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A Prospective Cohort Study of the Value of Maternal Plasma Concentrations of Angiogenic and Anti-angiogenic Factors in Early Pregnancy and Midtrimester in the Identification of Patients Destined to Develop Preeclampsia

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Abstract

OBJECTIVE—Changes in the maternal plasma concentrations of angiogenic (such as PlGF and VEGF) and anti-angiogenic factors (such as sEng and sVEGFR-1) precede the clinical presentation of preeclampsia. This study was conducted to examine the role of maternal plasma PlGF, sEng and sVEGFR-1 concentrations in early pregnancy and midtrimester in the identification of patients destined to develop preeclampsia.

METHODS—This longitudinal cohort study included 1,622 consecutive singleton pregnant women. Plasma samples were obtained in early pregnancy (6–15 weeks) and midtrimester (20–25 weeks). Maternal plasma PlGF, sEng and sVEGFR-1 concentrations were determined using sensitive and specific immunoassays. The primary outcome was the development of preeclampsia. Secondary outcomes included term, preterm and early-onset preeclampsia. Receiving operating characteristic (ROC) curves, sensitivity, specificity, positive and negative likelihood ratios, and multivariable logistic regression were used for statistical analyses. A p-value of <0.05 was considered significant.

RESULTS—1) The prevalence of preeclampsia, term, preterm (<37 weeks) and early-onset preeclampsia (<34 weeks) was 3.8% (62/1,622), 2.5% (40/1,622), 1.4% (22/1,622) and 0.6% (9/1,622), respectively; 2) Higher likelihood ratios were provided by ratios of midtrimester plasma concentrations of PlGF, sEng, and sVEGFR-1 than single analytes; 3) Individual angiogenic and anti-angiogenic factors did not perform well in the identification of preeclampsia as a whole; in particular, they perform poorly in the prediction of term preeclampsia; 4) In contrast, a

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combination of these analytes such as the PlGF/sEng ratio, its delta and slope had the best predictive performance with a sensitivity of 100%, a specificity of 98%–99%, and likelihood ratios for a positive test of 57.6, 55.6 and 89.6, respectively, for predicting early-onset preeclampsia.

CONCLUSIONS—1) The PlGF/sEng ratio and its delta and slope had an excellent predictive performance for the prediction of early-onset preeclampsia, with very high likelihood ratios for a positive test result and very low likelihood ratios for a negative test result; and 2) Although the positive likelihood ratios are high and the positive predictive values low, the number of patients needed to be closely followed is 4:1 for the PlGF/sEng ratio and 3:1 for the slope of PlF/sEng.

Keywords

angiogenic factors; anti-angiogenic state; sFlt-1; sVEGFR-1; PlGF; placental growth factor; sEng; soluble Endoglin; vascular endothelial growth factor; prediction; cohort study; uterine artery Doppler velocimetry; early-onset preeclampsia

INTRODUCTION

Accumulating evidence suggests that an imbalance between circulating angiogenic factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), and anti-angiogenic factors such as soluble vascular endothelial growth factor receptor-1 [sVEGFR-1, also referred to as soluble fms-like tyrosine kinase 1 (sFlt1)] and the soluble form of Endoglin (sEng) is central to the pathophysiology of preeclampsia.[1–47] Indeed, patients with preeclampsia have higher plasma concentrations of sVEGFR-1[7–10,12,13,16,21,22,24,27,29,29,31,33,34,39,41,42,46,48] and sEng[25,30,34–36,42,45,46,48] and lower plasma concentration of VEGF[8,49] and PlGF[3,5,6,8,11,12,14,27,29,33,38,39,41,42,46,49–51] than patients with normal pregnancies at the time of the clinical diagnosis of preeclampsia. These differences have been observed even before the clinical presentation of the disease.[5,6,11,12,14,16,33,35,37,38,40,42,45,50,52–58] However, an anti-angiogenic state is not limited to patients with preeclampsia since it has also been described in those with small-for-gestational age (SGA) fetuses,[14,24,40,43,59–64] placental abruption,[65,66] “mirror syndrome,”[67,68] preeclampsia with parvovirus-induced hydrops,[69] molar pregnancy[70] and unexplained fetal death.[71]

Changes in the maternal plasma concentrations of angiogenic/anti-angiogenic factors[5,11,12,14,16] and abnormal uterine artery Doppler velocimetry (UADV)[72–77] are considered risk factors for the subsequent development of preeclampsia. It is possible that identification of patients at risk for preeclampsia associated with closer follow-up and prophylactic interventions may prevent or delay the clinical presentation of the disease and/or reduce its complications. Thus far, the determination of maternal plasma/serum concentrations of angiogenic and anti-angiogenic factors has been proposed as a promising tool that could help in the identification of women destined to develop preeclampsia. However, with the exception of a recent large cohort study that combines UADV and maternal plasma PlGF concentrations between 22 and 26 weeks of gestation,[32] all studies that have reported on predictive accuracy of angiogenic and anti-angiogenic factors differ in study design, sample size and inclusion of low- or high-risk populations. The objective of this study was to determine if individual maternal plasma PlGF, sEng, and sVEGFR-1 concentrations in early pregnancy and/or midtrimester, or a combination of them, can identify patients destined to develop preeclampsia, as well as term, preterm and early-onset preeclampsia in a cohort of unselected population.

MATERIAL AND METHODS

Study design

A longitudinal cohort study was conducted between March of 2003 and March 2006 to examine the role of angiogenic and anti-angiogenic factors in early pregnancy and midtrimester, in the identification of patients destined to develop preeclampsia. Secondary outcomes included subsequent development of term, preterm and early-onset preeclampsia. Patients included in this study were enrolled in a longitudinal protocol whose aim was to identify biochemical factors for the prediction of adverse pregnancy outcomes. All women were enrolled in the prenatal clinic at the Sotero del Rio Hospital, Santiago, Chile, and followed until delivery. Plasma samples were obtained at the time of each prenatal visit, scheduled at 4-week intervals from the first or early second trimester until delivery. In this study, we included two samples per patient: the first sample was obtained between 6 and 15 weeks of gestation ("early pregnancy") and the second sample between 20 and 25 weeks of gestation ("midtrimester"). Patients with multiple gestations or major fetal anomalies were excluded. In order to be able to compare the diagnostic performance of angiogenic factors to that of the uterine artery Doppler velocimetry (UADV), we also excluded patients without the information of the UADV between 20 to 25 weeks of gestation. During the study period, 2,495 pregnant women with a plasma sample collected in early pregnancy were included in our database. Of those, 1,917 had an additional plasma sample obtained in the midtrimester, and uterine artery Doppler velocimetry results in the second trimester were available in 1,713 of them. Ninety-one patients (5.3%) were lost of follow-up; thus, 1,622 patients were included for analysis.

Definitions

Preeclampsia was diagnosed in the presence of gestational hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) and proteinuria (≥300 mg in a 24-hour urine collection, two dipstick measurement of 1+ or one dipstick measurement ≥2+) according to ACOG[78] and the National High Blood Pressure Education Program.[79] Patients with preeclampsia were sub-classified as term preeclampsia (≥37 weeks), preterm preeclampsia (<37 weeks), and early-onset preeclampsia (≤34 weeks) according to the gestational age at which preeclampsia was diagnosed. SGA was defined as a birthweight <10th percentile for the gestational age at birth according to the Chilean birth weight distribution of a Hispanic population.[80]

All women provided written informed consent before participating in the study. The use of clinical and ultrasound data and collection and utilization of maternal blood for research purposes was approved by the Institutional Review Boards of the Sotero del Rio Hospital, Santiago, Chile (an affiliated of the Pontificia Catholic University of Santiago, Chile), and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, DHHS.

Sample collection and immunoassays

Venipuncture was performed and the blood was collected into tubes containing EDTA. Samples were centrifuged and stored at −70°C. All samples were collected before the clinical diagnosis of preeclampsia. Maternal plasma concentrations of sVEGFR-1, PlGF, and sEng were determined by sensitive and specific immunoassays obtained from R&D Systems (Minneapolis, MN). All three immunoassays utilized the quantitative sandwich enzyme immunoassay technique. The concentrations of sVEGFR-1, PlGF, and sEng in maternal plasma were determined by interpolation from the standard curve. The inter- and intra-assay coefficients of variation obtained in our laboratory were: sVEGFR-1: 1.4% and 3.9%, respectively; PlGF: 6.02% and 4.8%, respectively; and sEng: 2.3% and 4.6%

respectively. The sensitivity of the assays was: sVEGFR-1: 16.97 pg/ml; PlGF: 9.52 pg/ml; and sEng: 0.08 ng/ml. The laboratory personnel performing the assays were blinded to the clinical information of each subject.

Uterine artery Doppler velocimetry

Five experienced sonographers performed Doppler ultrasound of the uterine arteries between 20 to 25 weeks using real-time ultrasound equipment ACUSON 128-XP (ACUSON Corporation, Mountain View, CA, USA) with a 3.5 MHz or a 5 MHz curvilinear probe. The right and left uterine arteries were identified in an oblique plane of the pelvis at the crossover with the external iliac arteries and the Doppler signals were sampled. When three similar consecutive waveforms were obtained, the pulsatility index (PI) of the right and left uterine arteries was measured and the mean PI of the two vessels was calculated. The presence of an early diastolic notch in the uterine arteries was determined using the criteria proposed by Bower et al.[81] Abnormal UADV was defined as either a mean PI >1.45 and/or the presence of bilateral uterine artery notches.[74]

Statistical analysis

The normality of the data was tested using the Kolmogorov-Smirnov test. Because maternal plasma concentrations of sVEGFR-1, PlGF and sEng were not normally distributed even after logarithmic transformation, non-parametric tests were used for analyses. Comparisons between proportions were performed with contingency tables, Chi-square or Fisher's exact test, and Mann-Whitney U test was used for comparisons of continuous variables. The following measures were included for both early pregnancy and midtrimester, individually: 1) maternal plasma concentrations of sVEGFR-1, PlGF, and sEng; and 2) the ratio between the maternal plasma concentrations of PlGF and sVEGFR-1 (PlGF/sVEGFR-1), PlGF and sEng (PlGF/sEng), PlGF and the product of sEng and sVEGFR-1 [PlGF/(sEng x sVEGFR-1)], and PlGF and the sum of sEng and sVEGFR-1 [PlGF/(sEng + sVEGFR-1)]. The change (delta) in the maternal plasma concentrations between the early pregnancy and midtrimester samples, and the slope of the change, were calculated for sVEGFR-1, PlGF, sEng, PlGF/sVEGFR-1, PlGF/sEng, PlGF/(sEng x sVEGFR-1), and PlGF/(sEng + sVEGFR-1). Slope was defined as the difference between the concentrations in the early pregnancy and midtrimester samples divided by the number of weeks between the measurements.

Receiver operating characteristic (ROC) curves were constructed to calculate the area under the curve (AUC) and the best cut-off point for sVEGFR-1, PlGF, sEng, their ratios, deltas and slopes in order to calculate their respective sensitivity, specificity, predictive values, and likelihood ratios in the prediction of preeclampsia, as well as term, preterm and early-onset preeclampsia. Multivariable logistic regression analysis was used to explore the relationship between the occurrence of the outcomes and the following explanatory variables: maternal plasma concentration of sVEGFR-1, PlGF, sEng, their ratios, deltas and slopes, maternal age, previous preeclampsia, nulliparity, pre-pregnancy body mass index (BMI), smoking status, gestational age at venipuncture, and sample storage time. Risk was calculated with the use of adjusted odds ratios (OR) and 95% confidence interval (CI). The statistical package used was SPSS v.15.0 (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered significant.

RESULTS

Prevalence of outcomes

This study included 1,622 consecutive singleton pregnant women. The prevalence of preeclampsia, term preeclampsia, preterm preeclampsia and early-onset preeclampsia was

3.8% (62/1,622), 2.5% (40/1,622), 1.4% (22/1,622) and 0.6% (9/1,622), respectively. Table I displays the demographic and clinical characteristics of the population. Patients with preeclampsia were significantly younger and had a higher pre-pregnancy BMI than those without preeclampsia. In addition, patients with preeclampsia had a significantly higher proportion of women that were nulliparae and that had a history of preeclampsia in a previous pregnancy than those without preeclampsia. The median gestational age at delivery and neonatal birth weight were significantly lower in women with preeclampsia than that of those with normal pregnancies. No significant differences were observed in the gestational age at the time of venipuncture in early pregnancy and midtrimester between patients with and without preeclampsia.

PlGF, sVEGFR-1 and sEng in early pregnancy and midtrimester in the identification of patients destined to develop preeclampsia

Early pregnancy—The maternal plasma concentrations of sEng were significantly higher, and that of sVEGFR-1, PlGF, and the ratios PlGF/sVEGFR-1, PlGF/sEng, PlGF/(sEng x sVEGFR-1), and PlGF/(sEng + sVEGFR-1) were significantly lower at 6 to 15 weeks in patients who subsequently developed preeclampsia than in those who did not (Table II). ROC curve analysis indicated that AUC ranged from 0.579 for sEng to 0.662 for PlGF/sEng ratio. Table III displays the predictive accuracy of maternal plasma concentrations of sVEGFR-1, PlGF, sEng, PlGF/sVEGFR-1, PlGF/sEng, PlGF/(sEng x sVEGFR-1), and PlGF/(sEng + sVEGFR-1) in early pregnancy in the identification of preeclampsia, using cutoffs derived from the ROC curves. The largest AUC (0.662) was observed for the PlGF/sEng ratio (Figure S-1). The best sensitivity (93.5%) was observed for the PlGF/sVEGFR-1 and PlGF/sEng ratios, although with a low specificity (31%) and positive predictive value (PPV, 5.1%). Overall, the likelihood ratios for a positive test were small, ranging between 1.2 for PlGF/sVEGFR-1 ratio and 1.9 for sEng.

Multivariable logistic regression analysis indicated that high maternal plasma concentrations of sEng, and low maternal plasma concentrations of sVEGFR-1, PlGF, PlGF/sVEGFR-1, PlGF/sEng, PlGF/(sEng x sVEGFR-1), and PlGF/(sEng + sVEGFR-1) in early pregnancy were associated with an increased risk for the occurrence of preeclampsia after adjusting for maternal age, previous preeclampsia, nulliparity, pre-pregnancy BMI, smoking status, gestational age at venipuncture, and sample storage time. The OR ranged from 1.8 for the PlGF/(sEng x sVEGFR-1) ratio to 5.8 for the PlGF/sEng ratio (Table IV).

Midtrimester—The maternal plasma concentrations of sEng were significantly higher, and that of PlGF, the ratios PlGF/sVEGFR-1, PlGF/sEng, PlGF/(sEng x sVEGFR-1), and PlGF/(sEng + sVEGFR-1), as well as their deltas and slopes were significantly lower at 20 to 25 weeks in patients who subsequently developed preeclampsia than in those who did not. Table III displays their predictive accuracy in the identification of preeclampsia, using cutoffs derived from the ROC curves. The largest AUC (0.691) was observed for the slope of PlGF/sEng ratio (Figure S-2). A sensitivity of 75.8% was observed for the slope of PlGF/(sEng x sVEGFR-1), with a specificity of 46.7% and a PPV of 5.3%. Overall, the likelihood ratios for a positive test were small to moderate, ranging between 1.4 for the slope of PlGF/(sEng x sVEGFR-1) and 7.0 for the delta of PlGF/sVEGFR-1. In contrast to early pregnancy, no significant differences were observed in maternal plasma concentrations of sVEGFR-1 between the groups (Table II). The predictive performance of sVEGFR-1 was not reported since the AUC was not significant (0.524; p=0.5).

Multivariable logistic regression analysis indicated that high maternal plasma concentrations of sEng, and low maternal plasma concentrations of PlGF, PlGF/sVEGFR-1, PlGF/sEng, PlGF/(sEng x sVEGFR-1), PlGF/(sEng + sVEGFR-1), and their deltas and slopes in

midtrimester were associated with an increased risk for the subsequent diagnosis of preeclampsia. The OR ranged from 1.8 for the delta of PlGF/(sEng x sVEGFR-1) ratio and the slope of sVEGFR-1 to 6.7 for the delta of PlGF/sVEGFR-1 ratio (Table IV).

The results of PlGF, sVEGFR-1 and sEng in early pregnancy and midtrimester for the identification of patients destined to develop term and preterm preeclampsia are reported in the supplementary material section.

PlGF, sVEGFR-1 and sEng in early pregnancy and midtrimester in the identification of patients destined to develop early-onset preeclampsia

Early pregnancy—Patients who subsequently developed early-onset preeclampsia had significantly lower maternal plasma concentrations of PlGF, and the ratios PlGF/sEng and PlGF/(sEng + sVEGFR-1) at 6 to 15 weeks than those who did not develop early-onset preeclampsia. No significant differences were observed in the maternal plasma concentrations of sVEGFR-1, sEng, and the ratios of PlGF/sVEGFR-1 and PlGF/(sEng x sVEGFR-1) (Table V).

Table VI displays the predictive indices of maternal plasma concentrations of PlGF, PlGF/sEng and PlGF/(sEng + sVEGFR-1) in early pregnancy in the identification of early-onset preeclampsia, using cutoffs derived from the ROC curves. The highest AUC (0.745) was observed for the PlGF/sEng ratio (Figure S-3). The same sensitivity (77.8%) was observed for PlGF and the two ratios, with a specificity of 72.7% and PPV of 1.6% for PlGF/(sEng + sVEGFR-1). Overall, the likelihood ratios for a positive test were small, ranging between 2.6 and 2.9.

Midtrimester—The maternal plasma concentrations of sVEGFR-1 and sEng were significantly higher, and that of PlGF, the ratios PlGF/sVEGFR-1, PlGF/sEng, PlGF/(sEng x sVEGFR-1), and PlGF/(sEng + sVEGFR-1), as well as their deltas and slopes were significantly lower at 20 to 25 weeks in patients who subsequently developed early-onset preeclampsia than in those who did not (Table V).

The maternal plasma concentrations of PlGF, sVEGFR-1, sEng, and their ratios, deltas and slopes in midtrimester could be used in the identification of patients destined to develop early-onset preeclampsia. Table VI displays their predictive indices using cutoffs derived from ROC curves. The highest AUC (0.998) was observed for the slope of PlGF/sEng ratio (Figure S-4), and five other ratios had an AUC of 0.997. Most angiogenic and anti-angiogenic factors, ratios, deltas and slopes reached a sensitivity of 100%. The best diagnostic performance was observed for the slope of PlGF/sEng ratio, with a sensitivity of 100%, specificity 98.9%, PPV 33.3% and NPV 100%. Overall, the likelihood ratios for a positive test were small to large, ranging between 3.2 for the delta of sVEGFR-1 to 89.6 for the slope of PlGF/sEng ratio. Due to the low prevalence of early-onset preeclampsia, only 9 patients were included in this study that precluded us to conduct a multivariable logistic regression analysis.

Uterine artery Doppler velocimetry in the midtrimester in the identification of patients destined to develop preeclampsia, term preeclampsia, preterm preeclampsia and early-onset preeclampsia

An abnormal UADV was present in 12.6% (204/1,622) of the population. Table S-VII shows the predictive accuracy of an abnormal UADV at 20 to 25 weeks of gestation in the identification of patients destined to develop preeclampsia, as well as term, preterm and early-onset preeclampsia. The best predictive performance was observed for the diagnosis of early-onset preeclampsia, with a sensitivity of 77.8%, specificity 87.9%, PPV 3.5%, NPV

99.9% and a likelihood ratio for a positive test of 6.4. Multivariable logistic regression analysis indicated that an abnormal UADV at 20 to 25 weeks of gestation was associated with a high risk for the occurrence of preeclampsia, term preeclampsia and preterm preeclampsia after adjusting for maternal age, previous preeclampsia, nulliparity, pre-pregnancy BMI, smoking status, and gestational age at ultrasound. The highest OR was observed for the diagnosis of preterm preeclampsia (OR: 5.1, 95% CI 2.0–12.7; see Table S-VIII).

DISCUSSION

Principal findings of the study

1) Risk assessment for preeclampsia is feasible based on the maternal concentrations of angiogenic and anti-angiogenic factors; 2) the most informative analytes were PlGF and sEng; 3) the highest likelihood ratios were provided by ratios of midtrimester plasma concentrations of PlGF, sEng, and sVEGFR-1; 4) these angiogenic and anti-angiogenic factors did not perform well in the identification of preeclampsia as a whole; in particular, they perform poorly in the prediction of term preeclampsia; and 5) in contrast, a combination of these analytes such as the PlGF/sEng ratio, its delta and slope, had the best predictive indices with a sensitivity of 100% for all tests, a specificity between 98% and 99%, and likelihood ratios for a positive test of 57.6, 55.6 and 89.6, respectively, for predicting early-onset preeclampsia.

Angiogenic and anti-angiogenic factors in the prediction of preeclampsia

Since an imbalance between circulating angiogenic and anti-angiogenic factors has been observed at the time of the diagnosis of preeclampsia, and also even before the clinical presentation of disease, it has been proposed that maternal plasma/serum concentrations of angiogenic and anti-angiogenic factors may be of value in the screening or risk assessment for preeclampsia. Two nested case-control studies from the Calcium for Preeclampsia Prevention trial conducted by Levine et al[12,25] reported promising ORs for the diagnosis of preeclampsia, but specifically for preterm preeclampsia, based on the maternal serum concentrations of sFlt1 and sEng (highest quartile) and PlGF (lowest quartile) in the second trimester. Since then, several studies have reported on the predictive accuracy of angiogenic factors in the first[14] and second trimester[16,32,37,41,42,45,46,82–86] of pregnancy. Overall, the sensitivity, specificity, positive and negative likelihood ratios of PlGF, sVEGFR-1 and sEng for all cases of preeclampsia ranged between 59% and 100%, 43% and 100%, 1.4 to infinity, and 0.0 to 0.7, respectively (Conde-Agudelo A., Romero R., and Lindheimer M., in press).[87] This wide range in the diagnostic performance may be explained for the difference in populations included in those studies (low-risk, high-risk, nulliparae, multiparae, etc). Interestingly, the combination of these angiogenic factors as ratios has improved the diagnostic performance in predicting preeclampsia. The sFlt1/PlGF ratio has been proposed as a marker of anti-angiogenic activity based on the imbalance between sFlt1 and PlGF, which has been shown to be significantly associated with preterm preeclampsia,[25] and has a lower false-positive rate than sFlt1 or sEng alone. Yet, the diagnostic indices and ORs reported in recent studies that evaluated the sFlt1/PlGF ratio were similar to those reported for individual angiogenic factors alone.[37,41,42]

Recently, two case-control studies[57,58] reported the diagnostic performance of these analytes at 11 to 13.9 weeks for prediction of preeclampsia. Baumann et al[57] measured the maternal serum concentrations of sFlt-1, sEng and PlGF in women with a normal pregnancy and patients who subsequently developed late-onset preeclampsia (>34 weeks). Using cutoffs derived from ROC curves, the sensitivity and specificity of sFlt-1 in prediction of late-onset preeclampsia was 64% and 56%, respectively, whereas that of sEng was 63% and

57%, respectively. The authors found that the maternal serum concentrations of PlGF and the sFlt-1/PlGF ratio were not different between cases and controls. In contrast, Akolekar et al[58] reported that the maternal PlGF serum concentrations of patients who subsequently developed early- and late-onset preeclampsia were significantly lower than that of controls. Using fixed false-positive rates of 5% and 10%, the detection rates of early-onset preeclampsia were 75.9% and 89.7%, respectively, while those of late-onset preeclampsia were 29.6% and 49%, respectively, when maternal serum PlGF concentrations were combined with maternal characteristics, obstetrical history and uterine artery PI in the first trimester.

Changes in circulating concentrations of angiogenic and anti-angiogenic factors from first to second trimester

The diagnostic performance for preeclampsia of most studies described above have mainly focused on maternal circulating concentrations of angiogenic and/or anti-angiogenic factors at a single time-point either at the first or second trimester, but also in different types of populations. Since circulating concentrations of angiogenic and anti-angiogenic factors change with gestational age, it is possible that serial measurements of the concentrations of sVEGFR-1, PlGF and sEng could be more informative in assessing the risk for preeclampsia than is a single measurement. The diagnostic performance for prediction of preeclampsia for the slope of the change reported in the present study, using cutoffs derived from ROC curves, seems to be comparable to that of those for the change (delta) as well as the concentrations of individual angiogenic and anti-angiogenic factors and their ratios in the second trimester (Table III). For prediction of preterm preeclampsia, the diagnostic performance for the slope of the change was slightly better than that of the delta as well as the concentrations of individual angiogenic/anti-angiogenic factors and their ratios in the second trimester (Table S-V).

Until now, three studies have evaluated changes in circulating concentrations of angiogenic and anti-angiogenic factors from the first to second trimester as predictors of preeclampsia.[39,64] Vatten et al[39] conducted a longitudinal nested case-control study to determine maternal serum concentrations of PlGF and sFlt1 in patients with term and preterm preeclampsia, and compared the lowest and highest quartile of PlGF and sFlt1 as well as the change of every analyte from the first to the second trimester. For the diagnosis of preterm preeclampsia, the lowest quartile of PlGF had an OR of 2.9 (95% CI: 1.4–6.2) in the first and 7.0 (95% CI: 3.0–16.5) in the second trimester, whereas the highest quartile of sFlt1 had an OR of 0.2 (95% CI: 0.1–0.4) in early pregnancy (high risk in patients with low sFlt1 concentration in early pregnancy) and an OR of 3.1 (95% CI: 1.6–5.8) in the midtrimester. Overall, the ORs for the diagnosis of term preeclampsia were smaller than that of preterm preeclampsia for both PlGF and sFlt1. In addition, the lowest quartile of the change in PlGF concentrations from the first to second trimester was associated with an OR of 13.8 (95% CI: 4.4–43.2) for preterm and 4.0 (95% CI: 1.7–9.4) for term preeclampsia, while the highest quartile of change in sFlt1 concentrations from first to second trimester was associated with an OR of 9.2 (95% CI: 3.4–25.0) for preterm and 2.2 (95% CI: 1.0–4.9) for term preeclampsia. Interestingly, the combination of the lowest quartile of PlGF change and the highest quartile of sFlt1 change from first to second trimester was associated with an OR of 35.3 (95% CI: 7.6–164.2) for preterm preeclampsia. Similarly, Erez et al[47] studied the association of the change between the first and second trimesters of maternal plasma concentrations of PlGF, sVEGFR-1 and sEng and the subsequent development of preeclampsia. Patients with a low increase in the maternal plasma PlGF concentrations between the first and second trimesters (defined as a slope below the median for patients with normal pregnancies) had an OR of 4.3 (95% CI: 1.2–15.5) for the subsequent development of preterm preeclampsia. In comparison to patients with no change or a

decrease in concentrations of sVEGFR-1 or sEng between the first and second trimesters, those with an increase in sVEGFR-1 concentrations had an OR of 3.9 (95% CI: 1.2–12.6) for the development of preterm preeclampsia, whereas those with increase in sEng concentrations had an OR of 14.9 (95% CI: 4.9–45.1). Interestingly, a small change in the PlGF/sEng ratio (change below the median slope for patients with normal pregnancies) conferred an OR of 7.7 (95% CI: 1.7–34.7) for the development of preterm preeclampsia, while patients with a high change in the sEng x sVEGFR-1 product had an OR of 10.4 (95% CI: 3.2–33.8). Recently, Sibai et al[44] reported the diagnostic performance of serum inhibin A, sFlt1, PlGF and the sFlt1/PlGF ratio for the diagnosis of preeclampsia at 12 to 19.9 weeks and 24 to 28 weeks of gestation, as well as the change of these analytes between the two intervals, in patients with previous preeclampsia and/or chronic hypertension enrolled in a randomized, placebo-controlled trial of vitamins C and E.

After fixing the specificity to 90% (false positive rate of 10%), the sensitivity of those analytes ranged between 16 to 36% for the diagnosis of preterm preeclampsia, and between 44% and 67% for the diagnosis of preeclampsia <27 weeks of gestation. The authors concluded that, in this high-risk population, circulating concentrations of angiogenic factors in early pregnancy are not clinically useful for predicting preeclampsia.

Uterine Artery Doppler Velocimetry

Failure of physiologic transformation of the spiral arteries in placental bed biopsies has been associated with high impedance to blood flow in the uterine arteries and decreased perfusion of the placenta, which has been considered to play a role in the pathophysiology of preeclampsia.[88–92] An updated systematic review[77] on the predictive accuracy of uterine artery Doppler velocimetry for preeclampsia concluded that, in low risk populations, the sensitivity and specificity of the uterine artery Doppler indices ranged from 34% to 76%, and between 83 and 93%, respectively.[87] In this study, the sensitivity of an abnormal uterine artery Doppler velocimetry in the midtrimester for predicting preeclampsia, as well as preterm and early-onset preeclampsia was 32%, 43% and 78%, with a positive likelihood ratio of 2.7, 3.5 and 6.4, respectively. These results are in agreement with others previously reported in unselected populations. An abnormal uterine artery Doppler velocimetry in the second trimester has been associated with a higher risk to develop early-onset than late-onset preeclampsia.[73–76] A small number of studies[32,74,93–100] have reported the predictive accuracy of uterine artery Doppler velocimetry for early-onset and/or severe preeclampsia, with sensitivities and specificities ranging from 26% to 95% and 31% to 99%, respectively. Despite of the index (resistance index, pulsatility index) or combinations of indices used (resistance index or pulsatility index and uterine artery notches), uterine artery Doppler velocimetry is a moderate to good predictor for the development of early-onset preeclampsia, with positive likelihood ratios ranging from 5 to 20.[87]

Angiogenic and anti-angiogenic factors in prediction of early-onset preeclampsia

Early-onset preeclampsia is associated with a higher rate of maternal death,[101] severe preeclampsia,[102] growth-restricted fetuses,[102] and placental pathology[103,104] than late-onset preeclampsia. Chaiworapongsa et al[10] reported that patients with preeclampsia have higher plasma concentrations of sVEGFR-1 than normal pregnant women at the time of the diagnosis of disease. The authors reported that the magnitude of the increase of sVEGFR-1 concentrations is associated with the severity of the disease, and that sVEGFR-1 concentrations are significantly higher in early-onset or preterm than in late-onset or term preeclampsia.

In a cross-sectional study, Polliotti et al[105] demonstrate that low serum concentrations of either VEGF or PlGF in the midtrimester were associated with ORs of 15.5 and 4.2,

respectively, for developing early-onset preeclampsia. Moore Simas[33] measured longitudinal maternal serum concentrations of sFlt1 and PlGF between 22–36 weeks of gestation in patients at high-risk for preeclampsia. Results from ROC curves including the first sample obtained between 22–26 weeks of gestation suggest that the sFlt1/PlGF ratio was slightly more accurate in predicting early-onset preeclampsia than sFlt1 alone (AUCs 97.1% and 90.1%, respectively).[87] Among patients with abnormal uterine artery Doppler velocimetry in the second trimester, Stepan et al[37,45] reported a sensitivity and specificity of sFlt1, PlGF, sFlt1/PlGF ratio and sEng ranging from 50% to 83% and 51% to 95%, respectively, for prediction of early-onset preeclampsia, while Diab et al[41] reported a sensitivity of 100% and specificity between 76% and 90% for sFlt1, PlGF and the sFlt1/PlGF. Recently, Espinoza et al conducted a prospective cohort study that included 3,348 women for the prediction of preeclampsia using a combination of maternal plasma concentrations of PlGF and uterine artery Doppler velocimetry between 22 and 26 weeks of gestation. For the prediction of early-onset preeclampsia, the sensitivities of maternal plasma PlGF concentration <280 pg/mL, abnormal uterine artery Doppler velocimetry, and the combination of these tests were 80%, 72%, and 64%, respectively. The corresponding specificities were 51%, 90%, and 96%, respectively. The combination of tests improved the specificity, PPV and positive likelihood ratio of each test alone in the prediction of early-onset preeclampsia, although with a slight reduction in the sensitivity.

The study reported herein demonstrated that the predictive performance of maternal plasma angiogenic and anti-angiogenic factors in early pregnancy was slightly higher for the identification of women destined to develop early-onset preeclampsia than for women who developed preterm preeclampsia. This predictive performance improved significantly in the midtrimester, where several tests had a sensitivity of 100%, with a specificity ranging from 68% to 99%. Of note, the PlGF/sEng ratio, its delta and slope, had the best predictive indices with a sensitivity of 100% for all tests, a specificity between 98% and 99%, and likelihood ratios for a positive test of 57.6, 55.6 and 89.6, respectively, for predicting early-onset preeclampsia. Similar results were observed for the PlGF/sEng+sVEGFR-1 ratio and its slope. Interestingly, this study demonstrated that a PlGF/sEng ratio of ≤13.44 in the midtrimester identifies all patients that will develop the early form of the disease, approximately 5 weeks before its clinical diagnosis. Although the predictive performance of the slope of PlGF/sEng ratio seems to be better than that of the PlGF/sEng ratio, the advantage of the latter is that it only requires one measurement in the midtrimester, whereas an extra measurement in the first trimester is needed to calculate the slope.

The predictive accuracy of angiogenic and anti-angiogenic factors in the midtrimester is higher for early-onset preeclampsia than for term or preterm preeclampsia. This may be explained for two reasons: 1) patients with early-onset preeclampsia had significantly different median maternal plasma concentrations of sVEGFR-1, PlGF and sEng than patients who develop preeclampsia >34 weeks of gestation (sVEGFR-1: 4162.3 pg/ml vs. 1532.3 pg/ml, $p<0.001$; PlGF: 42.1 pg/ml vs. 273.4 pg/ml, $p<0.001$; and sEng: 14.9 ng/ml vs. 6.7 ng/ml, $p<0.001$), respectively; and 2) plasma concentrations of sVEGFR-1, PlGF and sEng were measured at a median of 22.9 weeks of gestation, and the diagnosis of early-onset preeclampsia was performed at a median gestational age of 28.4 weeks. Thus, the closer to the clinical diagnosis, the better is the prediction of the disease.

We have proposed that efforts should be focusedon the identification of patients at high risk to develop early-onset preeclampsia, in order to reduce the morbidity and mortality associated with this form of the disease.[32] However, the conceptual framework to screen for complex diseases such as preeclampsia, preterm parturition, fetal growth restriction and fetal death is scarce.[106] In addition to an anti-angiogenic state, other mechanisms of disease had been proposed in preeclampsia, including: 1) abnormal physiologic

transformation of the spiral arteries;[90,107–112] 2) chronic uteroplacental ischemia;[73–75,93,113–122] 3) immune maladaptation;[118] 4) increased trophoblast apoptosis/necrosis;[123–126] 5) exaggerated maternal inflammatory response to deported trophoblast;[127–130] 6) endothelial cell dysfunction;[20,131–138] 7) very low-density lipoprotein toxicity;[118] and 8) genetic imprinting.[118] Therefore, since multiple pathological processes are involved in the etiology of preeclampsia, it seems unlikely that a single marker or a combination of them will have a high diagnostic performance in the prediction of this disease. Indeed, a systematic review concluded that there is no clinically useful screening test to predict the development of preeclampsia,[77] and even if we have that test, the only treatment available to date is the delivery of the fetus and the placenta. Results of three randomized clinical trials of vitamin C and E supplementation for the prevention of preeclampsia and serious morbidity associated to hypertension in pregnancy in low-[139,140] and high-risk[141] populations reported negative results. Recently, administration of recombinant VEGF121 (a splice variant of VEGF) to a rat model of preeclampsia showed promising results in reducing systolic blood pressure and improving kidney damage;[142] however, further research is needed to consider VEGF121 as a potentialtherapeutic agent for preeclampsia.

The consequence of lack of a useful screening test to predict preeclampsia (low PPV) is that most patients with a positive test will not develop the disease, and prophylactic interventions (if any) in the group of patients with a positive test may expose a large proportion of them to that intervention, but maybe without any benefit. Ideally, the PPV of a test should be high in order to reduce the number of false-positive cases that will be the subject of an intervention. In the context of early-onset preeclampsia, although the sensitivity and specificity of most tests reported in this study were very high, the PPV was low. This can be explained due to the low prevalence of the early form of the disease. For example, the use of proteomics to identify serum markers for the diagnosis of ovarian cancer has been reported to have a very high sensitivity (100%), specificity (95%) and PPV (94%), but this diagnostic performance was obtained in the context of a case-control study with a prevalence for ovarian cancer of almost 45%.[143] However, if the same test is applied to a low-risk population with prevalence for ovarian cancer of approximately 1/2,500, the PPV will be close to 1%.[144,145] In the present study, the PPV of the PlGF/sEng ratio and the slope of PlGF/sEng was 24% and 33%, respectively. In the case of a PlGF/sEng ratio ≤13.44 in the midtrimester, 2.3% (37/1,622) of the individuals included in this cohort had a positive test, being nine of them early-onset preeclampsia, one preterm and one term preeclampsia, two cases of gestational hypertension, one of chronic hypertension, one patient with gestational diabetes, two cases of spontaneous preterm delivery, nine SGA neonates and 11 normal pregnant women. In the case of the slope of PlGF/sEng ≤0.94 in the midtrimester, 1.7% (27/1,622) of individuals included in this cohort had a positive test. Nine patients were diagnosed with early-onset preeclampsia, one preterm and two term preeclampsia, one case of gestational hypertension, one of chronic hypertension, two cases of spontaneous preterm delivery, five SGA neonates and six normal pregnant women. Interestingly, 41% (15/37) of patients with a positive PlGF/sEng ratio and 52% of those with a positive slope PlGF/sEng test delivered <37 weeks of gestation. Thus, a small number of patients will be exposed to interventions, but a significant proportion of patients identified with a positive test may benefit of those interventions, such as closer follow-up and steroids administration. On the other hand, a positive test result of the slope of PlGF/sEng in the midtrimester, which was the analyte with the highest likelihood ratio for a positive test result (89.6) in this population, increases the pre-test probability of early-onset preeclampsia from 0.6% to 35.1%. Conversely, a negative test result of this analyte (likelihood ratio for a negative test result = 0.0) decreases the pre-test probability of early-onset preeclampsia from 0.6% to 0.0%.

Table S-IX displays the angiogenic and anti-angiogenic factors with the highest AUC and OR in early pregnancy and midtrimester for the identification of preeclampsia as a whole as well as term, preterm and early-onset preeclampsia. For the screening purpose, the AUCs suggest that it could be feasible for early-onset preeclampsia, especially in the midtrimester. For other forms of preeclampsia, we could determine individual risk by using OR in both early pregnancy and midtrimester.

Strengths and limitations of the study

To our knowledge, this is the largest longitudinal cohort study in an unselected population reported to date that evaluated risk assessment for preeclampsia, based on the maternal plasma concentrations of PlGF, sEng, and sVEGFR-1 in early pregnancy and midtrimester. Moreover, patients with preeclampsia were subdivided into term, preterm and early-onset preeclampsia allowing to determine the diagnostic performance of angiogenic factors in conditions that may be associated with different mechanisms of disease. Interestingly, the PlGF/sEng ratio and its slope emerge as a novel and promising diagnostic tool for prediction of early-onset preeclampsia. The limitations of this study are that we only included patients from a Hispanic population, which has been reported to have an increased relative risk for preeclampsia than that of non-Hispanic Caucasian women [2.0 (95% CI, 1.2 to 3.4; $P = 0.01$)].[146] In addition, the number of patients with early-onset preeclampsia was small (9 cases), although it reflects the real prevalence of the early form of the disease, which is approximately 0.8%.[32] Finally, it may be considered that prediction for preeclampsia at 20–25 weeks of gestation is relatively late. Recent studies are focusing in predicting preeclampsia with use of uterine artery Doppler velocimetry and other biochemical markers in the first trimester.[100,147–156]

Conclusions

Although maternal plasma concentrations of angiogenic and anti-angiogenic factors did not perform well as a screening test for preeclampsia as a whole, they are a promising tool in the risk assessment for early-onset preeclampsia. The best diagnostic performances were obtained by ratios in the midtrimester and the slopes of plasma concentrations of PlGF, sEng, and sVEGFR-1 between the first and second trimester; but despite very high likelihood ratios, the positive predictive values were low because of the low prevalence of the disease. These analytes, in combination with other demographic, biochemical or biophysical parameters may help improving the risk assessment for preeclampsia, specifically, the early-onset form of the disease. Further research is needed to discover other markers with a similar or better diagnostic performance in order to improve the prediction of late-onset preeclampsia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

Demographic and clinical characteristics of the population

	Preeclampsia (n=62)	Normal pregnancy/other complications (n=1560)	p
Maternal age (yr)	23 (20–27)	26 (22–31)	0.007
Height (cm)	158 (153–163)	156 (153–161)	0.2
Weight (Kg)	64 (57–74)	60 (53–68)	0.004
Pre-pregnancy BMI (Kg/m^2)	25.7 (23.7–29)	24.3 (21.9–27.4)	0.006
Obesity (BMI >30)	20 (12/60)	14.1 (210/1488)	0.2
Nulliparity (%)	61.3 (38/62)	39.7 (619/1560)	0.001
Previous preeclampsia (%)	12.9 (8/62)	2.6 (41/1560)	<0.001
Smoking (%)	6.5 (4/62)	11.3 (177/1560)	0.2
Gestational age at first sample (wk)	11.9 (10.4–13.1)	12.1 (10.7–13.4)	0.2
Gestational age at second sample (wk)	22.9 (21.4–23.9)	22.4 (21.1–23.7)	0.4
Gestational age at delivery (wk)	38.2 (36.3–39.3)	39.4 (38.6–40.3)	<0.001
Delivery <37 weeks (%)	29 (18/62)	5.4 (84/1560)	<0.001
Birth weight (g)	3,025 (2,365–3,470)	3,380 (3,080–3,690)	<0.001
SGA neonate (%)	29 (18/62)	12.4 (194–1559)	<0.001
Storage time first sample (yr)	2.3 (1.7–2.9)	2.3 (1.7–2.8)	0.8
Storage time second sample (yr)	2.1 (1.4–2.7)	2.1 (1.5–2.6)	0.9

The results are expressed as percentage (proportion) or median (inter-quartile range)

BMI: body mass index; **SGA:** small-for-gestational age

Table II

Maternal plasma concentrations of sVEGFR-1, PlGF, sEng, and their ratios in early pregnancy and midtrimester of patients who subsequently developed preeclampsia

Analyte	Preeclampsia (n=62)	Normal pregnancy/other complications (n=1560)	p
Early pregnancy			
sVEGFR-1	1426.3 (597.9–4546.5)	1725.8 (48.6–13575.1)	0.02
PlGF	23.5 (0.0–77.1)	33.8 (0.0–451.9)	<0.001
sEng	7.4 (4.1–13.3)	7.1 (3.3–26.9)	0.04
PlGF/sVEGFR-1	0.016 (0.0–0.06)	0.018 (0.0–0.47)	0.01
PlGF/sEng	3.1 (0.0–10.5)	4.6 (0.0–60)	<0.001
PlGF/sEng x sVEGFR-1	0.0019 (0.0–0.01)	0.0025 (0.0–0.06)	0.004
PlGF/sEng + sVEGFR-1	0.0025 (0.0–0.008)	0.0036 (0.0–0.05)	<0.001
Midtrimester			
sVEGFR-1	1637.4 (325.1–17768.9)	1612.1 (245–10595.5)	0.5
PlGF	213.9 (0.0–969.6)	329.8 (22.3–2894.4)	<0.001
sEng	6.9 (3–47)	5.9 (2.4–29.6)	<0.001
PlGF/sVEGFR-1	0.17 (0.0–1)	0.21 (0.008–4.6)	0.006
PlGF/sEng	36.9 (0.0–157.8)	55.5 (1.2–354.9)	<0.001
PlGF/sEng x sVEGFR-1	0.025 (0.0–0.2)	0.036 (0.0–0.9)	<0.001
PlGF/sEng + sVEGFR-1	0.028 (0.0–0.1)	0.042 (0.001–0.3)	<0.001
Delta sVEGFR-1	157.4 (−1053–16476.6)	−129.8 (−12093.3–4120.4)	0.003
Delta PlGF	181.1 (0.0–902.3)	290.7 (−72.9–2798.6)	<0.001
Delta sEng	−0.8 (−4.9–41.5)	−1.2 (−14.2–18.8)	0.02
Delta PlGF/sVEGFR-1	0.16 (−0.05–1)	0.18 (−0.04–4.4)	0.01
Delta PlGF/sEng	34.1 (−2–147.3)	49.8 (−8.4–340.8)	<0.001
Delta PlGF/sEng x sVEGFR-1	0.023 (−0.01–0.2)	0.032 (−0.005–0.9)	0.001
Delta PlGF/sEng + sVEGFR-1	0.025 (−0.002–0.1)	0.038 (−0.007–0.3)	<0.001
Slope sVEGFR-1	14.4 (−109.4–1109)	−13.3 (−1019.9–379.7)	0.003
Slope PlGF	18.1 (0.0–96.1)	28.5 (−6.2–321.2)	<0.001
Slope sEng	−0.07 (−0.6–2.8)	−0.12 (−1.3–1.8)	0.01
Slope PlGF/sVEGFR-1	0.014 (−0.005–0.09)	0.018 (−0.004–0.4)	0.002
Slope PlGF/sEng	2.9 (−0.2–15.9)	5 (−0.7–39.1)	<0.001
Slope PlGF/sEng x sVEGFR-1	0.0021 (−0.001–0.02)	0.0032 (0.0–0.09)	<0.001
Slope PlGF/sEng + sVEGFR-1	0.0024 (0.0–0.01)	0.0038 (−0.001–0.03)	<0.001

The results are expressed as median (range)

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Table III

Predictive accuracy of maternal plasma concentrations of PlGF, sVEGFR-1, sEng, and their ratios in early pregnancy and midtrimester for the diagnosis of preeclampsia

Analyte	AUC	ROC curve p-value	Cutoff	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Early pregnancy									
sVEGFR-1	0.587	0.02	≤1405.41	50%	68%	5.8%	97.2%	1.6 (1.2–2.0)	0.7 (0.6–0.9)
PlGF	0.647	<0.001	≤28.04	62.9%	60.4%	5.9%	97.6%	1.6 (1.3–1.9)	0.6 (0.4–0.8)
sEng	0.579	0.04	≥8.59	40.3%	79%	7.1%	97.1%	1.9 (1.4–2.6)	0.8 (0.6–0.9)
PlGF/sVEGFR-1	0.592	0.01	≤0.033	93.5%	22.2%	4.6%	98.9%	1.2 (1.1–1.3)	0.3 (0.1–0.7)
PlGF/sEng	0.662	<0.001	≤6.69	93.5%	31%	5.1%	99.2%	1.3 (1.2–1.4)	0.2 (0.1–0.5)
PlGF/sEng x sVEGFR-1	0.608	0.004	≤0.0022	59.7%	56.6%	5.2%	97.2%	1.4 (1.1–1.7)	0.7 (0.5–0.9)
PlGF/sEng + sVEGFR-1	0.649	<0.001	≤0.0035	67.7%	53.7%	5.5%	97.7%	1.5 (1.2–1.7)	0.6 (0.4–0.8)
Midtrimester									
PlGF	0.650	<0.001	≤215.04	51.6%	76.4%	8%	97.5%	2.2 (1.7–2.7)	0.6 (0.5–0.8)
sEng	0.680	<0.001	≥6.7	58.1%	73.3%	8%	97.8%	2.2 (1.7–2.6)	0.6 (0.4–0.7)
PlGF/sVEGFR-1	0.602	0.006	≤0.12	40.3%	78.5%	6.9%	97.1%	1.9 (1.3–2.5)	0.8 (0.6–0.9)
PlGF/sEng	0.681	<0.001	≤48.28	69.4%	60.6%	6.5%	98%	1.8 (1.4–2.0)	0.5 (0.3–0.7)
PlGF/sEng x sVEGFR-1	0.631	<0.001	≤0.019	43.5%	77.8%	7.2%	97.2%	2.0 (1.4–2.6)	0.7 (0.6–0.9)
PlGF/sEng + sVEGFR-1	0.664	<0.001	≤0.025	48.4%	81.9%	9.6%	97.6%	2.7 (2.0–3.4)	0.6 (0.5–0.8)
Delta sVEGFR-1	0.610	0.003	≥176.62	50%	68.7%	6%	97.2%	1.6 (1.2–2.0)	0.7 (0.6–0.9)
Delta PlGF	0.635	<0.001	≤183.25	51.6%	76.4%	8%	97.5%	2.2 (1.7–2.7)	0.6 (0.5–0.8)
Delta sEng	0.591	0.02	≥ −0.53	48.4%	74%	6.9%	97.3%	1.9 (1.4–2.4)	0.7 (0.5–0.9)
Delta PlGF/sVEGFR-1	0.594	0.01	≤0.039	19.4%	97.2%	21.8%	96.8%	7.0 (3.9–12.3)	0.8 (0.7–0.9)
Delta PlGF/sEng	0.667	<0.001	≤27.88	45.2%	82.5%	9.3%	97.4%	2.6 (1.9–3.4)	0.7 (0.5–0.8)
Delta PlGF/sEng x sVEGFR-1	0.622	0.001	≤0.019	46.8%	71.8%	6.2%	97.1%	1.7 (1.2–2.1)	0.7 (0.6–0.9)
Delta PlGF/sEng + sVEGFR-1	0.650	<0.001	≤0.024	50%	77.9%	8.2%	97.5%	2.3 (1.7–2.9)	0.6 (0.5–0.8)
Slope sVEGFR-1	0.611	0.003	≥13.51	51.6%	66.5%	5.8%	97.2%	1.5 (1.2–1.9)	0.7 (0.5–0.9)

Analyte	AUC	ROC curve p-value	Cutoff	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Slope PlGF	0.660	<0.001	≤18.14	51.6%	77.1%	8.2%	97.6%	2.3 (1.7–2.8)	0.6 (0.5–0.8)
Slope sEng	0.592	0.01	≥ −0.055	50%	72.6%	6.8%	97.3%	1.8 (1.4–2.3)	0.7 (0.5–0.9)
Slope PlGF/sVEGFR-1	0.613	0.002	≤0.0089	38.7%	82.6%	8.1%	97.1%	2.2 (1.6–3.0)	0.7 (0.6–0.9)
Slope PlGF/sEng	0.691	<0.001	≤2.9	51.6%	80.8%	9.6%	97.7%	2.7 (2.0–3.4)	0.6 (0.5–0.8)
Slope PlGF/sEng x sVEGFR-1	0.642	<0.001	≤0.0034	75.8%	46.7%	5.3%	98%	1.4 (1.2–1.6)	0.5 (0.3–0.8)
Slope PlGF/sEng + sVEGFR-1	0.677	<0.001	≤0.0026	56.5%	74.5%	8.1%	97.7%	2.2 (1.7–2.7)	0.6 (0.4–0.8)

Prevalence of preeclampsia: 3.8% (62/1622)

AUC: area under the curve; **ROC:** receiver operating characteristic

Table IV

Logistic regression analysis of maternal plasma concentrations of sVEGFR-1, PlGF, sEng, and their ratios in early pregnancy and midtrimester, for the prediction of preeclampsia after adjusting for maternal age, previous preeclampsia, pre-pregnancy BMI, nulliparity, smoking status, gestational age at venipuncture, and storage time

Analyte	Cutoff	Odds Ratio	95% C.I.	p-value
Early pregnancy				
sVEGFR-1	≤1405.41	2.2	1.3 – 3.8	0.003
PlGF	≤28.04	2.3	1.3 – 3.9	0.003
sEng	≥8.59	3.1	1.7 – 5.4	<0.001
PlGF/sVEGFR-1	≤0.033	3.7	1.3 – 10.3	0.01
PlGF/sEng	≤6.69	5.8	2.1 – 16.1	0.001
PlGF/sEng x sVEGFR-1	≤0.0022	1.8	1.03 – 3.0	0.04
PlGF/sEng + sVEGFR-1	≤0.0035	2.1	1.2 – 3.6	0.01
Midtrimester				
PlGF	≤215.04	3.8	2.2 – 6.7	<0.001
sEng	≥6.7	4.6	2.6 – 8.0	<0.001
PlGF/sVEGFR-1	≤0.12	2.0	1.1 – 3.4	0.02
PlGF/sEng	≤48.28	3.9	2.1 – 7.0	<0.001
PlGF/sEng x sVEGFR-1	≤0.019	2.2	1.2 – 3.7	0.006
PlGF/sEng + sVEGFR-1	≤0.025	4.5	2.6 – 7.8	<0.001
Delta sVEGFR-1	≥176.62	1.9	1.1 – 3.2	0.02
Delta PlGF	≤183.25	3.2	1.9 – 5.5	<0.001
Delta sEng	≥ −0.53	2.7	1.6 – 4.5	<0.001
Delta PlGF/sVEGFR-1	≤0.039	6.7	3.2 – 14.1	<0.001
Delta PlGF/sEng	≤27.88	3.8	2.2 – 6.5	<0.001
Delta PlGF/sEng x sVEGFR-1	≤0.019	1.8	1.1 – 3.1	0.03
Delta PlGF/sEng + sVEGFR-1	≤0.024	3.3	2.0 – 5.7	<0.001
Slope sVEGFR-1	≥13.51	1.8	1.1 – 3.1	0.03
Slope PlGF	≤18.14	3.1	1.8 – 5.3	<0.001
Slope sEng	≥ −0.055	2.7	1.6 – 4.6	<0.001
Slope PlGF/sVEGFR-1	≤0.0089	2.4	1.4 – 4.2	0.002
Slope PlGF/sEng	≤2.9	4.1	2.4 – 7.1	<0.001
Slope PlGF/sEng x sVEGFR-1	≤0.0034	2.4	1.3 – 4.4	0.005
Slope PlGF/sEng + sVEGFR-1	≤0.0026	3.5	2.1 – 6.1	<0.001

CI: confidence interval

Table V

Maternal plasma concentrations of sVEGFR-1, PlGF, sEng, and their ratios deltas and slopes in early pregnancy and midtrimester of patients who subsequently developed early-onset preeclampsia

Analyte	Early-onset preeclampsia (n=9)	Normal pregnancy/other complications (n=1613)	p
Early pregnancy			
sVEGFR-1	1307.7 (597.9–4546.5)	1719.2 (48.6–13575.1)	0.3
PlGF	16.9 (0.0–44.1)	33.4 (0.0–451.9)	0.01
sEng	8.6 (4.7–11.4)	7.1 (3.3–26.9)	0.3
PlGF/sVEGFR-1	0.012 (0.0–0.06)	0.018 (0.0–0.5)	0.08
PlGF/sEng	2.0 (0.0–6.3)	4.6 (0.0–60)	0.01
PlGF/sEng x sVEGFR-1	0.0015 (0.0–0.01)	0.0025 (0.0–0.06)	0.07
PlGF/sEng + sVEGFR-1	0.0017 (0.0–0.006)	0.0036 (0.0–0.05)	0.02
Midtrimester			
sVEGFR-1	4162.3 (1536–17768.9)	1610.7 (245–10595.5)	<0.001
PlGF	42.1 (0.0–126.3)	329.1 (22.3–2894.4)	<0.001
sEng	14.9 (7.9–47)	5.9 (2.4–29.6)	<0.001
PlGF/sVEGFR-1	0.01 (0.0–0.08)	0.2 (0.008–4.6)	<0.001
PlGF/sEng	4.4 (0.0–13.3)	55.0 (1.2–354.9)	<0.001
PlGF/sEng x sVEGFR-1	0.001 (0.0–0.009)	0.04 (0.0003–0.9)	<0.001
PlGF/sEng + sVEGFR-1	0.003 (0.0–0.01)	0.04 (0.001–0.3)	<0.001
Delta sVEGFR-1	3170.9 177.5–16476.6)	−129.5 (−12093.3–4120.4)	<0.001
Delta PlGF	21.0 (0.0–104.9)	288.9 (−72.9–2798.6)	<0.001
Delta sEng	9.1 (−1–41.5)	−1.2 (−14.2–18.8)	<0.001
Delta PlGF/sVEGFR-1	0.0 (v0.05–0.07)	0.2 (−0.04–4.4)	<0.001
Delta PlGF/sEng	0.0	49.1	<0.001
Delta PlGF/sEng x sVEGFR-1	0.0 (−0.01–0.007)	0.03 (v0.005–0.9)	<0.001
Delta PlGF/sEng + sVEGFR-1	0.0 (−0.002–0.009)	0.04 (−0.007–0.3)	<0.001
Slope sVEGFR-1	352.3 (15.3–1109)	−13.2 (−1019.9–379.7)	<0.001
Slope PlGF	2.1 (0.0–9.1)	28.2 (−6.2–321.2)	<0.001
Slope sEng	0.9 (−0.1–2.8)	−0.1 (−1.3–1.8)	<0.001
Slope PlGF/sVEGFR-1	0.0 (−0.005–0.006)	0.02 (−0.004–0.4)	<0.001
Slope PlGF/sEng	0.0 (−0.2–1)	4.9 (−0.7–39.1)	<0.001
Slope PlGF/sEng x sVEGFR-1	0.0 (−0.0009–0.0006)	0.003 (−0.0004–0.09)	<0.001
Slope PlGF/sEng + sVEGFR-1	0.0 (−0.0002–0.0008)	0.004 (−0.0006–0.03)	<0.001

Values are expressed as median (range)

Table VI

Predictive accuracy of maternal plasma concentrations of PlGF, sVEGFR-1, sEng, and their ratios, deltas and slopes in early pregnancy and midtrimester for the diagnosis of early-onset preeclampsia

Analyte	AUC	ROC curve p-value	Cutoff	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Early pregnancy									
PlGF	0.741	0.012	≤22.93	77.8%	69.7%	1.4%	99.8%	2.6 (1.5–3.1)	0.3 (0.09–0.8)
PlGF/sEng	0.745	0.011	≤2.91	77.8%	71.5%	1.5%	99.8%	2.7 (1.6–3.3)	0.3 (0.09–0.8)
PlGF/sEng + sVEGFR-1	0.733	0.016	≤0.0023	77.8%	72.7%	1.6%	99.8%	2.9 (1.7–3.4)	0.3 (0.09–0.8)
Midtrimester									
sVEGFR-1	0.865	<0.001	≥3460.4	66.7%	93.2%	5.2%	99.8%	9.8 (5.1–13.1)	0.4 (0.1–0.7)
PlGF	0.994	<0.001	≤126.42	100%	95.8%	11.8%	100%	24.1 (16.4–24.1)	0.0 (0.0–0.3)
sEng	0.973	<0.001	≥7.85	100%	89.8%	5.2%	100%	9.8 (6.8–9.8)	0.0 (0.0–0.3)
PlGF/sVEGFR-1	0.987	<0.001	≤0.082	100%	89.1%	4.9%	100%	9.2 (6.3–9.2)	0.0 (0.0–0.3)
PlGF/sEng	0.997	<0.001	≤13.44	100%	98.3%	24.3%	100%	57.6 (37.6–57.6)	0.0 (0.0–0.3)
PlGF/sEng x sVEGFR-1	0.993	<0.001	≤0.0087	100%	95.3%	10.6%	100%	21.2 (14.5–21.2)	0.0 (0.0–0.3)
PlGF/sEng + sVEGFR-1	0.997	<0.001	≤0.012	100%	98%	22%	100%	50.4 (33.2–50.4)	0.0 (0.0–0.3)
Delta sVEGFR-1	0.922	<0.001	≥176.62	100%	68.3%	1.7%	100%	3.2 (2.2–3.2)	0.0 (0.0–0.4)
Delta PlGF	0.993	<0.001	≤104.98	100%	94.9%	9.9%	100%	19.7 (13.4–19.7)	0.0 (0.0–0.3)
Delta sEng	0.949	<0.001	≥0.82	88.9%	96.5%	12.3%	99.9%	25.2 (15.4–28.1)	0.1 (0.02–0.4)
Delta PlGF/sVEGFR-1	0.988	<0.001	≤0.067	100%	90.5%	5.5%	100%	10.5 (7.2–10.5)	0.0 (0.0–0.3)
Delta PlGF/sEng	0.997	<0.001	≤10.95	100%	98.2%	23.7%	100%	55.6 (36.4–55.6)	0.0 (0.0–0.3)
Delta PlGF/sEng x sVEGFR-1	0.994	<0.001	≤0.0069	100%	96%	12.2%	100%	24.8 (16.9–24.8)	0.0 (0.0–0.3)
Delta PlGF/sEng+ sVEGFR-1	0.997	<0.001	≤0.0094	100%	97.9%	20.9%	100%	47.4 (31.4–47.4)	0.0 (0.0–0.3)
Slope sVEGFR-1	0.931	<0.001	≥45.67	88.9%	81.2%	2.6%	99.9%	4.7 (3.0–5.2)	0.1 (0.03–0.5)
Slope PlGF	0.995	<0.001	≤9.19	100%	97%	15.5%	100%	32.9 (22.1–32.9)	0.0 (0.0–0.3)
Slope sEng	0.933	<0.001	≥0.071	88.9%	95.9%	10.8%	99.9%	21.7 (13.4–24.3)	0.1 (0.02–0.4)
Slope PlGF/sVEGFR-1	0.990	<0.001	≤0.0058	100%	92.6%	7%	100%	13.6 (9.3–13.6)	0.0 (0.0–0.3)
Slope PlGF/sEng	0.998	<0.001	≤0.94	100%	98.9%	33.3%	100%	89.6 (56.4–89.6)	0.0 (0.0–0.3)

Analyte	AUC	ROC curve p-value	Cutoff	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
Slope PlGF/sEng x sVEGFR-1	0.995	<0.001	≤0.00059	100%	97%	15.5%	100%	32.9 (22.1–32.9)	0.0 (0.0–0.3)
Slope PlGF/sEng + sVEGFR-1	0.997	<0.001	≤0.00081	100%	98.6%	28.1%	100%	70.1 (45.1–70.1)	0.0 (0.0–0.3)

Prevalence of early-onset preeclampsia: 0.6% (9/1622)

AUC: area under the curve; **ROC:** receiver operating characteristic

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