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# THE CHANGE IN CONCENTRATIONS OF ANGIOGENIC AND ANTI-ANGIOGENIC FACTORS IN MATERNAL PLASMA BETWEEN THE FIRST AND SECOND TRIMESTERS IN RISK ASSESSMENT FOR THE SUBSEQUENT DEVELOPMENT OF PREECLAMPSIA AND SGA

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## Abstract

**Introduction—**An imbalance between angiogenic and anti-angiogenic factors has been proposed as central to the pathophysiology of preeclampsia (PE). Indeed, patients with PE and those delivering small-for-gestational age (SGA) neonates have higher plasma concentrations of soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) and the soluble form of endoglin (s-Eng), as well as lower plasma concentrations of vascual endothelial growth factor (VEGF) and placental growth factor (PlGF) than do patients with normal pregnancies. Of note, this imbalance has been observed before the clinical presentation of PE or the delivery of an SGA neonate. The objective of this study was to determine if changes in the profile of angiogenic and anti-angiogenic factors in maternal plasma between the first and second trimesters are associated with a high risk for the subsequent development of preeclampsia and/or delivery of an SGA neonate.

**Methods—**This longitudinal case-control study included 402 singleton pregnancies in the following groups: 1) normal pregnancies with appropiate for gestational age (AGA) neonates (n=201); 2) patients who delivered an SGA neonate (n=145); and 3) patients who developed PE (n=56). Maternal 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: 1) first sample obtained between 6 and 15 weeks of gestation (“first trimester” sample); and 2) second

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sample obtained between 20 and 25 weeks of gestation ("second trimester" sample). Plasma concentrations of s-Eng, sVEGFR-1 and PlGF were determined by specific and sensitive immunoassays. Changes in the maternal plasma concentrations of these angiogenesis-related factors were compared among normal patients and those destined to develop PE or deliver an SGA neonate while adjusting for maternal age, nulliparity and body mass index (BMI). General linear models and polytomous logistic regression models were used to relate the analyte concentrations, ratios, and product to the subsequent development of delivery of an SGA neonate.

**Results—**1) An increase in the maternal plasma concentration of s-Eng between the first and second trimesters conferred risk for the development of preterm PE and SGA (OR 14.9, 95% CI 4.9-45.0, and OR 2.9, 95% CI 1.5-5.6, respectively); 2) An increase in the maternal plasma concentration of sVEGFR-1 between the first and second trimester conferred risk for the development of preterm PE (OR 3.9, 95% CI 1.2-12.6); 3) A subnormal increase in maternal plasma PlGF concentration between the first and the second trimester was a risk factor for the subsequent development of preterm and term PE (OR 4.3, 95% CI 1.2-15.5, and OR 2.7, 95% CI 1.2-5.9, respectively); 4) In addition, the combination of the three analytes into a pro-angiogenic versus anti-angiogenic ratio [PlGF/(sEng x VEGFR-1)] conferred risk for the subsequent development of preterm preeclampsia (OR 3.7, 95% CI 1.1-12.1); 5) Importantly, patients with a high change in the s-Eng x sVEGFR-1 product had an OR of 10.38 (95% CI 3.18-33.84) for the development of preterm PE and 1.62 (95% CI 1.01-2.60) for the development of SGA.

**Conclusion—**Changes in the maternal plasma concentrations of s-Eng, sVEGFR-1, PlGF or their ratios between the first and second trimesters of pregnancy confer an increased risk to deliver a SGA neonate and/or develop PE.

### Keywords

SGA; longitudinal; PlGF; endoglin; sVEGFR-1

## INTRODUCTION

An "anti-angiogenic state" has been implicated as a mechanism of disease in preeclampsia (PE) [1-23], HELLP syndrome [23], and for delivery of a small for gestational age (SGA) neonate [11,23-29]. This state appears to result from an imbalance in the production and circulating concentrations of angiogenic factors such as placental growth factor (PlGF) and vascular endothelial growth factor (VEGF) and anti-angiogenic factors such as soluble VEGF receptor-1 (sVEGFR-1) and soluble endoglin (s-Eng). Elevated serum and plasma concentrations of sVEGFR-1 and s-Eng have been observed after the diagnosis of preeclampsia [1-3,7-9,[11],[12],[15],18,19,21-23] and before the recognition of clinical disease [4-6,10,13,[14],[16],17,20,30-32].

A natural consequence of the observations that changes in the serum/plasma concentrations of angiogenic and anti-angiogenic factors can be detected prior to the clinical recognition of the disease is that assays for such factors may be useful in the risk assessment for PE. Indeed, several studies have addressed this issue using a single analyte or a combination of analytes with the results of uterine artery Doppler velocimetry [24,33-36], as well as clinical risk factors. These studies have largely focused on one determination of the plasma/serum concentrations of angiogenic and/or anti-angiogenic factors. Recently, it has been proposed that serial determinations of the concentrations of sVEGFR-1 [37,38], PlGF [37], and s-Eng [38] are more informative in assessing the risk for PE than are single measurements in the first or second trimesters. This is plausible because PlGF, s-Eng, and sVEGFR-1 are produced by the trophoblast [23,39-44] and, therefore, maternal plasma concentrations can change with placental development from the first to the second trimester.

The purpose of this study was to determine if the changes between the first and second trimesters in the maternal plasma concentrations of PlGF, s-Eng, sVEGFR-1, or measures combining these analytes are risk factors for the development of PE. Because an anti-angiogenic state has also been postulated to exist in mothers delivering SGA neonates [11, 23-29], we have also determined the relationship between serial measures of these factors and the delivery of an SGA neonate.

## MATERIAL AND METHODS

### Study design

This retrospective longitudinal case-control study was designed to include patients in the following groups: 1) normal pregnancies; 2) patients who delivered an SGA neonate; and 3) patients who developed PE. Patients were considered to have a normal pregnancy if they did not have any obstetrical, medical, or surgical complication and had a term delivery (37-42 weeks) of a normal neonate with a birthweight appropriate for gestational age. SGA was defined as a birth weight below the $10^{th}$ percentile for gestational age [45]. Preeclampsia was diagnosed in the presence of systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on at least two occasions, 4 hours to 1 week apart, and proteinuria ≥300 mg in a 24 hours urine collection, or one dipstick with ≥2+ [46,47]. Patients with PE were classified as preterm (<37 weeks) or term (≥37 weeks), according to the gestational age at which PE was diagnosed.

Patients included in this study were enrolled in a longitudinal study whose aim was to identify biochemical factors for the prediction of adverse pregnancy outcomes. Plasma samples were obtained at the time of each prenatal visit, scheduled at 4-weeks 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 ("first trimester" sample) and the second between 20 and 25 weeks of gestation ("second trimester" sample). All pregnant women signed a consent form approved by the Human Investigation Committee of Sotero del Rio Hospital, Santiago, Chile and the IRB of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development.

Each case of PE or SGA was matched by maternal age, BMI and parity with a patient who had a normal pregnancy outcome. Matching by maternal age was conducted within each of the following age groups: 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, and 45-49 years. Matching for BMI was within 2 $kg/m^2$ and nulliparous or multiparous for parity. The rationale for the matching was that high and low maternal age, nulliparity and high BMI are risk factors for preeclampsia [48-56].

### Sample collection and human PlGF, soluble endoglin (s-Eng), and sVEGFR-1 immunoassays

Blood samples were collected into tubes containing EDTA. The samples were centrifuged and stored at -70°C. Laboratory personnel were blinded to clinical diagnosis. Maternal plasma concentrations of PlGF, s-Eng, and sVEGFR-1 were determined by sensitive and specific immunoassays (R&D Systems. Minneapolis, MN). All three immunoassays utilized a sandwich enzyme immunoassay technique and had been validated for plasma determinations of the analytes. The sensitivity, inter- and intra-assay coefficients of variation for each analyte obtained in our laboratory have been previously reported [57].

### Statistical Analysis

Measures of s-Eng, PlGF, and sVEGFR-1 were compared among women who subsequently had a normal pregnancy, those who developed term and preterm PE, and those who delivered

SGA neonates. Before adjusting for confounding variables, comparisons among groups were performed using Kruskal-Wallis, with Mann-Whitney U test for comparisons between groups.

The following measures were included for both the first and second trimesters, individually: 1) concentrations of s-Eng, PlGF, and sVEGFR-1; 2) the ratio between the maternal plasma concentrations of PlGF and s-Eng (PlGF/s-Eng); 3) the ratio between the maternal plasma concentrations of PlGF and sVEGFR-1 (PlGF/sVEGFR-1); 4) the product of the maternal plasma concentrations of s-Eng and sVEGFR-1 (s-Eng x sVEGFR-1); and 5) the ratio between the maternal plasma concentrations of PlGF and the product of s-Eng and sVEGFR-1 [PlGF/(s-Eng x sVEGFR-1)].

General linear models were used to identify significant differences among groups in single analytes and their ratios and products in the first and the second trimesters and the changes between the two trimesters. These analyses were adjusted for maternal age, BMI and nulliparity because these variables were not matched between patients who developed PE and those who delivered an SGA neonate. Bonferroni correction was used to adjust for multiple comparisons. Odds ratios for each single analyte, ratio or product as continuous variables were calculated with polytomous logistic regression adjusting for the same confounding factors mentioned above.

Slopes of PlGF, s-Eng, sVEGFR-1, PlGF/s-Eng, PlGF/sVEGFR-1, s-Eng x sVEGFR-1 and PlGF/(s-Eng x sVEGFR-1) were computed between the first and second trimesters (the difference between the concentrations in the first and second trimesters divided by the number of weeks between the measurements). The slopes of s-Eng, sVEGFR-1, and s-Eng x sVEGFR-1 between the first and second trimesters were dichotomized by direction of change for each patient (increase: positive or no change/decrease: negative). Because the slopes of PlGF, PlGF/s-Eng, PlGF/sVEGFR-1 and PlGF/(s-Eng x sVEGFR-1) were always greater than or equal to zero, the slopes were dichotomized at the median for the normal pregnancy group (above or below the median).

Odds ratios for the development of term PE, preterm PE, and SGA were calculated based on: 1) positive or negative values of slope for s-Eng, sVEGFR-1, and s-Eng x sVEGFR-1; and 2) values of slopes that were above or below the median for PlGF, PlGF/s-Eng, PlGF/sVEGFR-1 and PlGF/(s-Eng x sVEGFR-1) using polytomous logistic regression analysis, adjusting for maternal age, BMI and nulliparity.

SAS (version 9.1, SAS Institute Inc., Cary, NC, USA) and SPSS (version 14.0, SPSS Inc., Chicago, IL, USA) were used for analysis. A p-value of $<0.05$ was considered significant.

## RESULTS

### Patient population

This study included a total of 402 singleton pregnancies in the following groups: 1) normal pregnancies (n=201); 2) patients who delivered SGA neonates (n=145); 3) patients who developed term PE (n=39); and 4) patients who developed preterm PE (n=17). The demographic and clinical characteristics of the study groups are displayed in Table I. Patients with preterm PE had a significantly higher BMI than did patients with SGA (p=0.0069).

### Maternal plasma concentrations of PlGF, s-Eng, and sVEGFR-1 in the first or second trimester (and their ratios and product) in patients who subsequently had a normal pregnancy, preeclampsia, or delivered an SGA neonate

Median maternal plasma concentrations of PlGF, s-Eng, and sVEGFR-1 in the first and second trimesters are presented in Table II.

In the first trimester, patients destined to develop preterm or term PE had a lower median maternal plasma concentration of PlGF than those with normal pregnancies (p=0.002 and p=0.003, respectively). In addition, patients destined to develop preterm PE had a lower median maternal plasma PlGF concentration than those who delivered SGA neonates (p=0.02). In the second trimester, patients destined to develop preterm PE had a lower median maternal plasma concentration of PlGF than patients who had a normal pregnancy (p<0.0001), those destined to develop term PE (p=0.002), and women who delivered SGA neonates (p<0.0001). Moreover, women who developed term PE had lower plasma PlGF concentrations than those who had normal pregnancies (p=0.03) (see Table II).

Maternal plasma s-Eng concentrations in the second trimester were higher in patients destined to develop preterm PE than in those in women with normal pregnancies (p<0.0001), patients destined to develop term PE (p=0.004), and those who delivered SGA neonates (p-0.001). In addition, patients destined to develop term PE had a higher median s-Eng maternal plasma concentration than those who had a normal pregnancy (p=0.028). No significant differences were found among groups in the plasma concentration of s-Eng in the first trimester (see Table II).

The first trimester median plasma concentration of sVEGFR-1 was significantly lower in patients who developed preterm and term PE than those with normal pregnancies (p=0.025 and p=0.020, respectively). No significant differences were found among groups in plasma sVEGFR-1 concentration in the second trimester (see Table II).

### General linear model of the maternal plasma concentrations of PlGF, s-Eng, and sVEGFR-1 in the first or second trimester in patients who subsequently had a normal pregnancy, preeclampsia, or delivered an SGA neonate

After adjusting for confounding variables (maternal age, BMI, and nulliparity), the mean plasma concentration of PlGF was significantly different among diagnosis groups in the first and second trimesters (p=0.005 and p=0.0002, respectively). The mean plasma concentration of s-Eng was significantly different among diagnosis groups only in the second trimester (p<0.0001). In contrast, the mean plasma concentration of sVEGFR-1 was not significantly different among diagnosis groups in either the first or second trimesters. The PlGF/s-Eng ratio in the second trimester was significantly different among diagnosis groups (p<0.0001). The PlGF/sVEGFR-1 ratio and the s-Eng x sVEGFR-1 product were not significantly different among diagnosis groups in either the first or the second trimester. The odd ratios generated by the logistic regression model were consistent with the results of the general linear model and are presented in Table III.

### Changes in the maternal plasma concentrations of PlGF, s-Eng, and sVEGFR-1 (and their ratios and product) between the first and second trimesters and the subsequent development of preeclampsia and SGA

**PlGF slope—**Patients with a low increase in the maternal plasma PlGF concentration between the first and second trimesters (slope below than the median for patients with normal pregnancies) had an increased risk for the subsequent development of preterm and term PE, (OR 4.28, 95% CI 1.18-15.45; OR 2.7, 95% CI 1.24-5.89, respectively) but not SGA (Table IV).

**s-Eng direction of change between the first and second trimester—**We have previously demonstrated that the maternal plasma concentration of s-Eng decreases from the first to the second trimester in normal pregnancy [57]. Patients with an increase in s-Eng plasma concentration between the first and second trimesters (in comparison to those with no change or a decrease in the plasma concentration of s-Eng) had an increased risk for the subsequent

development of preterm PE (OR 14.92, 95% CI 4.94-45.08) or the delivery of an SGA neonate (OR 2.88, 95% CI 1.48-5.58) (Table IV).

**sVEGFR-1 direction of change between the first and second trimesters—**Patients with an increase in sVEGFR-1 maternal plasma concentrations between the first and second trimesters (in comparison to those with no change or a decrease in the concentration of sVEGFR-1) had an increased risk for the development of preterm PE (OR 3.90, 95% CI 1.21-12.59) (Table IV)

**Slopes of angiogenic to anti-angiogenic factor ratios and the product of s-Eng x sVEGFR-1—**Patients with a low change in the PlGF/s-Eng ratio (below the median slope for patients with normal pregnancies) had a higher risk for the development of preterm PE (OR 7.68, 95% CI 1.7-34.74) and term PE (OR 2.46, 95% CI 1.15-5.26), but not SGA. A low change in the PlGF/sVEGFR-1 ratio (below the median slope for patients with normal pregnancies) conferred a higher risk only for the development of preterm PE (OR 3.28, 95% CI 1.02-10.59). Patients with a low change in the PlGF/(s-Eng x sVEGFR-1) ratio also had an increased risk for the development of preterm PE (OR 3.71, 95% CI 1.14-12.11). Interestingly, a high change in the s-Eng x sVEGFR-1 product (above the median slope for patients with normal pregnancies) conferred an odds ratio of 10.38 (95% CI 3.18-33.84) for the development of preterm PE and 1.62 (95% CI 1.01-2.60) for the development of SGA (Table V).

**Combination of PlGF, s-Eng, and sVEGFR-1 slopes—**The combination of a PlGF slope below the median and positive s-Eng and sVEGFR-1 slopes was found in 0.99% (2/201) of patients with normal pregnancies and in 58.8% (10/17) of patients who developed preterm PE ($p<0.0001$). In contrast, the combination of a positive PlGF slope and negative s-Eng and sVEGFR-1 slopes was found in 23.4% (47/201) of patients with normal pregnancies and only in 5.9% (1/17) of patients who developed preterm PE ($p=0.13$).

## DISCUSSION

### Principal findings of the study

1) The profile of maternal plasma concentrations of angiogenic (PlGF) and anti-angiogenic factors (s-Eng and sVEGFR-1) between the first and second trimesters is significantly different among patients who subsequently had a normal pregnancy and those destined to develop PE or to deliver SGA neonates. 2) An increase in the maternal plasma concentration of s-Eng and sVEGFR-1 between the first and second trimester conferred risk for the development of preterm PE. 3) Moreover, a subnormal increase in maternal plasma PlGF between the first and the second trimesters was a risk factor for the subsequent development of preterm and term PE. 4) Importantly, the combination of the three analytes into a pro-angiogenic versus anti-angiogenic ratio [PlGF/(s-Eng x VEGFR-1)] conferred risk for the subsequent development of preterm PE. 5) A patient with a subnormal increase of PlGF, and increases of s-Eng and sVEGFR-1 from the first to the second trimester was at substantial risk for the development of preterm and term PE, and SGA.

### The profile of placental growth factor concentration in normal pregnancy, preeclampsia, and SGA

Placental growth factor is detectable in the plasma of most pregnant women from 9-11 weeks of gestation [57]. Thereafter, the concentration increases, reaching a peak at approximately 33 weeks, and subsequently declines as term approaches. The results of the current study indicate that patients with a subnormal increase in maternal plasma PlGF concentrations between the first and second trimesters of pregnancy are at increased risk for the development of PE

(preterm PE and term PE). In this study, no patients had concentrations of PlGF that decreased between the first and second trimesters.

### The profile of soluble endoglin concentration in normal pregnancy, PE, and SGA

Soluble endoglin has been detected in the plasma of normal pregnant women in the first and second trimesters of pregnancy. Its plasma concentrations decrease from the first to second trimester, but subsequently increase mildly [57]. The results of the present study indicate that a subset of patients destined to develop preterm PE and SGA have increasing concentrations of s-Eng between the first and second trimesters of pregnancy. Thus, serial evaluation of this anti-angiogenic factor identifies a subgroup at risk for adverse pregnancy outcome.

### The profile of soluble VEGFR-1 concentration in normal pregnancy, preeclampsia, and SGA

In normal pregnancy, maternal plasma concentrations of sVEGFR-1 remain largely unchanged between the first and second trimesters, and increase modestly thereafter. We found that an increase in sVEGFR-1 between the first and second trimesters conferred an increased risk for the development of preterm PE.

### The balance between an angiogenic factor (PlGF) and two anti-angiogenic factors (s-Eng and sVEGFR-1) in normal pregnancy, PE, and SGA

PE and SGA are often associated with a profile of angiogenic and anti-angiogenic factors which favors anti-angiogenesis (low PlGF, high s-Eng, high sVEGFR-1). Longitudinal studies have demonstrated that these changes precede the development of clinical disease or delivery of an SGA neonate [12,14,17,21,57]. The observations reported herein indicate that changes in the plasma concentrations of these factors can be detected between the first and second trimesters of pregnancy, and that a stereotypic pattern confers risk for PE and SGA. For example, most patients with a subnormal increase in PlGF and increasing concentrations of s-Eng and sVEGFR-1 (10 out of 17 patients) developed preterm PE.

### Strengths and limitations of this study

The strength of the current study is that this is the first study to have examined one angiogenic factor (PlGF) and two anti-angiogenic factors (s-Eng and sVEGFR-1) in normal pregnancies as well as two complications of pregnancy (PE and SGA). Most studies to date have focused on PE, and have not considered that SGA is also an anti-angiogenic state. In addition, we have adjusted for the effects of confounding factors such as parity, BMI, and maternal age. Limitations include the study design (nested case-control), which is susceptible to biases, and the sample size. A large cohort study is required to assess the likelihood ratios for the development of PE and SGA based on the angiogenic and anti-angiogenic factors studied herein.

### Conclusion

Serial determinations of PlGF, s-Eng, and sVEGFR-1 between the first and second trimesters are of value in the risk assessment for PE and SGA.

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## Table I

Demographic and clinical characteristics of the study groups

| | Normal Pregnancy (n=201) | SGA (n=145) | Preterm preeclampsia (n=17) | Term preeclampsia (n=39) |
|---|---|---|---|---|
| **Maternal Age (years)** | 24 (21-29) | 24 (21-30) | 25 (21-32) | 22 (19-26) |
| **Maternal height (cm)** | 156 (153-160) | 154 (151-159) *a* | 157 (154-163) | 158 (153-163) |
| **Pre-pregnancy weight (kg)** | 58 (52-67) | 55 (50-65) | 65 (59-78) *b* | 62 (56-73) *b* |
| **BMI (kg/m$^2$)** | 23.8 (21.2-26.9) | 23.4 (20.5-27) | 25.6 (23.6-30.5) *b* | 25 (23.4-27.8) |
| **Nulliparity (%)** | 49.3 (99/201) | 52.4 (76/145) | 52.9 (9/17) | 33.3 (13/39) |
| **GA at first sample (weeks)** | 12.2 (11-13.4) | 12.0 (10.7-13.7) | 11.6 (9.9-13.5) | 12 (10-12.7) |
| **GA at second sample (weeks)** | 22.3 (21.1-23.7) | 22.7 (21.3-23.9) | 23.4 (21.9-23.9) | 22.5 (21.3-23.6) |
| **GA at delivery (weeks)** | 39.7 (38.9-40.3) *c* | 39.4 (38.6-40.1) *c* | 34.7 (31.0-36.3) | 39 (38.1-39.6) *c* |
| **Smoking (%)** | 8 (16/201) | 10.3 (15/145) | 0 | 7.7 (3/39) |
| **Birthweight (grams)** | 3400 (3180-3655) *b,c,d* | 2780 (2560-2900) *a,c,d* | 1940 (1175-2470) *a,b, d* | 3270 (2820-3550) *a,b,c* |
| **SGA neonate (%)** | 0 *b,c,d* | 100 (145/145) *a,c,d* | 35.3 (6/17) *a,b* | 25.6 (10/39) *a,b* |

Data expressed as median (interquartile range) and percentage (proportion).

**BMI:** body mass index; **GA:** gestational age, **SGA:** small for gestational age.

*a* Significantly different from normal pregnancy

*b* Significantly different from SGA

*c* Significantly different from preterm preeclampsia

*d* Significantly different from term preeclampsia

## Table II

Median maternal plasma concentrations of PlGF, soluble endoglin, and sVEGFR-1 by study group and study visit

| | Normal Pregnancy (n=201) | SGA (n=145) | Preterm preeclampsia (n=17) | Term preeclampsia (n=39) |
|---|---|---|---|---|
| **PlGF (pg/mL) 1st trimester** | 35.4 (20.5-53.5) | 30 (18.3-51.9) | 20.3 (0-34.1) | 26.2 (13.6-37.8) |
| **PlGF (pg/mL) 2nd trimester** | 344. 8 (217.5-465-3) | 320.4 (207.9-468.1) | 126.3 (45.7-286.3) | 273.4 (175.2-385.8) |
| **s-Eng (ng/mL) 1st trimester** | 7.2 (6.3-8.3) | 7.1 (6.1-8.3) | 8 (5.8-8.8) | 7.3 (6.3-9.2) |
| **s-Eng (ng/mL) 2nd trimester** | 5.9 (5.1-6.8) | 6 (5.2-7.5) | 8 (6.7-15.1) | 6.5 (5.6-7.2) |
| **sVEGFR-1 (pg/mL) 1st trimester** | 1788 (1330.5-2398.6) | 1615.8 (1307-2294.9) | 1307.7 (1107.2-1760.3) | 1448 (1175.4-1962.4) |
| **sVEGFR-1 (pg/mL) 2nd trimester** | 1799.5 (1098.6-2571.7) | 1687 (1200.9-2513.2) | 1946.3 (1324.7-4266.3) | 1532.3 (956.3-2007.4) |

Data expressed as median (interquartile range).

**PlGF:** placental growth factor; **s-Eng:** soluble endoglin; **sVEGFR-1:** soluble vascular endothelial growth factor receptor-1; **SGA:** small for gestational age.

**Table III**

Polytomous logistic regression model for the estimation of the association between PlGF, s-Eng, and sVEGFR-1 plasma concentrations, ratios and product with the subsequent development of preeclampsia and delivery of an SGA neonate

| | | Preterm preeclampsia* | | Term preeclampsia | | SGA | | P value |
|---|---|---|---|---|---|---|---|---|
| | | OR | 95% CI | OR | 95% CI | OR | 95% CI | |
| PlGF | 1st trimester | 0.963 | 0.936-0.991 | 0.978 | 0.961-0.995 | 0.990 | 0.980-0.9996 | 0.0042 |
| | 2nd trimester | 0.988 | 0.982-0.994 | 0.998 | 0.995-1.0005 | 0.999 | 0.998-1.0005 | 0.0007 |
| s-Eng | 1st trimester | 1.060 | 0.752-1.496 | 1.241 | 0.996-1.547 | 0.943 | 0.817-1.089 | 0.1394 |
| | 2nd trimester | 3.211 | 1.784-5.781 | 1.474 | 1.115-1.948 | 1.107 | 0.933-1.314 | 0.0002 |
| sVEGFR-1 | 1st trimester | 0.999 | 0.998-1.000 | 0.999 | 0.999-1.000 | 1.000 | 0.999-1.000 | 0.0326 |
| | 2nd trimester | 1.000 | 0.999-1.001 | 1.000 | 0.999-1.000 | 1.000 | 1.000-1.000 | 0.3097 |
| PlGF / s-Eng | 1st trimester* | 0.307 | 0.115-0.815 | 0.481 | 0.254-0.911 | 0.812 | 0.554-1.191 | 0.0231 |
| | 2nd trimester* | 0.042 | 0.009-0.206 | 0.485 | 0.221-1.064 | 0.576 | 0.361-0.919 | 0.0002 |
| PlGF / sVEGFR-1 | 1st trimester* | 0.575 | 0.248-1.334 | 0.792 | 0.459-1.368 | 0.971 | 0.692-1.362 | 0.5361 |
| | 2nd trimester* | 0.254 | 0.091-0.705 | 0.920 | 0.551-1.537 | 0.932 | 0.682-1.275 | 0.0740 |
| s-Eng x sVEGFR-1 | 1st trimester* | 0.295 | 0.079,1.106 | 0.582 | 0.275-1.231 | 0.675 | 0.437-1.041 | 0.0867 |
| | 2nd trimester* | 0.773 | 0.218-2.740 | 0.921 | 0.469-1.808 | 1.016 | 0.665-1.551 | 0.9719 |

The polytomous logistic regressions were adjusted for maternal age, BMI and nulliparity. Odds ratio calculation is based on polytomous logistic regression, women with normal pregnancy serve as reference.

**PlGF:** placental growth factor; **s-Eng:** soluble endoglin; **sVEGFR-1:** soluble vascular endothelial growth factor receptor-1; **SGA:** small for gestational age; BMI- body mass index

**Table IV**

Odds ratios for association of the slopes of PlGF, s-Eng, and sVEGFR-1 maternal plasma concentrations between the first and second trimesters with the subsequent development of preterm PE, term PE, and delivery of an SGA neonate

| | Normal Pregnancy | Preterm preeclampsia | | | Term preeclampsia | | | SGA | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **n** | **n** | **OR** | **95%CI** | **n** | **OR** | **95%CI** | **n** | **OR** | **95%CI** |
| **PlGF slope between the 1st and 2nd trimesters** | | | | | | | | | | |
| **Below median** | 100 | 14 | 4.28 | 1.18-15.45 | 29 | 2.70 | 1.24-5.89 | 86 | 1.54 | 0.99-2.38 |
| **Above median** | 101 | 3 | 1 | Reference | 10 | 1 | Reference | 59 | 1 | Reference |
| s-Eng direction of change between the 1st and 2ndtrimesters | | | | | | | | | | |
| **≤ 0** | 185 | 7 | 1 | Reference | 33 | 1 | Reference | 117 | 1 | Reference |
| **> 0** | 16 | 10 | 14.92 | 4.94-45.08 | 6 | 2.01 | 0.7-5.61 | 28 | 2.88 | 1.48-5.58 |
| sVEGFR-1 direction of change between the 1st and 2nd trimesters | | | | | | | | | | |
| **≤ 0** | 108 | 4 | 1 | Reference | 19 | 1 | Reference | 75 | 1 | Reference |
| **> 0** | 93 | 13 | 3.90 | 1.21-12.59 | 20 | 1.14 | 0.57-2.29 | 70 | 1.12 | 0.73-1.73 |

Odds ratios are estimated from a polytomous logistic regression model adjusted for BMI, maternal age and nulliparity, with additional adjustment for gestational age.

**PlGF:** placental growth factor; **s-Eng:** soluble endoglin; **sVEGFR-1:** soluble vascular endothelial growth factor receptor-1; **SGA:** small for gestational age.

## Tables V

Odds ratios for association of the slopes of PlGF/sVEGFR-1, PlGF/s-Eng, PlGF/(s-Eng x sVEGFR-1) ratios and the s-Eng x sVEGFR-1 product between the first and second trimesters with the subsequent development of preterm PE, term PE, and delivery of an SGA neonate

| | **Normal Pregnancy** | **Preterm preeclampsia** | | | **Term preeclampsia** | | | **SGA** | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **n** | **n** | | **95%CI** | **n** | **OR** | **95%CI** | **n** | **OR** | **95%CI** |
| PlGF/s-Eng slope between the 1st and 2nd trimesters | | | | | | | | | | |
| Below median | 101 | 15 | 7.68 | 1.7-34.74 | 28 | 2.46 | 1.15-5.26 | 86 | 1.47 | 0.95-2.26 |
| Above median | 100 | 2 | 1 | Reference | 11 | 1 | Reference | 59 | 1 | Reference |
| PlGF/sVEGFR-1 slope between the 1st and 2nd trimesters | | | | | | | | | | |
| Below median | 101 | 13 | 3.28 | 1.02-10.59 | 19 | 0.83 | 0.41-1.67 | 76 | 1.13 | 0.73-1.74 |
| Above median | 100 | 4 | 1 | Reference | 20 | 1 | Reference | 69 | 1 | Reference |
| PlGF/(s-Eng x sVEGFR-1) slope between the 1st and 2nd trimesters | | | | | | | | | | |
| Below median | 100 | 13 | 3.71 | 1.14-12.11 | 22 | 1.20 | 0.59-2.45 | 71 | 0.99 | 0.64-1.53 |
| Above median | 101 | 4 | 1 | Reference | 17 | 1 | Reference | 74 | 1 | Reference |
| s-Eng x sVEGFR-1 direction of change between the 1st and 2nd trimesters | | | | | | | | | | |
| ≤ 0 | 151 | 4 | 1 | Reference | 28 | 1 | Reference | 95 | 1 | Reference |
| > 0 | 50 | 13 | 10.38 | 3.18-33.84 | 11 | 1.15 | 0.53-2.50 | 50 | 1.62 | 1.01-2.60 |

Odds ratios are estimated from a polytomous logistic regression model adjusted for BMI, maternal age and nulliparity, with additional adjustment for gestational age.

**PlGF:** placental growth factor; **s-Eng:** soluble endoglin; **sVEGFR-1:** soluble vascular endothelial growth factor receptor-1; **SGA:** small for gestational age.