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ORIGINAL RESEARCH

Placental growth factor in early pregnancy: Gestational week-specific reference intervals and influence of maternal factors across three automated immunoassays in a Swedish cohort

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Abstract

Introduction: Placental growth factor (PlGF) is an established biomarker for first-trimester preeclampsia prediction. However, concentrations vary between assay platforms due to calibration and methodological differences. Gestational age-specific PlGF reference intervals are limited. We aimed to derive gestational week-specific PlGF reference intervals across three platforms and to assess factors associated with PlGF concentrations in a Swedish population.

Material and Methods: This descriptive cross-sectional study used data from the Swedish IMPACT cohort. Blood samples collected at 11 + 0 to 14 + 6 weeks were analyzed for PlGF on Revvity, Roche Diagnostics, and Thermo Fisher Scientific platforms.

Abbreviations: CI, confidence interval; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; IQR, interquartile range; MoM, multiple of the median; PlGF, placental growth factor; R^2, coefficient of determination; SD, standard deviation.

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A reference subgroup of uncomplicated singleton pregnancies was used to derive gestational week-specific reference intervals. Associations between maternal and pregnancy-related factors and PlGF were examined in the full study population using log-linear regression. Variable importance was assessed using Shapley values.

Results: Of 12 908 IMPACT participants, 12 099 had a valid PlGF measurement and were included in the study population. The healthy reference subgroup comprised 7719 participants. In this subgroup, PlGF concentrations rose 23% per week across platforms. At 11 + 0 to 11 + 6 weeks, reference intervals (2.5th–97.5th percentiles) were 6.0–50.8 ng/L for Revvity, 16.4–67.7 ng/L for Roche, and 10.0–51.0 ng/L for Thermo Fisher. At 12 + 0 to 12 + 6 weeks, intervals were 8.9–69.5, 18.1–84.8, and 16.0–75.0 ng/L, respectively. At 13 + 0 to 13 + 6 weeks, intervals were 10.4–82.8, 22.2–105.5, and 20.0–98.0 ng/L. At 14 + 0 to 14 + 6 weeks, intervals were 27.4–149.7 ng/L for Roche and 27.0–133.0 ng/L for Thermo Fisher; no reference interval was established for Revvity due to limited sample size ($n < 40$).

In the full study population, smoking (+53%), Afro-Caribbean origin (+49%), and non-monochorionic multiple pregnancies (+43%) were associated with higher PlGF concentrations, while parous women had lower levels (−32% with and − 24% without prior preeclampsia). The multivariable model explained 27% of the total variance, with gestational age, assay platform, and smoking contributing most.

Conclusions: PlGF reference intervals in early pregnancy differ by gestational week and assay platform. These data, together with knowledge of factors influencing PlGF concentrations, support the development and validation of gestational age- and platform-specific interpretation in early pregnancy screening models.

KEYWORDS
assay comparison, first-trimester screening, immunoassay platforms, placental growth factor, preeclampsia, reference intervals

1 | INTRODUCTION

Preeclampsia affects 2–6% of pregnancies and remains a leading cause of maternal and perinatal morbidity and mortality worldwide.[1] Early identification of women at increased risk enables timely interventions that improve both maternal and neonatal outcomes. Prophylactic low-dose acetylsalicylic acid initiated before 20 weeks of gestation reduces the incidence of preterm preeclampsia.[2] Several multivariable prediction models have been developed for first-trimester screening, incorporating maternal characteristics, medical history, physical examinations, and blood-based biomarkers.

Placental growth factor (PlGF), a proangiogenic protein involved in placental development, is a key biomarker for preeclampsia. Low maternal circulating PlGF levels in early pregnancy are associated with increased risk of preeclampsia, fetal growth restriction, and stillbirth.[3] Consequently, PlGF has been incorporated into several prediction models for preeclampsia and other pregnancy-related complications.[4–6]

Previous studies comparing PlGF concentrations across assay platforms have shown strong correlations but also systematic differences in calibration, making clinical cut-offs difficult to apply across platforms.[7–9] In addition, PlGF concentrations are influenced by maternal and pregnancy-related factors, such as gestational age at sampling, maternal age and weight, ethnicity, smoking, and diabetes.[10] Obstetric history, including gestational age at previous birth and offspring birth weight, has also been associated with PlGF concentrations.[10]

A prerequisite for clinical measurement of any biomarker is the availability of population-specific reference intervals. While some manufacturers provide reference data and median values within their instructions for use, independent gestational week-specific

Key message

PlGF concentrations in early pregnancy vary substantially by gestational week and assay platform and are influenced by maternal characteristics. This large multicenter study provides reference intervals that account for gestational age and platform differences, highlighting the importance of context-specific PlGF interpretation.

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reference intervals that allow comparison across platforms and populations remain limited.

The aims of this study were to (1) establish gestational week-specific reference intervals for PlGF concentrations between 11+0 and 14+6 weeks of gestation across three widely used clinical assay platforms (Revvity, Roche Diagnostics, and Thermo Fisher Scientific), and (2) evaluate the influence of maternal and pregnancy-related variables on PlGF concentrations in early pregnancy within a Swedish population.

2 | MATERIAL AND METHODS

This descriptive cross-sectional study was conducted within the Swedish study for Improving Maternal Pregnancy And Child ouTcomes (IMPACT) cohort (ClinicalTrials.gov NCT03831490),[11] a prospective multicenter cohort study aimed to develop and validate biomarkers and prediction models for pregnancy complications. Between November 2018 and December 2022, pregnant women were enrolled during their routine first-trimester ultrasound examination (11+0 to 14+6 weeks of gestation) across seven Swedish regions: Dalarna, Skåne, Stockholm, Uppsala, Värmland, Västra Götaland, and Örebro. Gestational age was determined by ultrasound biometry, using fetal crown-rump length or biparietal diameter if ≥21 mm. Exclusion criteria were maternal age < 18 years at enrollment or inability to understand the study information and provide informed consent due to persistent language barriers despite interpreter support. Written information was available in 11 languages. Demographic, medical, and obstetric data were collected through structured interviews and clinical examinations. Additional information was retrieved from the Swedish Pregnancy Register, a national quality register introduced in 2014 containing demographic, medical, and obstetric data and covering >98% of deliveries in Sweden.[12] The IMPACT protocol has been published previously.[11]

The study population for the current analysis included all participants in the IMPACT study cohort with valid PlGF measurements obtained within ±3 days of the ultrasound examination and confirmed dating between 11+0 and 14+6 weeks of gestation. Participants with missing or invalid PlGF measurements were excluded. To establish PlGF reference intervals representative of uncomplicated singleton pregnancies, a healthy reference subgroup was defined by excluding participants with maternal conditions or pregnancy characteristics or outcomes known or considered likely to influence placental function or early pregnancy PlGF concentrations. Accordingly, women with chronic maternal conditions (e.g., cardiovascular disease, autoimmune disorders, pregestational diabetes), hypertensive disorders, treatment with insulin or metformin, assisted reproduction, multiple pregnancy, smoking in early pregnancy, preterm birth, low birth weight, stillbirth, or loss to follow-up were excluded from the reference population (Table S1).

Blood samples were collected at study inclusion and stored at −80°C in biobanks at the respective sites, in accordance with the Biobank Sweden protocol and under the governance of Biobank Sweden, until analysis. For PlGF measurement, samples were thawed, mixed, and analyzed in Turku (Finland), Uppsala, and Gothenburg using the Revvity, Roche Diagnostics, and Thermo Fisher Scientific platforms, respectively. Samples from Stockholm were shipped to Turku, where the AutoDELFIA® immunoassay system (Revvity, Turku, Finland) was used. In Uppsala, the Cobas® 6000, e601 electrochemiluminescence system (Roche Diagnostics GmbH, Mannheim, Germany) was used, and in Gothenburg, the BRAHMS PlGF plus assay on a KRYPTOR® compact PLUS instrument (Thermo Fisher Scientific, Hennigsdorf, Germany) was used. The Uppsala laboratory also analyzed samples collected from Dalarna, Skåne, Värmland, and Örebro. Revvity analyses were performed in August 2020, from July to December 2021, and in March 2023. Roche analyses were performed at approximately six-month intervals, whereas Thermo Fisher analyses were performed at approximately monthly intervals.

The influence of maternal characteristics and medical and obstetric history on PlGF concentrations from 11+0 to 14+6 weeks of gestation was evaluated in the study population. Variables analyzed were selected based on associations reported in previous studies.[10] Maternal characteristics included maternal early pregnancy age, weight, ethnicity, and smoking status. Medical conditions and treatments included a diagnosis of diabetes and treatment with insulin or metformin. Reproductive factors included in-vitro fertilization, use of ovulation induction drugs, and parity (nulliparous, parous with or without previous preeclampsia). Pregnancy characteristics included gestational age at blood sampling and plurality/chorionicity (singleton, monochorionic twin pregnancy, or non-monochorionic multiple pregnancy). In addition, assay platform (Revvity, Roche, Thermo Fisher) was included as a technical variable.

2.1 | Statistical analyses

Descriptive data were presented as means with standard deviations (SDs) or medians with interquartile ranges (IQRs) for continuous variables, and as counts with percentages for categorical variables.

Median PlGF concentrations and reference intervals (2.5th and 97.5th percentiles) were estimated non-parametrically by gestational week and assay platform, with 90% confidence intervals (CIs), in accordance with Clinical and Laboratory Standards Institute guideline EP28-A3c.[13] CIs for the reference limits were obtained using the non-parametric bootstrap percentile method with 1000 replicates. Outliers were assessed using Dixon's range statistic. Reference intervals were not calculated for subgroups with fewer than 40 participants, as percentile-based reference limits cannot be reliably estimated in very small subgroups.

To evaluate associations between maternal and pregnancy-related factors and PlGF concentrations, multivariable linear regression models were applied using natural log-transformed PlGF as the outcome. Results were reported as fold changes (geometric mean ratios) with 95% CIs, representing the multiplicative change in PlGF concentration per unit increase in each explanatory variable,

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obtained by exponentiating the estimated regression coefficients. Analyses were conducted separately for each assay platform, and a combined model including interaction terms was used to assess potential differences in associations across platforms.

Variable importance was assessed using Shapley value decomposition, which partitions the total model R^2 (coefficient of determination) into the marginal contributions of each predictor.

Statistical analyses were performed using R software, version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria). Reference intervals were calculated using RefVal 4.0 (SourceForge), in accordance with recommendations from the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).[14,15] Variable importance was assessed using the domir R package (version 1.2.0).

3 | RESULTS

A total of 12908 individuals were enrolled in the IMPACT cohort. For this cross-sectional study, 809 were excluded due to missing or invalid PlGF data. This resulted in 12099 participants with valid PlGF measurements in the current study population (Table 1). Out of these, 4380 individuals had predefined major maternal comorbidities or complications leading to exclusion from the healthy reference subgroup (Table S1), resulting in a healthy reference subgroup of 7719 participants.

In the study population, the mean (SD) maternal age was 31.7 (4.7) years, mean weight was 71.1 (14.2) kg, and median (IQR) gestational age at examination was 12+6 weeks of gestation (12+4 to 13+2). Overall, 10805 (89.3%) of participants were of European origin, nulliparous women accounted for 5576 (46%), and 455 (3.8%) were parous with a history of preeclampsia. Participants in the healthy reference subgroup were similar to the study population in baseline characteristics but had lower weight and BMI (Table 1).

A total of 2511 samples (20.8%) were analyzed using Revvity, 6452 (53.3%) using Roche, and 3136 (25.9%) using Thermo Fisher. Participant characteristics were generally similar across assay platforms, although participants analyzed with the Roche platform were younger, more frequently of European origin, and more likely to report smoking in early pregnancy, whereas those analyzed with the Revvity platform had lower mean weight and body mass index (Tables S2 and S3).

In the healthy reference subgroup, raw (unadjusted) PlGF concentrations increased by 23% per week (95% CI, 21–25%) between 11+0 and 14+6 weeks of gestation (Figure 1). For the Revvity platform, median PlGF concentrations rose from 25.6 ng/L at 11+0 to 11+6 weeks to 44.5 ng/L at 14+0 to 14+6 weeks. For Roche Diagnostics, the corresponding increase was from 36.0 to 63.5 ng/L, and for Thermo Fisher Scientific, from 31.0 to 60.0 ng/L. Week-specific median values for each assay platform are presented in Table 2. Comparable changes were observed in the study population overall, where raw PlGF concentrations increased by 23% per week (95% CI, 22–25%) over the same gestational interval.

No outliers were identified in the distribution of PlGF concentrations. For the Revvity platform, reference intervals (2.5th–97.5th percentiles) were 6.0–50.8 ng/L at 11+0 to 11+6 weeks, 8.9–69.5 ng/L at 12+0 to 12+6 weeks, and 10.4–82.8 ng/L at 13+0 to 13+6 weeks. Reference intervals were not established for 14+0 to 14+6 weeks due to insufficient sample size ($n=10$). For Roche Diagnostics, the corresponding reference intervals were 16.4–67.7, 18.1–84.8, 22.2–105.5, and 27.4–149.7 ng/L at gestational weeks 11, 12, 13, and 14, respectively. For Thermo Fisher Scientific, intervals ranged from 10.0–51.0 ng/L at 11 weeks, to 16.0–75.0 ng/L at 12 weeks, 20.0–98.0 ng/L at 13 weeks, and 27.0–133.0 ng/L at 14 weeks of gestation (Table 2).

In multivariable analyses including the full study population, PlGF concentrations were 53% higher among smokers (95% CI, 47–61%) compared with non-smokers. Higher levels were also observed among women of Afro-Caribbean origin (+49%, 41–58%), South Asian origin (+26%, 19–33%), and Middle Eastern origin (+12%, 7–16%) relative to those of European background. Non-monochorionic multiple pregnancies were associated with a 43% (26–63%) increase in PlGF concentrations, whereas no association with PlGF was observed for monochorionic twin pregnancies. Maternal age was associated with a 2% (1–3%) increase in PlGF per 5-year increment, while maternal weight was associated with a 3% (3–4%) decrease per 10 kg increment. PlGF concentrations were 32% (15–45%) lower in parous women with a history of preeclampsia and 24% (5–39%) lower in parous women without such a history compared to nulliparous women (Figure 2). Associations were generally similar across platforms, although some evidence of between-platform differences was observed for maternal weight, smoking, and chorionicity (Table S4).

Gestational age at sampling and assay platform explained the largest proportions of variation in log-transformed PlGF concentrations, accounting for 10.4% and 8.3% of total model R^2, respectively. Smoking contributed 2.7%, followed by ethnicity (2.2%), maternal weight (1.0%), and birth weight in the most recent pregnancy (0.8%). All remaining variables, including maternal age, parity, and chorionicity, each explained less than 1% of the variation. Overall, the evaluated variables accounted for 26.8% of the variance in PlGF concentrations (Figure 3).

4 | DISCUSSION

In this large, multicenter cross-sectional descriptive study, we established gestational week-specific reference intervals for PlGF in early pregnancy in a healthy reference subgroup of women with uncomplicated singleton pregnancies across three widely used commercial immunoassay platforms. Distributions of PlGF differed systematically between samples analyzed using the Revvity, Roche Diagnostics, and Thermo Fisher Scientific assay platforms,

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TABLE 1 Maternal demographics, medical history, and obstetric characteristics in the study population overall, and in the healthy reference subgroup.

	Study population overall ($n = 12\,099$)	Healthy reference subgroup ($n = 7719$)
Maternal characteristics		
Maternal age (years)	31.7 (4.7)	31.4 (4.5)
Height (cm)	167.0 (6.4)	167.0 (6.3)
Weight (kg)	71.1 (14.2)	69.3 (12.8)
Body mass index (kg/m^2)	25.5 (4.8)	24.8 (4.3)
Gestational age at examination (weeks + days)	12 + 6 (12 + 4, 13 + 2)	12 + 6 (12 + 4, 13 + 2)
Ethnicity		
European	10 805 (89.3%)	6884 (89.2%)
Afro-Caribbean	251 (2.1%)	166 (2.2%)
Middle Eastern	481 (4.0%)	332 (4.3%)
South Asian	238 (2.0%)	143 (1.9%)
East Asian	147 (1.2%)	89 (1.2%)
Mixed/other/unknown	177 (1.5%)	105 (1.4%)
Mode of conception		
Spontaneous	11 285 (93.3%)	7719 (100.0%)
In-vitro fertilization	784 (6.5%)	0 (0.0%)
Ovulation induction	30 (0.2%)	0 (0.0%)
Chorionicity		
Singleton	12 041 (99.5%)	7719 (100.0%)
Monochorionic twin pregnancy	13 (0.1%)	0 (0.0%)
Non-monochorionic multiple pregnancy	45 (0.4%)	0 (0.0%)
Smoking in early pregnancy	356 (2.9%)	0 (0.0%)
Medical history		
Chronic hypertension	130 (1.1%)	0 (0.0%)
Diabetes mellitus type 1	142 (1.2%)	0 (0.0%)
Diabetes mellitus type 2	53 (0.4%)	0 (0.0%)
Obstetric history		
Nulliparous	5576 (46.1%)	3336 (43.2%)
Parous without preeclampsia	6068 (50.2%)	4209 (54.5%)
Parous with preeclampsia	455 (3.8%)	174 (2.3%)
Gestational age at delivery of last pregnancy (weeks + days)	40 + 0 (39 + 0, 40 + 6)	40 + 1 (39 + 1, 41 + 0)
Birth weight of the neonate in the previous pregnancy (g)	3490 (560)	3500 (540)

Note: Data are presented as mean (standard deviation) or median (interquartile range) for continuous variables, and as counts with percentages for categorical variables. The healthy reference population was derived by excluding individuals with chronic medical conditions (e.g., cardiovascular disease, diabetes, autoimmune disorders), pregnancy complications (e.g., preeclampsia, gestational hypertension, preterm delivery), smoking, assisted reproductive technologies, multiple gestation, and other factors potentially influencing placental function or placental growth factor levels, as detailed in Table S1.

underscoring the need for platform-specific reference data for accurate interpretation. While some assay manufacturers provide gestational age-specific median values and reference data within their instructions for use, independent reference intervals that allow comparison across platforms and populations remain limited. This is particularly relevant in the Swedish context, where different assay platforms are used across regions, and consistent interpretation is essential for reliable first-trimester risk prediction.

Few studies have reported raw PlGF concentrations and reference intervals in early pregnancy; those that exist typically present values pooled across wider gestational age ranges, and data from European populations remain limited.[16,17] A recent study from Indonesia reported higher reference intervals for gestational weeks 11 to 14 combined, using the Roche assay platform, with a median concentration of 50.4 ng/L (range 1.1–265.2).[17] These higher values align with our observation that South Asian origin was associated

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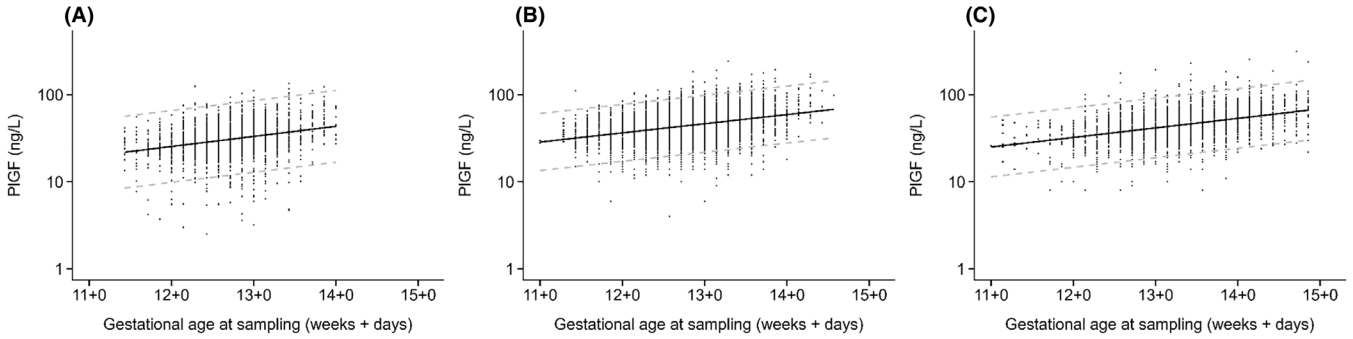

FIGURE 1 Placental growth factor (PlGF) concentrations from 11 + 0 to 14 + 6 weeks of gestation in the healthy reference population, stratified by assay platform. (A) Revvity (AutoDELFIA®); (B) Roche (Cobas); (C) Thermo Fisher (Kryptor). Points represent observed values, solid black lines show the fitted median PlGF curves, and dashed gray lines represent 95% prediction intervals.

TABLE 2 Gestational age-specific median values and reference intervals (2.5th and 97.5th percentiles) for placental growth factor (PlGF) concentrations (ng/L) measured using the Revvity, Roche, and Thermo Fisher platforms.

PlGF assay platform/gestational age (weeks + days)	Median (90% CI)	2.5th percentile (90% CI)	97.5th percentile (90% CI)
Revvity			
11 + 0–11 + 6 (*n* = 92)	25.6 (23.8, 27.3)	6.0 (2.1, 9.9)	50.8 (45.2, 56.5)
12 + 0–12 + 6 (*n* = 906)	30.6 (29.6, 31.4)	8.9 (7.3, 10.5)	69.5 (64.6, 74.4)
13 + 0–13 + 6 (*n* = 601)	36.8 (35.4, 38.5)	10.4 (8.8, 12.0)	82.8 (74.4, 91.1)
14 + 0–14 + 6 (*n* = 10)	44.5 (34.6, 70.0)	NA	NA
Roche			
11 + 0–11 + 6 (*n* = 282)	36.0 (34.0, 37.0)	16.4 (13.6, 19.1)	67.7 (62.0, 73.5)
12 + 0–12 + 6 (*n* = 2113)	42.0 (42.0, 43.0)	18.1 (17.1, 19.1)	84.8 (80.6, 89.0)
13 + 0–13 + 6 (*n* = 1612)	50.0 (49.0, 51.0)	22.2 (21.1, 23.4)	105.5 (99.8, 111.2)
14 + 0–14 + 6 (*n* = 72)	63.5 (58.0, 71.0)	27.4 (17.9, 36.9)	149.7 (113.8, 185.6)
Thermo Fisher			
11 + 0–11 + 6 (*n* = 57)	31.0 (28.0, 35.0)	10.0 (7.0, 14.0)	51.0 (50.0, 52.0)
12 + 0–12 + 6 (*n* = 565)	38.0 (36.0, 39.0)	16.0 (15.0, 17.0)	75.0 (68.0, 83.0)
13 + 0–13 + 6 (*n* = 1052)	46.0 (45.0, 47.0)	20.0 (19.0, 21.0)	98.0 (92.0, 104.0)
14 + 0–14 + 6 (*n* = 357)	60.0 (58.0, 63.0)	27.0 (26.0, 28.0)	133.0 (108.0, 159.0)

Note: Values are presented with 90% confidence intervals (CIs), calculated using the non-parametric bootstrap percentile method with 1000 resamples. The Revvity measurements were performed using the AutoDELFIA® immunoassay system, Roche using the Cobas® 6000, e601 electrochemiluminescence immunoassay, and Thermo Fisher using the Kryptor® immunofluorescence assay. Reference intervals were not calculated for Revvity at 14 + 0 to 14 + 6 weeks due to small sample size ($n < 40$).

Abbreviations: CI, confidence interval; NA, not available; PlGF, placental growth factor.

with higher PlGF concentrations. Unlike previous studies, our study provides gestational week-specific PlGF reference intervals across weeks 11 + 0 to 14 + 6. This corresponds to the period when most women undergo their first-trimester scan and when prediction models for preeclampsia are typically applied. In line with previous reports,[10,16] we observed a marked rise in PlGF concentrations with advancing gestational age during the first trimester, with an average increase of about 23% per week. These findings highlight the need for precise, week-specific reference intervals to support accurate clinical interpretation.

The reference intervals were derived from a subgroup of women with uncomplicated singleton pregnancies rather than from the overall obstetric population. Women with maternal comorbidities and future adverse pregnancy outcomes may differ with respect to early pregnancy PlGF concentrations and were therefore excluded from the reference subgroup. A more unselected obstetric population would provide a description of PlGF concentrations in routine obstetric practice but would be less suited to defining physiological reference values.

Associations between PlGF and maternal characteristics such as smoking, ethnicity, parity, and chorionicity were broadly consistent with previous studies.[10,18,19] Smoking and non-monochorionic multiple pregnancy were associated with higher concentrations, whereas parous women, particularly those with previous preeclampsia, had

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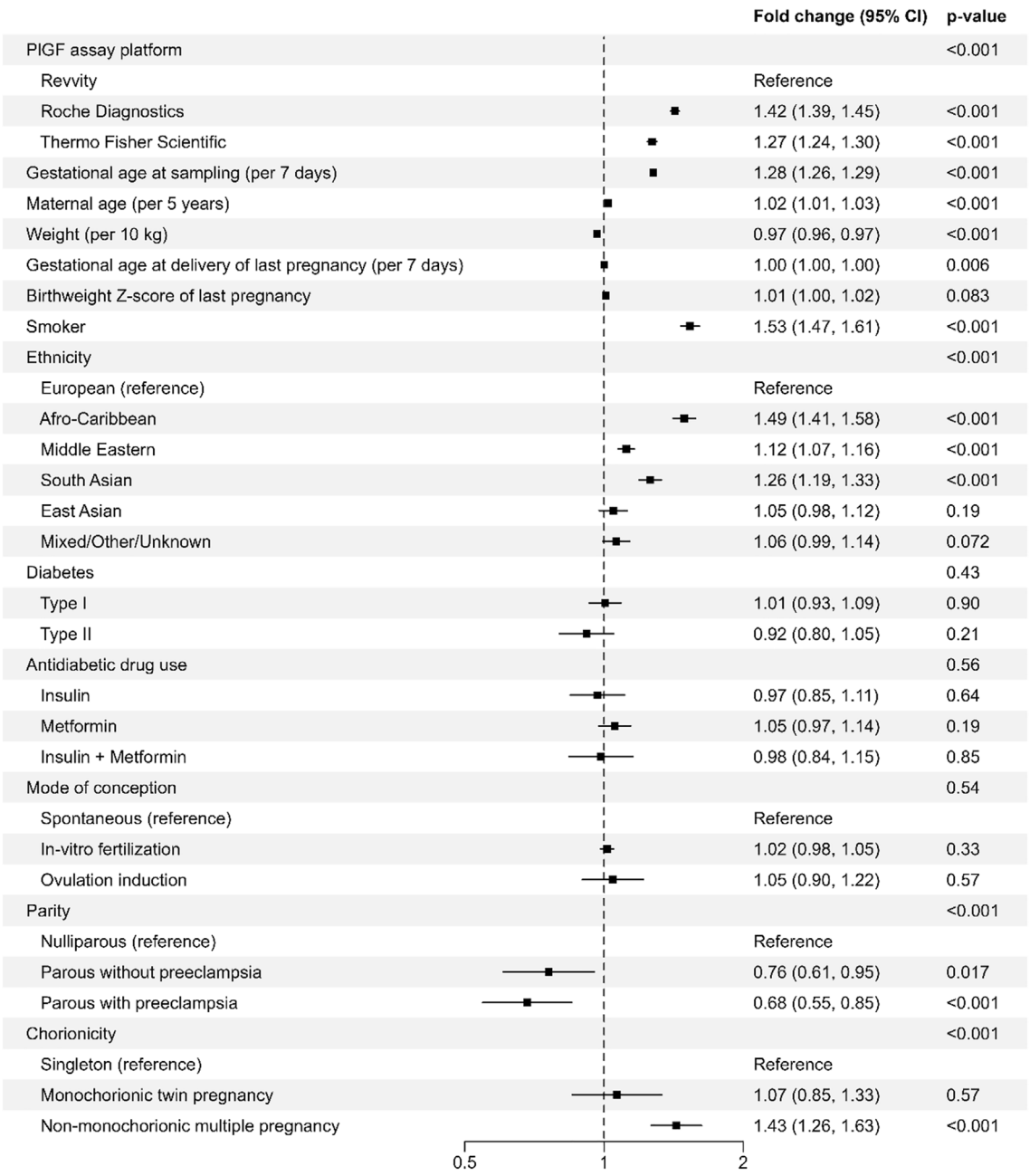

FIGURE 2 Adjusted fold changes (geometric mean ratios) in placental growth factor (PlGF) concentrations from multivariable analyses for maternal and pregnancy-related factors in the study population overall, combining all assay platforms. Points indicate estimated fold changes, and error bars represent 95% confidence intervals (CIs). Fold changes greater than 1 correspond to higher PlGF concentrations. The dashed vertical line represents no association (fold change = 1.0).

lower levels. In a large United Kingdom study, diabetes mellitus was identified as an independent determinant of PlGF.[10] In our cohort, pre-existing type 1 or type 2 diabetes mellitus was not associated with PlGF concentrations. This is consistent with findings from an Asian study in which diabetes was not included in the prediction model.[18] Overall, maternal and pregnancy-related factors explained only a modest proportion of the variance compared with gestational age and assay platform. The full model explained about 27% of the variation in PlGF concentrations, leaving approximately three-quarters unexplained. This indicates that other biological, technical, or unmeasured factors also contribute substantially to inter-individual variation. Nonetheless, maternal and pregnancy-related factors may still have substantial influence at the individual level and remain relevant for gestational age- and platform-specific interpretation of PlGF concentrations.

Together, our results provide supporting data for gestational age- and platform-specific interpretation of PlGF concentrations in early pregnancy. Gestational week- and platform-specific reference intervals are particularly important because PlGF rises rapidly in early pregnancy and differs systematically between samples analyzed using

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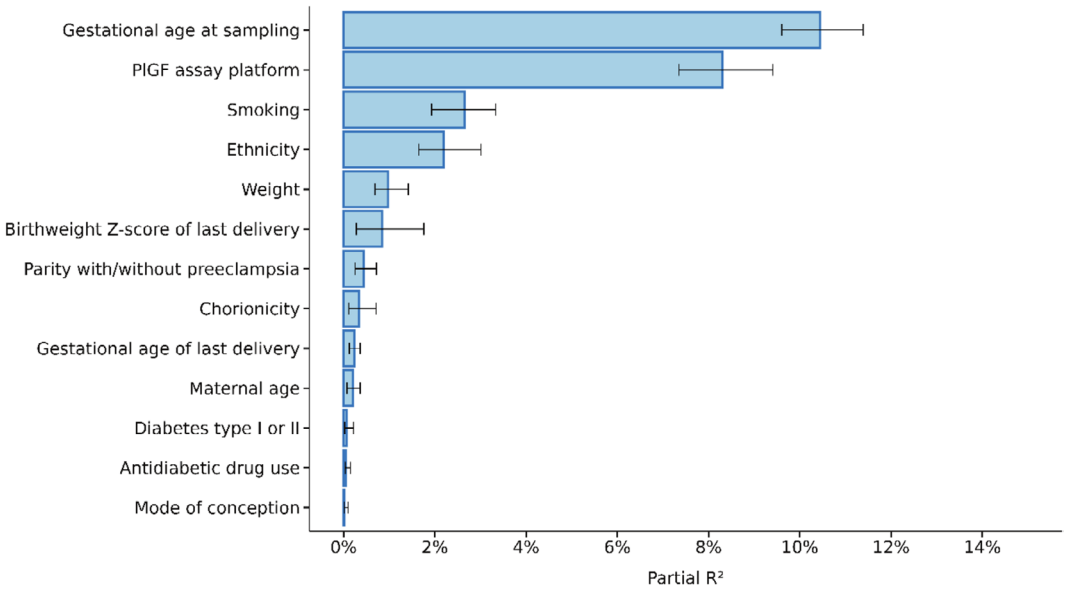

FIGURE 3 Variable importance of maternal and pregnancy-related factors for placental growth factor (PlGF) concentrations during 11 + 0 to 14 + 6 weeks of gestation. Bars represent the partial R^2 for each variable, indicating the proportion of total variation in log-transformed PlGF values explained by that factor. Variable importance was estimated using Shapley value decomposition of the total model R^2 (26.8%).

different assay platforms, making assay-specific reference values essential to avoid misclassification. The reference intervals characterize the expected distribution of PlGF concentrations and may support the development and validation of gestational age- and platform-specific approaches to PlGF interpretation in early gestation, as well as consistent clinical interpretation across assay platforms. These findings may help clinicians and laboratories harmonize reporting and interpretation across regions using different platforms and may also support timely identification of women who may benefit from preventive strategies such as low-dose acetylsalicylic acid.

Strengths of this study include the large sample size, multicenter recruitment, and analysis of samples on three widely used assay platforms, enabling the derivation of both assay- and gestational week-specific reference intervals. Standardized biobank handling and linkage to high-quality registry data further enhance validity. Limitations include the cross-sectional design, which precludes assessment of intra-individual changes over time, and limited sample sizes in certain subgroups, particularly for Revvity at later gestational weeks. The limited number of Revvity samples at 14 + 0 to 14 + 6 weeks reflects the regional organization of study inclusion. Revvity analyses were performed on samples from the Stockholm region, where participants were predominantly recruited in connection with first-trimester combined screening at 11 + 0 to 13 + 6 weeks. In addition, blood samples were collected from 11 + 0 weeks of gestation; therefore, the reference intervals do not cover earlier blood sampling that may occur as part of first-trimester screening. Because only one blood sample per participant was available, and each sample was analyzed on only one platform, direct within-sample comparisons across assays were not possible. Additionally, as each assay platform was linked to a specific laboratory, the observed differences between platforms may also partly reflect laboratory-specific factors, including sample handling and analytical procedures. Consequently, the observed differences cannot be attributed solely to the assay platform. Moreover, although the cohort was population-based, the representation of non-European ethnic groups was relatively small, which may limit the generalizability to populations with a different ethnic composition.

5 | CONCLUSION

This study established gestational week-specific reference intervals for PlGF in early pregnancy across three clinical assay platforms in a Swedish cohort. Gestational age and assay platform were the main determinants of PlGF concentrations, whereas maternal and pregnancy-related factors contributed modestly. These findings provide independent reference data to support gestational age- and platform-specific interpretation of PlGF concentrations in early pregnancy and the development and validation of early pregnancy screening models.

AUTHOR CONTRIBUTIONS

AL conceived the study and contributed to writing, reviewing, and editing the manuscript. HI contributed to the conceptualization, methodology, formal analysis, and drafting of the manuscript. KJ contributed to conceptualization, methodology, and writing of the original draft. VL performed the statistical analyses and contributed to reviewing and editing the manuscript. LB, YC, PC, MK, PL, AS, and AL are members of the IMPACT study steering group and ensured that the clinical study was conducted and monitored according to protocol. They also oversaw data acquisition for the cohort on which

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the present analysis is based. All authors reviewed and approved the final version of the manuscript.

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CONFLICTS OF INTEREST

Revvity, Roche Diagnostics, and Thermo Fisher Scientific provided reagents at no cost for the analyses of placental growth factor. LB has served as a speaker at an educational event organized by Thermo Fisher Scientific in 2024 and has consulted for DiaMedica. All other authors declare no 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

This study was conducted in accordance with the principles of the Declaration of Helsinki. The IMPACT study was approved by the Uppsala Regional Ethical Review Board (approval numbers and dates: 2018/231, 4 July 2018; 2018/231/1, 14 November 2018) and the Swedish Ethical Review Authority (approval numbers and dates: 2020-00319, 12 February 2020; 2021-05679-02, 22 December 2021; 2022-05690-02, 25 October 2022; 2023-01380-02, 15 March 2023; and 2025-00467-02, 24 February 2025). National biobank approval was obtained from Uppsala Biobank (reference 18237 2 2018 231). All participants provided written informed consent prior to inclusion. Data confidentiality was maintained through secure storage and encryption, in compliance with the General Data Protection Regulation (GDPR) and relevant ethical guidelines. This study is registered at ClinicalTrials.gov (Identifier NCT03831490; URL: https://clinicaltrials.gov/ct2/show/NCT03831490).

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