeks' gestation. Blood pressure was measured in accordance with international guidelines³⁰, using an automated blood pressure measurement station³¹, and measurements of right and left UtA-PI by pulsed-wave transabdominal color Doppler were made by sonographers who had obtained the FMF certificate of competence in PE screening³². Data on ASA use among participants were verified in maternal records.

Outcomes

Pregnancy outcomes, including GA at delivery and PE diagnosis, were collected from birth registries. For women with a diagnosis of PE or preterm birth, and for a random sample of 15% without PE, the diagnosis was validated by information obtained from the maternal records.

Outcomes for women with PE were categorized consistent with the International Federation of Gynecology and Obstetrics (FIGO) initiative on PE³⁰, according to GA at delivery in the following groups: PE with delivery < 37 weeks (preterm PE) and PE with delivery $\geq$ 37 weeks (term PE). PE was defined according to 2018 guidelines from the International Society for the Study of Hypertension in Pregnancy³³. GA at birth was calculated using the estimated due date based on measurement of crown–rump length at cFTS.

Statistical analysis

Data are summarized, according to GA at PIGF sampling, as median (interquartile range) for continuous variables and as n (%) for categorical variables.

Multiple linear regression models were fitted to $\log_{10}$ PIGF concentrations from the routine sample with the outcome, maternal characteristics, medical history, and GA at delivery with PE as covariates. Backwards elimination was used for model selection. Partial residuals from the fitted models excluding the contribution of PE, comprised the $\log_{10}$ multiples of the median (MoM) values. Median PIGF MoM, grouped by PE < 37 weeks, PE $\geq$ 37 weeks and no PE, were plotted against GA at sampling to assess discrimination between the three groups by GA at sampling. Plots of PIGF MoM against GA at delivery with PE were produced to visually inspect the suitability of the 11–14 weeks FMF parameters on early PIGF. The competing-risks model was used to estimate patient-specific risk of delivery with PE by a combination of maternal demographic characteristics and medical history, and MAP, UtA-PI and PIGF MoM. In the risk calculations, after computing MoM values specific to the early GA sampling, it was assumed that the likelihood function was the same for early measurements of PIGF as the later measurements.

Performance of screening using PIGF from cFTS blood samples collected at 8–14 weeks' gestation was assessed in

terms of detection rate (DR) for a 10% SPR. A proportion of the study group, expected to be 3.5%³⁴, was prescribed ASA based on current Danish guidelines. Treatment with ASA was recorded, as it biases the assessment of PE screening performance. To minimize bias resulting from ASA use, imputation was implemented as described in the PRESIDE study²².

R software was used for all statistical analyses^{35,36}.

RESULTS

The median age among the 8386 participants was 30.8 (interquartile range, 28.1–33.9) years, 7960 (95%) were white and 4467 (53%) were nulliparous (Table 1). Autoimmune diseases, such as antiphospholipid syndrome or systemic lupus erythematosus, were reported by 24 (0.3%) women, seven (0.1%) had pregestational diabetes mellitus and 39 (0.5%) had chronic hypertension. Treatment with ASA was reported by 253 (3.0%) women at inclusion. In total, 313 (3.7%) women developed PE, including 62 (0.7%) with PE < 37 weeks and 251 (3.0%) with PE $\geq$ 37 weeks.

Termination before 21 + 6 weeks' gestation was performed in 13 (0.2%) women, 18 (0.2%) had a miscarriage, there were two (0.02%) intrauterine deaths $\geq$ 22 + 0 weeks, 19 (0.2%) gave birth at home or at a private clinic and 73 (0.9%) were lost to follow-up (moved out of Denmark (n = 34) or records were not accessible (n = 39)). The abovementioned women were treated as not having PE in the analyses.

The GA distribution at the time of routine cFTS sampling is shown in Figure 1. The proportion of sampling before 11 weeks was 73% (n = 6160), 47% (n = 3944) had their sample collected before 10 weeks' gestation and 26% (n = 2216) had the sample collected at 10 weeks' gestation. There were no significant differences in maternal characteristics in relation to GA at routine blood sampling.

The FMF default model for calculating PIGF MoM involves extrapolating to week 8 from a model fitted to GAs between 11 and 14 weeks. We therefore fitted a model to the data in this study (Table 2).

The prevalence of PE < 37 weeks was 0.7% (29/3944) in women with blood samples collected before 10 weeks, 0.7% (16/2216) in women with blood samples collected at 10 weeks and 0.8% (17/2226) in women with blood samples collected $\geq$ 11 weeks' gestation. For blood samples collected before 10 weeks' gestation, there appeared to be little difference between PIGF levels in pregnancies developing PE compared to unaffected pregnancies (Figure 2). Pregnancies with preterm and term PE had median PIGF MoM values of 0.97 (95% CI, 0.82–1.16) and 0.95 (95% CI, 0.87–1.03), respectively. However, PIGF levels in blood samples collected at 10 weeks were significantly lower for pregnancies developing preterm PE compared with unaffected pregnancies (median PIGF MoM for pregnancies developing preterm PE was 0.61 (95% CI, 0.43–0.85)). For pregnancies developing term PE, the median PIGF MoM value did not differ significantly

from unaffected pregnancies (0.97 (95% CI, 0.88–1.07)). As expected, levels of PlGF in blood samples collected ≥ 11 weeks' gestation were significantly lower in both pregnancies developing preterm PE (0.45 (95% CI, 0.24–0.86)) and term PE (0.75 (95% CI, 0.65–0.86)) compared with unaffected pregnancies.

When comparing with measurements from 8152 blood samples from the PRESIDE study, which were all collected ≥ 11 weeks' gestation²², we found similar PlGF MoM in pregnancies with preterm and term PE (Figure S1).

We investigated the benefit, in terms of DR at a 10% fixed SPR for preterm PE and all PE, of including PlGF in addition to maternal factors, MAP and UtA-PI in the following groups: PlGF samples collected before 10 weeks' gestation, at 10 weeks' gestation and ≥ 11 weeks' gestation (Figure 3). In the group with samples collected before 10 weeks, inclusion of PlGF did not improve the DR, and this reflects the low discriminatory value of PlGF at these GAs as seen in Figure 2. For preterm PE, the DR obtained when including PlGF from samples collected at 10 weeks was superior to the DR when using the FMF model (maternal factors + MAP + UtA-PI) alone, but it was inferior to the DR yielded when including PlGF samples from ≥ 11 weeks' gestation. For all PE, inclusion of PlGF measured in samples collected before 10 weeks and at 10 weeks did not improve the DR when using the FMF algorithm alone. Inclusion of PlGF at ≥ 11 weeks'

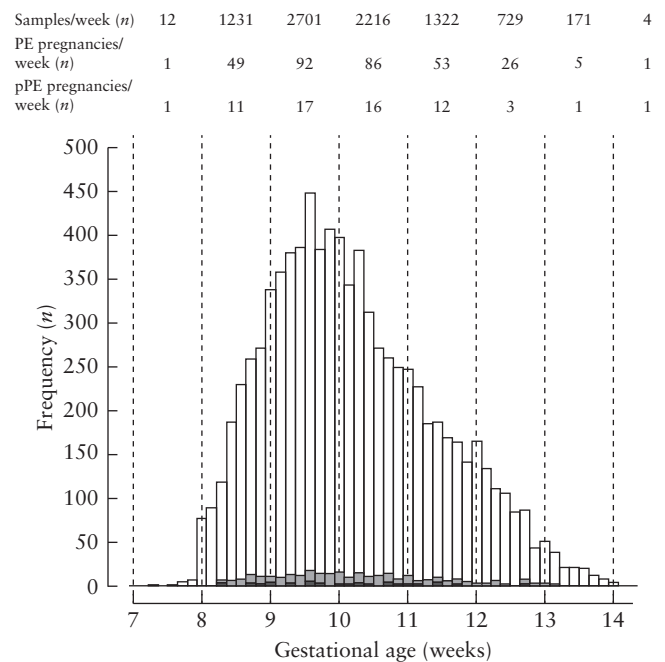


Figure 1 Histogram showing gestational-age distribution at time of routine combined first-trimester screening blood sample collection. Number (n) of samples per week, pregnancies affected by pre-eclampsia (PE) (at any gestational age) per week and pregnancies affected by preterm PE (pPE) (< 37 weeks) per week are shown. □, daily number of samples; ■, distribution of blood samples among women who subsequently developed any PE; ▨, distribution of blood samples among women who subsequently developed pPE.

Table 1 Maternal and pregnancy characteristics of study population, according to gestational age at which blood sample was collected for measurement of placental growth factor

Characteristic	Total cohort (n = 8386)	Gestational age at sampling	
		< 11 + 0 weeks (n = 6130)	$\geq 11 + 0$ weeks (n = 2256)
Age (years)	30.8 (28.1–33.9)	30.6 (27.9–33.7)	31.2 (28.6–34.4)
Weight (kg)	66.0 (60.0–75.8)	66.8 (60.0–70.0)	65.0 (59.0–74.0)
Height (cm)	168 (164–173)	168 (164–173)	168 (164–173)
Body mass index (kg/m ²)	23.4 (21.2–26.6)	23.5 (21.3–26.8)	22.9 (20.9–25.8)
Gestational age at scan (days)	89 (87–92)	89 (86–91)	91 (88–93)
Ethnic origin			
White	7960 (94.9)	5856 (95.5)	2104 (93.3)
South Asian	159 (1.9)	110 (1.8)	49 (2.2)
Mixed	118 (1.4)	73 (1.2)	45 (2.0)
East Asian	83 (1.0)	57 (0.9)	26 (1.2)
Black	63 (0.8)	33 (0.5)	30 (1.3)
Missing	3 (0.04)	1 (0.02)	2 (0.09)
Medical history			
Chronic hypertension	39 (0.5)	31 (0.5)	8 (0.4)
DM Type 1	4 (0)	2 (0)	2 (0.1)
DM Type 2	3 (0)	3 (0)	0 (0)
SLE/APS	24 (0.3)	16 (0.3)	8 (0.4)
Smoker	259 (3.1)	182 (3.0)	77 (3.4)
Method of conception			
Spontaneous	7569 (90.3)	5518 (90.0)	2051 (90.9)
In-vitro fertilization	563 (6.7)	429 (7.0)	134 (5.9)
Ovulation drugs	254 (3.0)	183 (3.0)	71 (3.1)
Parity			
Nulliparous	4467 (53.3)	3235 (52.8)	1232 (54.6)
Parous, no pre-eclampsia	3699 (44.1)	2732 (44.6)	967 (42.9)
Parous, pre-eclampsia	220 (2.6)	163 (2.7)	57 (2.5)
ASA use at inclusion	253 (3.0)	185 (3.0)	68 (3.0)

Data given as median (interquartile range) or n (%). APS, antiphospholipid syndrome; ASA, acetylsalicylic acid; DM, diabetes mellitus; SLE, systemic lupus erythematosus.

Table 2 Fitted regression model with maternal and pregnancy characteristics for log₁₀ placental growth factor for blood samples drawn < 11 weeks' gestation

Characteristic	Estimate (95% CI)	P
Intercept	1.38443 (1.37533 to 1.39354)	< 0.001
PE	−0.59446 (−0.90812 to −0.28080)	< 0.001
GA at delivery with PE (in weeks)	0.01375 (0.00559 to 0.02191)	< 0.001
GA at sampling − 77 (in days)	0.01072 (0.01008 to 0.01135)	< 0.001
(GA at sampling − 77) ² (in days)	−0.00010 (−0.00015 to −0.00005)	< 0.001
Maternal weight − 69 (in kg)	0.00075 (0.00040 to 0.00110)	< 0.001
Maternal height − 164 (in cm)	−0.00270 (−0.00340 to −0.00200)	< 0.001
Ethnic origin		
Black	0.09978 (0.048040 to 0.15153)	< 0.001
South Asian	0.04335 (0.01020 to 0.07649)	0.010
Parity		
Parous, no PE	0.02008 (0.01086 to 0.02930)	< 0.001
Parous, PE	−0.03121 (−0.05941 to −0.00302)	< 0.001

GA, gestational age; PE, pre-eclampsia.

gestation produced an all-PE DR superior to that of the FMF model without PlGF (Figure 3).

We examined further the predictive performance of PlGF at different GAs by plotting the MoM value from a routine cFTS blood sample collected at 8–10 weeks' gestation against the MoM value of the PRESIDE study blood sample collected from the same woman at 11–14 weeks' gestation (Figure S2). This scatter plot shows that samples collected at 11–14 weeks (the PRESIDE study samples) to a greater extent were associated with lower PlGF levels (< 1 MoM) for women with PE than the early routine samples collected at 8–10 weeks, which corresponds to a lower predictive performance of this biomarker when sampled at < 10 weeks' gestation. For samples collected at 10 weeks' gestation, only a small proportion of the routine PlGF MoM were > 1 MoM in pregnancies with PE, indicating that the predictive value of PlGF may be better at 10 weeks than before 10 weeks.

DISCUSSION

In this Danish multicenter study, we evaluated performance of the FMF first-trimester PE screening algorithm using PlGF from blood samples collected at 8–14 weeks' gestation. Our most important finding was that PlGF from samples collected at 10 weeks' gestation had similar discriminatory value to those collected at 11–14 weeks for PE with delivery before 37 weeks' gestation. This indicates that PlGF collected at 10 weeks' gestation may be useful in prediction of preterm PE. We found that the

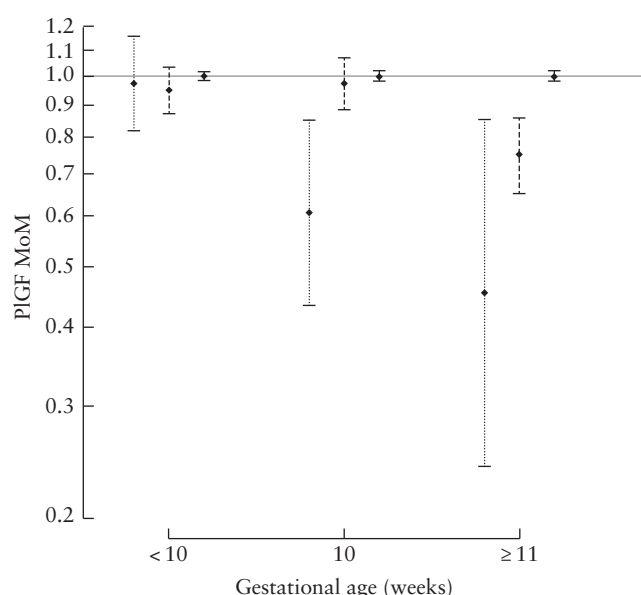


Figure 2 Median placental growth factor (PlGF) multiples of the median (MoM) values in pregnancies with preterm pre-eclampsia (PE) < 37 weeks (.....), term PE ≥ 37 weeks (-----) and unaffected pregnancies (—), according to gestational age at time of routine combined first-trimester screening blood sample collection. y-axis is on logarithmic scale. Bars are 95% CI.

discriminatory value of PlGF for preterm PE is relatively poor when measured in samples collected earlier than 10 weeks' gestation. Addition of PlGF collected before 10 weeks to the FMF model (which includes maternal risk factors, MAP and UtA-PI) did not improve the DR, whereas PlGF collected at 10 weeks increased the DR, but was inferior to PlGF in samples collected ≥ 11 weeks' gestation. DRs obtained using routine samples collected ≥ 11 weeks were comparable to DRs reported previously in the PRESIDE study using blood samples collected at 11–14 weeks' gestation²².

Our findings are in line with recent research indicating that the performance of PlGF in prediction of preterm PE increases after 11 weeks' gestation³⁷. Mendoza *et al.*³⁸ compared the predictive accuracy of first-trimester combined PE screening at 8–10 weeks with that at 11–13 weeks' gestation. The study found that the timing of PlGF measurement did not affect the performance of the FMF algorithm in predicting preterm PE. However, the study involved few cases of PE and lacked sufficient power to conclude that PlGF measured in blood samples before 11 weeks is equivalent to measurements in samples collected at 11–13 weeks' gestation.

Our results suggest that the discriminatory accuracy of PlGF as a marker for PE increases throughout the first trimester, possibly from 10 weeks' gestation. This tendency has been shown in one previous study³⁹, suggesting that the capability of PlGF to discriminate between pregnancies at increased risk for PE is better when assessed late in the first trimester or early in the second trimester. Studies on PlGF in late-first and second trimester indicate that the efficacy of this biomarker in prediction of preterm

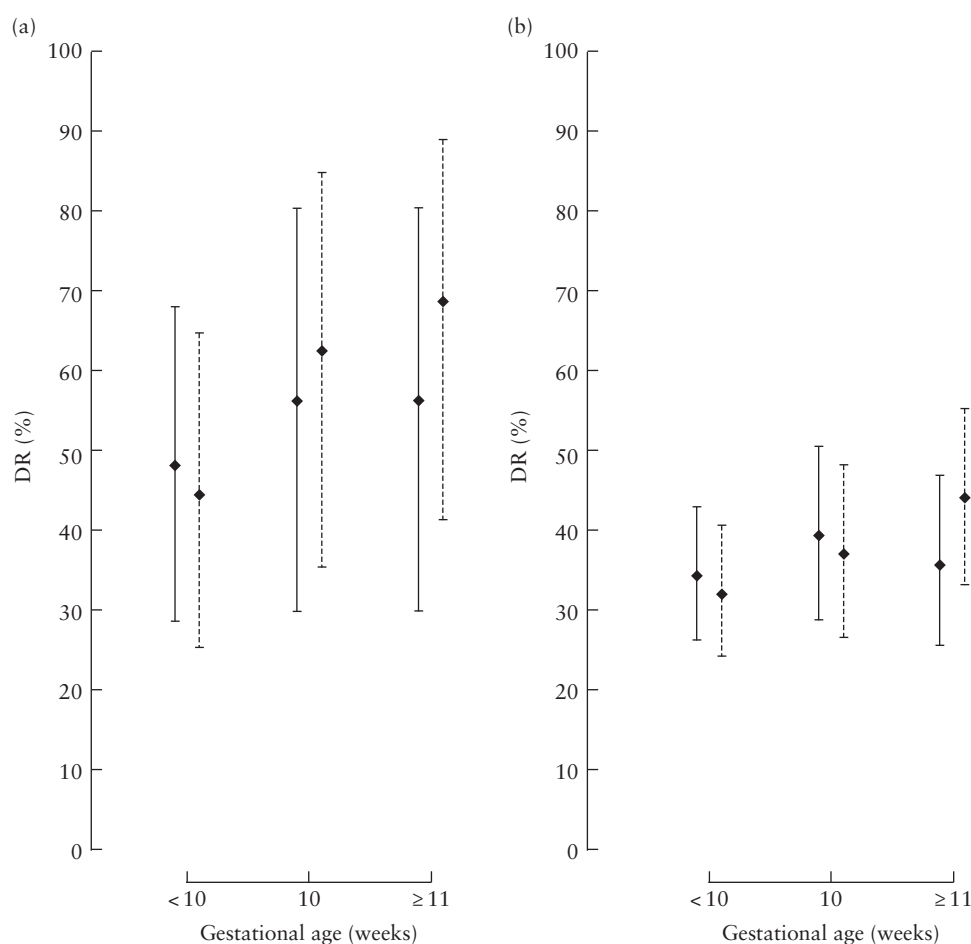


Figure 3 Detection rates (DR) at 10% fixed screen-positive rate for preterm pre-eclampsia (PE) (a) and all PE (b) using Fetal Medicine Foundation (FMF) algorithm alone (maternal characteristics + mean arterial pressure (MAP) + uterine artery pulsatility index (UtA-PI) (—)) or FMF algorithm (maternal characteristics + MAP + UtA-PI) and early placental growth factor (PIGF) (-----) according to gestational age at time of routine combined first-trimester screening blood sample collection.

PE may increase with advancing GA, and serial PIGF measurements throughout pregnancy have been proposed^{6,37}.

Whereas use of samples for PIGF collected before 10 weeks' gestation may reduce substantially the predictive performance of the FMF screening model, samples collected at 10 weeks may be useful, as they showed discriminatory value almost similar to samples collected at 11–14 weeks. Further research focusing on samples for PIGF collected at 10 weeks is needed to support this finding, as the number of women developing PE in this group was relatively small in this study ($n = 86$).

In settings in which blood samples for cFTS are drawn at 11–14 weeks, first-trimester PE screening could be readily implemented alongside cFTS measuring PIGF, PAPP-A and free β -hCG on the same sample. Studies have shown that blood sampling at ≤ 10 weeks' gestation for cFTS improves performance^{27,29}, and therefore a one-sample set-up at 11–14 weeks leads to a less optimal cFTS performance, but a better PE-screening performance. This challenge could perhaps be met by collecting one blood sample at around 10 weeks and combining biomarkers for cFTS and PE screening.

In settings in which aneuploidy screening is done in two steps with biochemical measurements targeted at

early GAs, performance of PE screening may be less optimal in women who have their blood sample collected before 10 weeks' gestation. In these women, collection of an additional blood sample for PIGF analysis at or after 10 weeks may be relevant. However, in the Danish population, almost 50% of cFTS blood samples are collected before 10 weeks' gestation. Before opting for this strategy, it is therefore important to examine the distribution of GA at the time of blood sampling in the local population.

Screening for trisomies by cell-free fetal DNA (cffDNA) testing is used widely in countries with populations comparable to the Danish. Testing by cffDNA has been shown to be feasible at 10–11 weeks' gestation, allowing for an early first-trimester diagnosis of aneuploidies. The results of this study may support the choice of a combination of cffDNA and PIGF in one sample around 10 weeks' gestation, although PIGF performance at 10 weeks should be confirmed in a larger cohort.

Strengths and limitations

A strength of this study is the multicenter set-up with involvement of several central laboratories, which mimics

the Danish healthcare system and strengthens the reproducibility of our findings. This study is one of the first to present data on the predictive performance of PlGF measured in blood samples collected before 11 weeks' gestation. Our findings are relevant in relation to a possible widespread implementation of the FMF screening for PE, particularly in countries with existing first-trimester screening for aneuploidies similar to Denmark.

This study has demonstrated that there is no evidence to support the use of PlGF when measured before 10 weeks' gestation. At 10 weeks and beyond, the discriminatory value of PlGF in this study is consistent with that from other studies in which PlGF was measured ≥ 11 weeks. However, this study lacks statistical power to demonstrate that PlGF measured at 10 weeks adds significantly to detection of preterm PE.

It may be considered a limitation of this study that PlGF was not measured in fresh samples. However, in whole blood, PlGF concentrations show $< 5\%$ change when stored for up to 9.7 h at 20°C and even longer for serum⁴⁰. Serum concentrations are stable for at least 3 years at -80°C and for at least three freeze–thaw cycles^{40,41}. Therefore, measurements were not likely to be affected significantly by the handling of samples in this study.

Although this study was based on a relatively large sample size compared to similar studies, the number of pregnancies affected by early-onset and preterm PE was relatively low, and our results should be interpreted within the context of this limitation.

Conclusions

GA for PlGF samples may be expanded from 11–14 weeks to 10–14 weeks when assessing the risk for PE using the FMF first-trimester screening model. There is little evidence to support the use of PlGF in samples collected before 10 weeks' gestation.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



Figure S1 Median placental growth factor (PlGF) multiples of the median (MoM) values in pregnancies with preterm pre-eclampsia (PE) < 37 weeks (red), term PE $\geq$ 37 weeks (blue) and unaffected pregnancies (black), according to gestational age at time of routine combined first-trimester screening blood sample collection. Dashed lines are PRESIDE study blood samples collected at 11–14 weeks’ gestation. y-axis is on logarithmic scale. Bars are 95% CI.

Figure S2 Scatterplots showing placental growth factor (PlGF) multiples of the median (MoM) values from combined first-trimester screening blood samples collected before 9 weeks’ gestation, at 9 weeks and at 10 weeks *vs* PlGF MoM values at 11–14 weeks in women with preterm pre-eclampsia < 37 weeks (●) and unaffected women (○).