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ORIGINAL RESEARCH

Placental growth factor before 11 weeks for screening of preterm preeclampsia: The PreMoM study

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Abstract

Introduction: Our objective was to compare the predictive performance of the Fetal Medicine Foundation (FMF) competing-risk model for preterm preeclampsia (PE) screening using placental growth factor (PlGF) measurements obtained at 11–13^{+6} weeks versus before 11 weeks of gestation.

Material and Methods: This multicenter prospective cohort study included women with singleton pregnancies attending their routine first-trimester assessment (11^{+0} to 13^{+6} weeks) in four hospitals across Spain from 2021 to 2023. Maternal characteristics, biophysical parameters (mean arterial pressure and uterine artery pulsatility index), and biochemical markers (PlGF measured twice in each woman, before 11 weeks and between 11 and 13^{+6} weeks) were assessed. Risk assessment for preterm PE was estimated by the FMF algorithm. Predictive performance was evaluated by comparing detection rates (DR) at different fixed screen-positive rates (SPR), area under the receiver-operating characteristic curve (AUROC), and calibration plots. Statistical adjustments were made to account for prophylactic aspirin use.

Abbreviations: AUROC, area under the receiver-operating characteristic curve; DR, detection rate; FMF, Fetal Medicine Foundation; PE, preeclampsia; PlGF, placental growth factor; SPR, screen-positive rate.

Results: The study population comprised 3448 women, including 19 (0.55%) who developed preterm preeclampsia and 47 (1.36%) who developed term preeclampsia. At 10% SPR, the detection rates (adjusted for aspirin use) were highest for the model incorporating PlGF between 11 and 13^{+6} weeks (72.9%; 95% CI, 42.2%–90.9%), compared to models with PlGF before 11 weeks (66.4%; 95% CI, 39.9%–85.4%) and without PlGF (66.0%; 95% CI, 39.3%–85.3%). Similar trends were observed at higher SPR thresholds. The best discrimination (AUROC: 0.863; 95% CI, 0.754–0.971) and calibration were also achieved by the model using PlGF between 11 and 13^{+6} weeks.

Conclusions: PlGF measured before 11 weeks did not improve preterm PE screening performance. Due to the small number of cases, further validation is needed. Maternal and biophysical markers remain a viable alternative when PlGF is unavailable.

KEYWORDS
first pregnancy trimester, maternal serum screening tests, placenta growth factor, preeclampsia

1 | INTRODUCTION

Preeclampsia (PE) affects approximately 3%–7% of pregnancies and represents a significant cause of maternal and perinatal morbidity and mortality worldwide, particularly when it occurs preterm (delivery with PE before 37 weeks).[1] In Spain, the incidence of preterm PE is approximately 0.7%, whereas term PE occurs in about 1.6% of pregnancies.[2] Early identification of high-risk pregnancies allows timely interventions, such as preventive aspirin administration initiated during the first trimester, which significantly reduces the incidence of preterm PE.[3,4]

Current screening models, including those from the Fetal Medicine Foundation (FMF),[5] BCNatal,[6] and MedFetal,[7] incorporate maternal characteristics, biophysical, and biochemical markers such as placental growth factor (PlGF). These models have demonstrated good predictive performance in the Spanish population, with the FMF model achieving a detection rate (DR) of 72.7% for preterm PE at a fixed 10% screen-positive rate (SPR).[8] However, this model uses PlGF measurements obtained between 11 and 13^{+6} weeks, which may present logistical challenges depending on whether the sample is collected on the same day as the ultrasound examination or a few days earlier, which is not available for many centers. Given that certain pregnancy screenings, such as those for aneuploidies or thyroid dysfunction, yield better performance when conducted earlier in pregnancy, incorporating PlGF measurement into the same early blood test could improve overall screening efficiency and reduce the need for repeat blood draws.

To address this issue, our study aimed to compare the predictive performance of the FMF competing-risk model for preterm PE screening using PlGF measurements obtained at 11–13^{+6} weeks versus before 11 weeks of gestation.

Key message

PlGF measured before 11 weeks did not improve the performance of the preterm preeclampsia screening model. Screening with maternal and biophysical markers alone remains a valid option when PlGF is not available during the standard 11- to 13^{+6}-week window.

2 | MATERIAL AND METHODS

2.1 | Study design and population

This multicenter prospective cohort study was conducted between January 2021 and December 2023 across four hospitals in different regions of Spain: Hospital Universitario Virgen de las Nieves (Granada), Hospital Universitario Clínico San Cecilio (Granada), Hospital Clínico Universitario Virgen de la Arrixaca (Murcia), and Hospital Universitario de Torrejón (Madrid). In all the participating centers, first-trimester screening of preeclampsia was conducted as part of a larger research study aimed to validate the FMF algorithm and evaluate its clinical implementation.[2] In brief, all women attending their routine first-trimester visits with a singleton pregnancy between 11^{+0} and 13^{+6} weeks of gestation were invited to participate in the study. Additionally, participants were asked to provide consent for the use of maternal blood samples collected earlier in pregnancy for fetal aneuploidy and hypothyroidism screening (between 8^{+0} and 10^{+6} weeks), which were stored by laboratories until acceptance or refusal of inclusion in the study.

Exclusion criteria included maternal age below 18 years, severe mental illness or intellectual disability, fetal aneuploidy or major

congenital anomalies, and pregnancy loss due to miscarriage, termination, or fetal death before 24 weeks of gestation.

2.2 | Study procedures

During the 11- to 13^{+6}-week visit, clinical characteristics and medical history were recorded in a dedicated clinical database (Astraia® software, Nexus/Astraia, Munich, Germany; and Viewpoint®, GE Healthcare, Munich, Germany). Maternal characteristics included age, weight, height, and self-reported ethnicity (White, Black, East Asian, South Asian, or Mixed). Information on conception type (spontaneous, in-vitro fertilization, or ovulation induction), smoking status, and medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus, or antiphospholipid syndrome was also collected. Finally, family history of PE and obstetric history, including parity (nulliparous, multiparous without PE, or multiparous with PE), were documented. Maternal mean arterial pressure (MAP) was measured using a validated and calibrated device, and the uterine artery pulsatility index (UtA-PI) was assessed via transabdominal color Doppler ultrasound. All measurements were performed following standardized protocols.[9,10] Quality control procedures for all biophysical biomarkers were conducted routinely.[2]

Follow-up data were retrieved from the patient's medical records or by contacting the delivering hospitals or the women's general medical practitioners/midwives. In all centers, the diagnosis of PE was established according to the criteria of the American College of Obstetricians and Gynecologists.[11] Pregnancy outcomes were carefully recorded, including aspirin use, gestational age at PE diagnosis and delivery, as well as birth weight.

2.3 | Blood sample collection and processing

During the study period, two blood samples were collected in each participant. The first maternal blood sample was taken between weeks 8^{+0} and 10^{+6}, where serum aneuploidy biomarkers, including pregnancy associated plasma protein A (PAPP-A) and free beta human chorionic gonadotropin (β-hCG), were assessed. The second blood sample was collected during the first-trimester screening visit, between weeks 11^{+0} and 13^{+6} of gestation.

Blood samples were obtained by venipuncture from the antecubital vein and collected in serum separating tubes (SST, Vacutainer SST II Tube 8.5 mL, Becton Dickinson, Sunnyvale, CA, USA). After collecting, the tubes were left to clot at room temperature for 30 min and then centrifuged at 1800× g for 10 min. Serum samples collected during the first visit were aliquoted in Eppendorf tubes and stored at −80°C until subsequent analysis.

Samples collected during the 11- to 13-week window were analyzed for PlGF levels using the Elecsys electrochemiluminescence immunoassay (Cobas e801 analyzer; Roche Diagnostics GmbH, Mannheim, Germany) within 24 h of collection, and the results were used for prospective clinical screening. For this study, surplus sample material was aliquoted and stored for subsequent analysis using two additional platforms: the BRAHMS KRYPTOR Compact PLUS analyzer (Thermo Fisher Scientific, Hennigsdorf, Germany) and the DELFIA® Xpress random-access immunoassay system (Revvity Omics Sweden, Sollentuna, Sweden). PlGF measurements were performed locally for the first two platforms, while samples for the DELFIA platform were shipped frozen on dry ice to a central laboratory in Sweden.

Each patient's sample was analyzed using all three commercial assays at both time points (<11 weeks and ≥11 weeks) to enable the development of a unified formula for multiples of the median (MoM) calculation applicable across platforms and gestational ages from 8 to 14 weeks. For the risk estimation and model performance analyses presented in this study, PlGF concentrations measured on the Cobas e801 platform were used as the primary source. If Cobas' data were not available, results from the BRAHMS KRYPTOR analyzer were used, and if neither was available, DELFIA® Xpress values were employed.

All measurements were performed following quality control protocols in accordance with the laboratories' established procedures to ensure accuracy and reliability.

2.4 | Statistical Analysis

Continuous variables were summarized using medians and interquartile ranges (IQR), while categorical variables were reported as frequencies and percentages.

Log10 PlGF values were estimated using a linear mixed-effects regression model, adjusted for gestational age, maternal characteristics, and assay platform as covariates. Model selection was performed using a genetic algorithm, with the optimal model having the lowest Akaike Information Criterion. Individual MoMs values were calculated as the ratio of measured Log10 PlGF concentrations to the predicted Log10 PlGF from the selected regression model. The discriminatory ability of early PlGF measurements was assessed by plotting MoM distributions according to the type of PE. Additionally, a linear regression model was fitted to explore the relationship between Log10 PlGF MoM values measured before 11 weeks and gestational age at delivery.

The risk of delivery with preeclampsia before 37 weeks was computed using the competing-risk model from the FMF, incorporating maternal characteristics, MAP, and UtA-PI.[5] Predictive performance of the screening models without PlGF, with PlGF measured before 11 weeks, and with PlGF measured between 11 and 13^{+6} weeks, was evaluated by calculating DR at fixed 10%, 15%, and 20% SPR. Model calibration was assessed visually by plotting observed incidences against predicted probabilities and quantitatively by estimating calibration-in-the-large and calibration slope. Discrimination was quantified using the area under the receiver-operating characteristic curve (AUROC).

Because aspirin prophylaxis (150 mg/day), prescribed in women with high risk of PE, can reduce the incidence of preeclampsia and thus

bias predictive performance assessment, an adjustment approach was implemented.[5,12] To address this issue, 100 datasets were simulated, assuming none of the participants received aspirin. Outcomes for women who received aspirin in the original dataset and delivered without PE were imputed using causal inference methods to estimate the probability of preeclampsia had aspirin not been administered. Estimates from these 100 simulated datasets were pooled according to Rubin's rules.

All statistical analyses were conducted using R software version 4.3.1.[13] Data cleaning and management were carried out with the *tidyverse* suite of packages.[14] Descriptive statistics and tables were generated using the *gtsummary* package.[15] The linear mixed-effects regression model was fitted using the *lme4* package,[16] and the model results were summarized using the *sjPlot* package.[17] Model selection was performed using the *glmulti* package.[18] Inverse probability weighting calculations were implemented with the *WeightIt* package.[19]

3 | RESULTS

3.1 | Description of the study population

The analysis included 3448 women with singleton pregnancies who underwent first-trimester screening, among whom 19 (0.55%) developed preterm PE and 47 (1.36%) developed term PE.

TABLE 1 Maternal and gestational characteristics of women with singleton pregnancies screened during the first-trimester visit.

Characteristic	Preterm PE $N=19$[a]	Term PE $N=47$[a]	No PE $N=3382$[a]
Maternal age, years	36.1 (32.2, 39.1)	33.7 (30.4, 38.7)	32.6 (28.6, 36.2)
Maternal weight, kg[b]	74.5 (67.0, 80.0)	72.0 (62.0, 87.0)	64.0 (57.0, 73.8)
Maternal height, cm	164.0 (161.0, 169.0)	164.0 (160.0, 167.5)	163.0 (159.0, 167.0)
Race			
White	18 (94.7%)	45 (95.7%)	3274 (96.8%)
Black	1 (5.3%)	1 (2.1%)	61 (1.8%)
East Asian	0 (0.0%)	0 (0.0%)	5 (0.1%)
South Asian	0 (0.0%)	0 (0.0%)	2 (0.1%)
Mixed	0 (0.0%)	1 (2.1%)	40 (1.2%)
Conception			
Spontaneous	13 (68.4%)	39 (83.0%)	3158 (93.4%)
IVF	5 (26.3%)	7 (14.9%)	213 (6.3%)
Ovulation drugs	1 (5.3%)	1 (2.1%)	11 (0.3%)
Obstetric history			
Nulliparous	15 (78.9%)	28 (59.6%)	1649 (48.8%)
Multiparous-no PE	3 (15.8%)	16 (34.0%)	1658 (49.0%)
Multiparous-PE	1 (5.3%)	3 (6.4%)	75 (2.2%)
Cigarette smoker	3 (15.8%)	1 (2.1%)	402 (11.9%)
Chronic hypertension	1 (5.3%)	0 (0.0%)	37 (1.1%)
Diabetes mellitus			
No	18 (94.7%)	46 (97.9%)	3357 (99.3%)
Type 1	1 (5.3%)	1 (2.1%)	19 (0.6%)
Type 2	0 (0.0%)	0 (0.0%)	6 (0.2%)
SLE	0 (0.0%)	0 (0.0%)	8 (0.2%)
APS	0 (0.0%)	0 (0.0%)	10 (0.3%)
Outcome			
Live birth	19 (100.0%)	47 (100.0%)	3374 (99.8%)
IUD	0 (0.0%)	0 (0.0%)	4 (0.1%)
NND	0 (0.0%)	0 (0.0%)	4 (0.1%)
Birthweight, g	1970.0 (1600.0, 2380.0)	3090.0 (2765.0, 3320.0)	3250.0 (2960.0, 3550.0)
Treated with ASA	9 (47.4%)	24 (51.1%)	468 (13.9%)

Abbreviations: APS, antiphospholipid syndrome; IUD, intrauterine death; IVF, in-vitro fertilization; NND, neonatal death; PE, preeclampsia; SLE, systemic lupus erythematosus.

[a]Median (Q1, Q3); *n* (%).

[b]Maternal weight refers to the measurement obtained during the first-trimester screening visit.

Maternal demographics and pregnancy characteristics according to pregnancy outcomes are presented in Table 1. Compared to women without preeclampsia, those with preterm PE were older, had higher maternal weight, and a higher prevalence of chronic hypertension, smoking status, and conception by assisted reproductive techniques. A total of 51 women were taking aspirin prior to inclusion in the study.

3.2 | PlGF MoM estimation

Raw serum concentrations of PlGF for each of the three assay platforms, stratified by gestational age at blood sampling (<11 weeks and ≥11 weeks), are provided in Table S1.

The detailed results of the fitted mixed-effects model are summarized in Table 2. Log-transformed PlGF levels were significantly associated with gestational age, maternal age, maternal weight, ethnicity, and smoking status, with differences observed among assay platforms. The model showed good predictive performance, with a marginal R^2 of 0.556 and a conditional R^2 of 0.848, indicating that a substantial proportion of variability in PlGF levels was explained by the predictors and random effects included in the analysis.

Figure 1A illustrates the distribution of PlGF MoMs according to pregnancy outcome and timing of PlGF measurement. In pregnancies complicated by preterm PE, the median PlGF MoM was 0.958 (IQR: 0.870–1.040) for measurements obtained before 11 weeks and 0.884 (IQR: 0.786–0.945) for measurements at or after 11 weeks, with a more pronounced reduction observed in measurements performed after 11 weeks. For pregnancies with term PE, median PlGF MoM values were 0.956 (IQR: 0.914–1.030) and 0.939 (IQR: 0.906–0.997), respectively. Median MoM values in pregnancies without preeclampsia were close to 1 for both measurement periods (1.010 [IQR: 0.940–1.070] before 11 weeks, and 0.998 [IQR: 0.935–1.060] after 11 weeks).

MoM values of PlGF measured before 11 weeks in pregnancies complicated by preeclampsia and their linear regression relationship with gestational age at delivery are shown in Figure 1B. Lower PlGF MoM values were associated with earlier gestational ages at delivery, as indicated by the fitted regression line (intercept = −0.61517, slope = 0.01553). The regression line intersects the reference value of 1 MoM near 40 weeks of gestation, suggesting that early PlGF measurement has limited predictive value for term preeclampsia, but suggests a stronger association and better predictive performance for identifying preterm preeclampsia.

TABLE 2 Summary of the linear mixed model for the estimation of Log_{10} PlGF.

Predictors	Estimates	Std. error	95% CI	*p*
Analyzer-dependent effects				
Cobas e801				
Intercept	1.55753	0.00367	1.55032 to 1.56474	<0.001
GA—77	0.01396	0.00017	0.01361 to 0.01430	<0.001
$(GA—77)^2$	−0.00003	0.00002	−0.00006 to 0.00000	0.071
BRAHMS KRYPTOR				
Intercept	1.45612	0.00347	1.44931 to 1.46292	<0.001
GA—77	−0.00317	0.00024	−0.00365 to −0.00269	<0.001
$(GA—77)^2$	0.00004	0.00002	0.00000 to 0.00007	0.030
DELFIA Xpress				
Intercept	1.25493	0.00402	1.24703 to 1.26283	<0.001
GA—77	−0.00279	0.00026	−0.00329 to −0.00228	<0.001
$(GA—77)^2$	0.00006	0.00002	0.00002 to 0.00010	0.001
Analyzer-independent effects				
Maternal age—32, years	0.00200	0.00044	0.00114 to 0.00286	<0.001
Maternal weight—64, kg	−0.00118	0.00018	−0.00153 to −0.00082	<0.001
Maternal height—163, cm	−0.00103	0.00042	−0.00184 to −0.00021	0.014
Ethnicity				
Black	0.07286	0.02056	0.03256 to 0.11316	<0.001
South Asian	0.19548	0.09603	0.00719 to 0.38376	0.042
Cigarette smoker	0.16518	0.00763	0.15022 to 0.18014	<0.001

Abbreviation: GA, gestational age in days.

3.3 | Predictive performance of screening models

At a 10% SPR, detection rates adjusted for aspirin use were highest for the model incorporating PlGF measured between 11 and 13^{+6} weeks (72.9%; 95% CI, 42.2%–90.9%), followed by the model including PlGF measured before 11 weeks (66.4%; 95% CI, 39.9%–85.4%), and the model without PlGF (66.0%; 95% CI, 39.3%–85.3%). At higher SPR thresholds (15% and 20%), a similar trend was observed, with consistently superior predictive performance in the model utilizing PlGF measured between 11 and 13^{+6} weeks. Notably, no marked differences were observed in detection rates between the models without PlGF and those incorporating PlGF measured before 11 weeks (Figure 2).

Calibration plots comparing the observed and predicted incidences of preterm preeclampsia for the three models are shown in Figure 3. The model incorporating PlGF measured between 11 and 13^{+6} weeks demonstrated the best calibration, reflected by an intercept of 0.27 (95% CI, −0.27 to 0.81) and a slope of 0.88 (95% CI, 0.56–1.19). Models using PlGF measured before 11 weeks and without PlGF showed comparable but slightly poorer calibration, with intercepts of 0.22 (95% CI, −0.22 to 0.66) and 0.11 (95% CI, −0.35 to 0.56), and slopes of 0.81 (95% CI, 0.55–1.08) and 0.80 (95% CI, 0.53–1.06), respectively. Consistent with these findings, discrimination was also highest for the model with PlGF measured between 11 and 13^{+6} weeks (AUC 0.863; 95% CI, 0.754–0.971), while the models incorporating earlier measurement or no measurement of PlGF presented similar, slightly lower AUC values (0.830 [95% CI, 0.729–0.932] and 0.827 [95% CI, 0.723–0.930], respectively).

4 | DISCUSSION

This study evaluated the predictive performance of a combined screening model for preterm PE incorporating early PlGF measurement (before 11 weeks of gestation) and compared it with the currently recommended model, which includes PlGF measured between 11 and 13^{+6} weeks. Our results indicate that although early PlGF measurement demonstrated some discriminatory ability, its predictive performance did not substantially surpass that of the

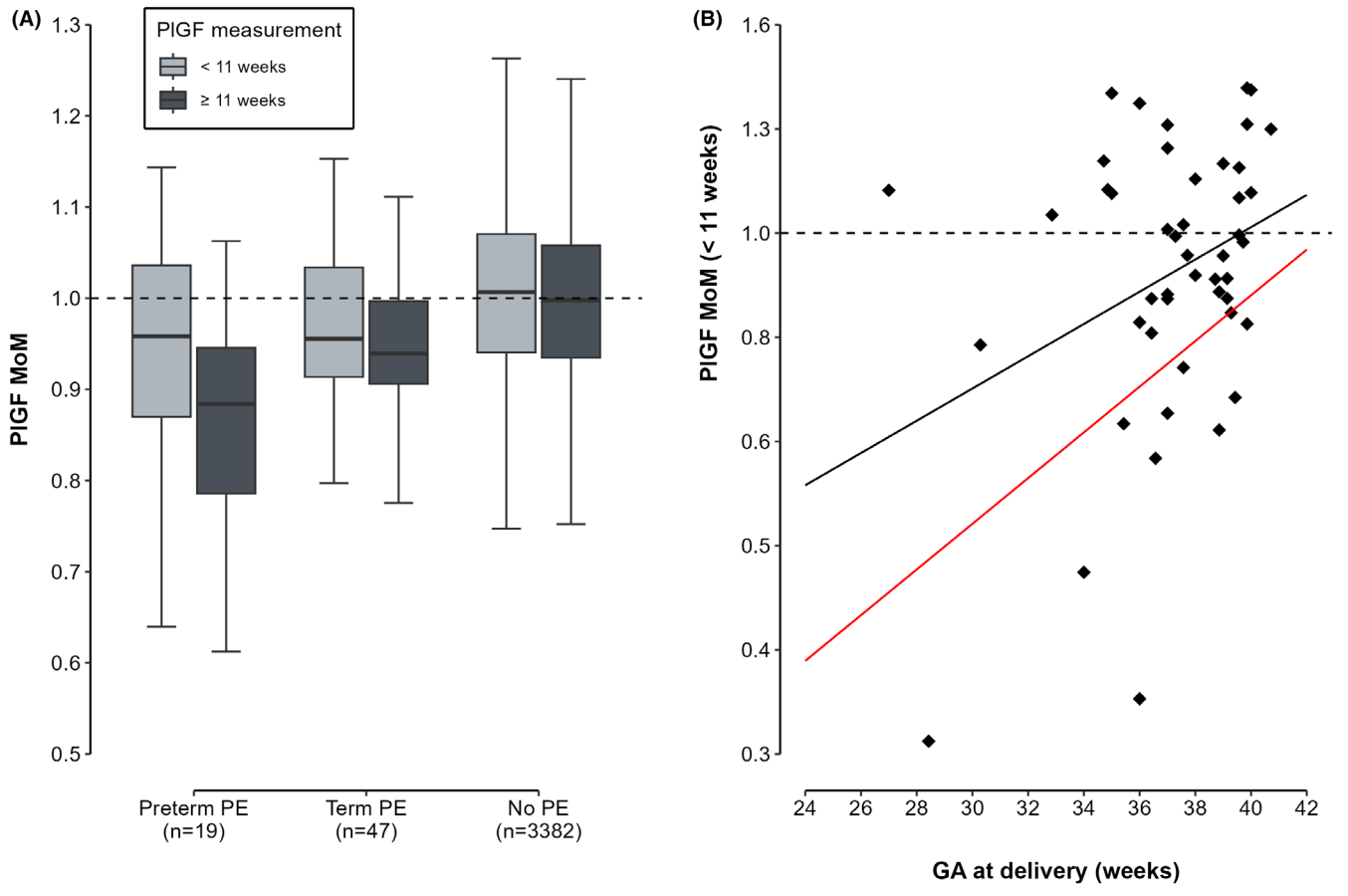

FIGURE 1 Distribution of PlGF multiples of the median (MoM) according to pregnancy outcomes and timing of measurement (A), and relationship between early PlGF MoM values and gestational age at delivery in preeclampsia (B). Panel A shows PlGF MoM distributions by pregnancy outcome and gestational age at blood sampling. Each woman contributed two measurements: One before 11 weeks and another between 11 and 13^{+6} weeks; therefore, the number of preterm PE cases ($n = 19$) and term PE cases ($n = 47$) remains the same at both time points. In panel B, the gray line represents the linear regression fitted to the data from this study, while the red line corresponds to the regression model previously published by Tan et al.[5], based on PlGF MoM values measured at or after 11 weeks of gestation.

model excluding this biomarker. Conversely, the model incorporating PlGF measurements obtained between 11 and 13^{+6} weeks consistently showed superior detection rates, discrimination, and calibration, supporting the clinical benefit of measuring PlGF within the standard recommended time frame.

A recent Danish multicenter study assessed the diagnostic performance of the FMF competing-risk model using serum PlGF measurements obtained at 8–9, 10, and 11–13^{+6} weeks of gestation.[20] The authors reported that incorporating PlGF measurements before 10 weeks did not significantly enhance the predictive capability of the PE screening model, highlighting the limited discriminative value of early first-trimester PlGF measurements, as previously noted by other researchers.[21,22] Nevertheless, PlGF values measured at 10 weeks yielded detection rates like those obtained with standard 11- to 13^{+6}-week measurements, suggesting a potential opportunity to slightly extend the screening window. Consistent with this, a secondary analysis from the same Danish cohort reported DRs of 68.8% for the model incorporating PlGF at 10–13^{+6} weeks and 67.3% when measured between 11 and 13^{+6} weeks, supporting the feasibility of extending PlGF screening to week 10.[23]

In another study by Mendoza et al.,[24] conducted in a Spanish population, no significant differences in detection rates for preterm PE screening models incorporating PlGF measurements before and after 11 weeks were found. The authors concluded that early measurement of PlGF could support a two-step screening approach without compromising predictive accuracy. However, that study involved relatively few cases of preeclampsia and thus lacked sufficient statistical power to definitively conclude that PlGF measurements before 11 weeks are equivalent in predictive value to those obtained between 11 and 13^{+6} weeks.

Differences observed among these studies may be attributed to variations in study populations, assay platforms, PlGF estimation models, and methodological approaches. These discrepancies underscore the necessity for additional validation studies in diverse populations to clarify the clinical utility and optimal timing for early PlGF measurement in preterm preeclampsia screening.

The DRs of preterm PE obtained with the model incorporating PlGF measurements between 11 and 13^{+6} weeks were similar to those previously reported in the literature.[5,8,25] However, the limited predictive value observed for PlGF measured before 11 weeks may be explained by physiological factors related to placental oxygenation. Between 8 and 10 weeks of gestation, placental oxygen tension is physiologically low due to the plugging of spiral arteries by extravillous trophoblast cells, suppressing PlGF gene expression and leading to low serum PlGF levels.[26,27] Toward the end of the first trimester, the progressive loss of these trophoblastic plugs increases

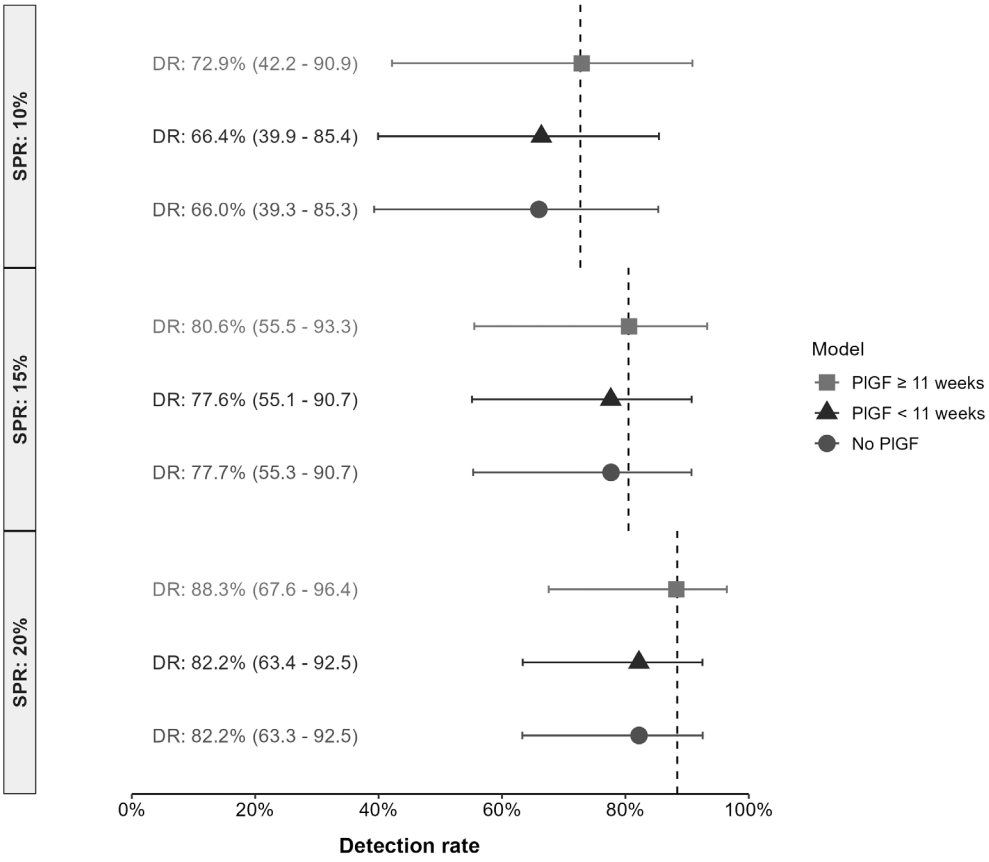

FIGURE 2 Detection rates (DR) for preterm preeclampsia by screening model at fixed screen-positive rates (SPR), adjusted for aspirin use. The vertical dashed reference lines indicate detection rates previously reported by other studies at fixed SPR: 72.7% at 10% SPR, 80.5% at 15% SPR, and 88.3% at 20% SPR, as published by prior research.[8] Values in parentheses are 95% CI.

placental oxygen availability, enhancing PlGF expression and allowing clearer discrimination of pathologically low PlGF levels among pregnancies at risk for preeclampsia.

The use of early PlGF measurements did not substantially enhance the predictive performance of the screening model compared to a model without PlGF. Therefore, the routine implementation of early PlGF testing cannot currently be recommended, particularly considering potential implications related to cost-effectiveness and clinical logistics. Although other authors[20,22,23] have suggested extending the screening window slightly earlier, up to 10 weeks of gestation, the limited sample sizes of these studies highlight the need for additional research to strengthen the evidence supporting this practice.

Our study also reported detection rates for preterm preeclampsia using the model without PlGF at higher screening thresholds (SPR of 15% and 20%). Decision-curve analyses performed by other authors suggest that probability thresholds up to 20% may offer greater net clinical benefit compared with a strategy of treating all patients with aspirin prophylaxis.[28] Therefore, in clinical settings with a low incidence of preterm preeclampsia, higher screening thresholds could be adopted, achieving detection rates as high as 77.7% and 82.2% at screen-positive rates of 15% and 20%, respectively.

The main strength of this study is its multicenter prospective design with longitudinal paired PlGF measurements in the same women before and after 11 weeks, enhancing the representativeness of our Spanish cohort and providing a realistic reflection of maternal characteristics and biomarker distributions. All centers adhered to standardized FMF-certified protocols with monthly audits to ensure protocol compliance and biomarker quality control. Additionally, we implemented three PlGF assay platforms (Cobas e801, BRAHMS KRYPTOR, DELFIA Xpress) across gestational windows, enabling a unified platform-agnostic MoM transformation that generalizes beyond specific analytical systems or sampling times. Finally, we addressed the potential influence of aspirin use on screening performance through appropriate statistical adjustments.

The main limitation of this study is the relatively small number of preterm PE cases, which limits the statistical power to detect subtle differences between screening models. Although our performance estimates are consistent with those reported in similar populations, the small sample size warrants cautious interpretation of the findings. Additionally, PE was defined according to ACOG criteria, which differ slightly from the International Society for the Study of Hypertension in Pregnancy definitions used in other FMF validation studies. This discrepancy may have led to a lower number of diagnosed cases and could partially explain variations in predictive performance across studies.

5 | CONCLUSION

Early measurement of PlGF before 11 weeks of gestation showed limited added predictive value for screening preterm PE and did not substantially improve the performance compared with a model excluding PlGF. Given the small number of preterm PE cases in our study, these findings should be interpreted with caution. Further studies with larger case numbers are needed to validate whether extending the screening window to 10 weeks could enhance predictive accuracy. In settings where PlGF measurement between 11 and 13^{+6} weeks is not feasible, screening based on maternal factors and biophysical markers, using screen-positive rate cutoffs of 15% or 20%, may represent a reasonable alternative strategy.

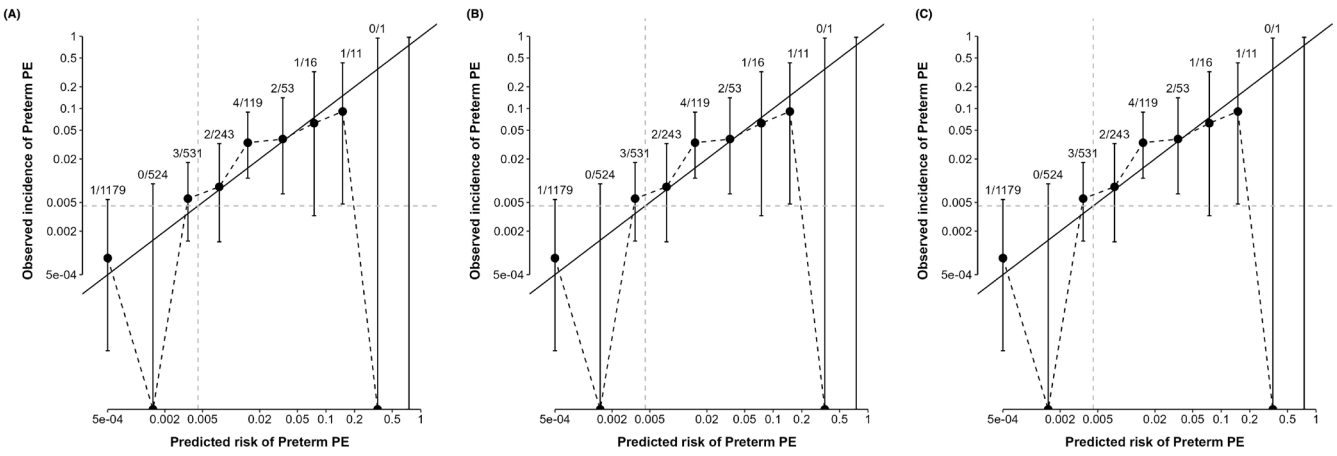

FIGURE 3 Calibration plots comparing predicted and observed risks of preterm preeclampsia in screening models without PlGF (A), with PlGF measured before 11 weeks (B), and with PlGF measured between 11 and 13^{+6} weeks (C). Calibration plots for each screening model illustrate the agreement between predicted and observed risk of preterm PE. The *x*-axis represents the predicted risk within predefined risk intervals, and the *y*-axis shows the corresponding observed incidence. Each dot indicates the observed incidence of preterm PE within a given risk interval, with vertical lines representing 95% confidence intervals. The fractions above the points denote the number of preterm PE cases relative to the number of women in each interval. The diagonal line represents perfect calibration, where predicted risk equals observed incidence. Deviations from this line indicate under- or overestimation by the model.

AUTHOR CONTRIBUTIONS

Rocío López Mármol: Data curation, formal analysis, investigation, writing—original draft, and writing—review and editing. **José Alejandro Ávila Cabreja:** Formal analysis, methodology, software, visualization, writing—original draft, and writing—review and editing. **Teresa de Haro Romero:** Data curation, formal analysis, investigation, and writing—review and editing. **Catalina de Paco Matallana** and **Juan Luis Delgado:** Data curation and investigation. **Olga Ocón Hernández:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, and writing—original draft. **Otilia González-Vanegas**, **Pilar Carretero Lucena**, and **María Paz Carrillo:** Data curation, investigation, and writing—review and editing. **Valeria Rolle:** Data curation, investigation, and validation. **Uzay Gormus** and **Liza Oraha:** Investigation and validation. **María M. Gil:** Conceptualization, funding acquisition, resources, supervision, validation, and writing—review and editing. **Francisca S. Molina:** Conceptualization, formal analysis, funding acquisition, investigation, project administration, supervision, and writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

Two authors (U.G. and L.O.) are employees of Revvity Omics Sweden (Sollentuna, Sweden), which provided reagents, analytical instrumentation, and human resources for the serum biomarker analyses conducted in this study. The remaining authors declare no other relevant conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The study was approved by the Research Ethics Committee of Granada (registration number: 1916-N-20) on October 28, 2020. The study was conducted in compliance with General Data Protection Regulation 2016/679 and Spanish Organic Law 3/2018 on Personal Data Protection and Guarantee of Digital Rights, to safeguard participants' rights and privacy.

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REFERENCES

1. Rolnik DL, Nicolaides KH, Poon LC. Prevention of preeclampsia with aspirin. *Am J Obstet Gynecol*. 2022;226(2):S1108-S1119. https://www.ajog.org/action/showFullText?pii=S0002937820308735
2. Cuenca-Gómez D, de Paco MC, Rolle V, et al. Performance of first-trimester combined screening for preterm pre-eclampsia: findings from cohort of 10 110 pregnancies in Spain. *Ultrasound Obstet Gynecol*. 2023;62(4):522-530. doi:10.1002/uog.26233
3. Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. *Am J Obstet Gynecol*. 2018;218(3):287-293.e1. https://www.ajog.org/action/showFullText?pii=S0002937817323268
4. Wang Y, Guo X, Obore N, Ding H, Wu C, Yu H. Aspirin for the prevention of preeclampsia: a systematic review and meta-analysis of randomized controlled studies. *Front Cardiovasc Med*. 2022;9:936560. https://pmc.ncbi.nlm.nih.gov/articles/PMC9682183/
5. Tan MY, Syngelaki A, Poon LC, et al. Screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation. *Ultrasound Obstet Gynecol*. 2018;52(2):186-195. doi:10.1002/uog.19112
6. Crovetto F, Figueras F, Triunfo S, et al. First trimester screening for early and late preeclampsia based on maternal characteristics, biophysical parameters, and angiogenic factors. *Prenat Diagn*. 2015;35(2):183-191. doi:10.1002/pd.4519
7. Serra B, Mendoza M, Scazzocchio E, et al. A new model for screening for early-onset preeclampsia. *Am J Obstet Gynecol*. 2020;222(6):608.e1-608.e18. https://www.ajog.org/action/showFullText?pii=S0002937820300272
8. Cuenca-Gómez D, De Paco MC, Rolle V, et al. Comparison of different methods of first-trimester screening for preterm pre-eclampsia: cohort study. *Ultrasound Obstet Gynecol*. 2024;64(1):57-64. doi:10.1002/uog.27622
9. Roberts L, Chaemsaithong P, Sahota DS, Nicolaides KH, Poon LCY. Protocol for measurement of mean arterial pressure at 10–40 weeks' gestation. *Pregnancy Hypertens*. 2017;10:155-160.

10. Khalil A, Nicolaides KH. How to record uterine artery Doppler in the first trimester. *Ultrasound Obstet Gynecol*. 2013;42(4):478-479. doi:10.1002/uog.12366
11. Gestational hypertension and preeclampsia: ACOG Practice Bulletin, Number 222. *Obstet Gynecol*. 2020;135(6):E237-E260. https://journals.lww.com/greenjournal/fulltext/2020/06000/gestational_hypertension_and_preeclampsia__acog.46.aspx
12. Chaemsaithong P, Pooh RK, Zheng M, et al. Prospective evaluation of screening performance of first-trimester prediction models for preterm preeclampsia in an Asian population. *Am J Obstet Gynecol*. 2019;221(6):650.e1-650.e16.
13. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. 2024. https://www.R-project.org/
14. Wickham H, Averick M, Bryan J, et al. Welcome to the tidyverse. *J Open Source Softw*. 2019;4(43):1686.
15. Sjoberg DD, Whiting K, Curry M, Lavery JA, Larmarange J. Reproducible summary tables with the gtsummary package. *R J*. 2021;13(1):570-580. doi:10.32614/RJ-2021-053
16. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *J Stat Softw*. 2015;67(1):1-48.
17. Lüdecke D. sjPlot: Data Visualization for Statistics in Social Science [Internet]. 2024. https://CRAN.R-project.org/package=sjPlot
18. Calcagno V. glmulti: Model Selection and Multimodel Inference Made Easy [Internet]. 2020. https://CRAN.R-project.org/package=glmulti
19. Greifer N. WeightIt: Weighting for Covariate Balance in Observational Studies [Internet]. 2024. https://CRAN.R-project.org/package=WeightIt
20. Riishede I, Ekelund CK, Sperling L, et al. Screening for pre-eclampsia with competing-risks model using placental growth factor measurement in blood samples collected before 11 weeks' gestation. *Ultrasound Obstet Gynecol*. 2024;63(3):342-349. doi:10.1002/uog.27462
21. Kuc S, Koster MPH, Franx A, Schielen PCJI, Visser GHA. Maternal characteristics, mean arterial pressure and serum markers in early prediction of preeclampsia. *PLoS One*. 2013;8(5):e63546. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0063546
22. Mosimann B, Amylidi-Mohr S, Höland K, Surbek D, Risch L, Raio L. Importance of timing first-trimester placental growth factor and use of serial first-trimester placental growth factor measurements in screening for preeclampsia. *Fetal Diagn Ther*. 2017;42(2):111-116. doi:10.1159/000455946
23. Rode L, Wright A, Wright D, et al. Screening for pre-eclampsia using pregnancy-associated plasma protein-A or placental growth factor measurements in blood samples collected at 8–14 weeks' gestation. *Ultrasound Obstet Gynecol*. 2025;65:567-574.
24. Mendoza M, Garcia-Manau P, Arévalo S, et al. Diagnostic accuracy of first-trimester combined screening for early-onset and preterm pre-eclampsia at 8–10 compared with 11–13 weeks' gestation. *Ultrasound Obstet Gynecol*. 2021;57(1):84-90. doi:10.1002/uog.22071
25. O'Gorman N, Wright D, Syngelaki A, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. *Am J Obstet Gynecol*. 2016;214(1):103.e1-103.e12.
26. Khaliq A, Dunk C, Jiang J, et al. Hypoxia down-regulates placenta growth factor, whereas fetal growth restriction up-regulates placenta growth factor expression: Molecular evidence for "placental hyperoxia" in intrauterine growth restriction. *Lab Investig*. 1999;79:151-170.
27. Gobble RM, Groesch KA, Chang M, Torry RJ, Torry DS. Differential regulation of human PlGF gene expression in trophoblast and non-trophoblast cells by oxygen tension. *Placenta*. 2009;30(10):869-875.
28. Poon LC, Wright D, Thornton S, Akolekar R, Brocklehurst P, Nicolaides KH. Mini-combined test compared with NICE guidelines for early risk-assessment for pre-eclampsia: the SPREE diagnostic accuracy study. *Efficacy Mech Eval*. 2020;7(8):1-156. https://www.ncbi.nlm.nih.gov/books/NBK564204/

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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