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Circulating Angiogenic and Anti-Angiogenic Factors in Pregnant Women with Eclampsia

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Abstract

Objective—To determine if eclampsia has a different circulating profile of angiogenic [placental growth factor (PlGF)] and anti-angiogenic factors [soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) and soluble endoglin (sEng)] than severe preeclampsia.

Study Design—This cross-sectional study included women in the following groups: 1) normal pregnancy (n=40); 2) severe preeclampsia (n=40); and 3) eclampsia (n=20). Maternal serum PlGF, sVEGFR-1, and sEng concentrations were determined using ELISA.

Results—1) The median concentration of sVEGFR-1 and sEng was higher and of PlGF lower in severe preeclampsia or eclampsia than in normal pregnancy ($p<0.001$ for all); 2) the median concentrations of these 3 analytes did not differ significantly between the severe preeclampsia and eclampsia groups.

Conclusions—Eclampsia is associated with higher maternal circulating concentrations of sVEGFR-1 and sEng and lower concentrations of PlGF than normal pregnancy, but with similar concentrations to severe preeclampsia. These findings suggest that eclampsia shares a common pathogenic pathway as severe preeclampsia.

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Keywords

placental growth factor; PlGF; preeclampsia; pregnancy; sEng; sFlt-1; soluble endoglin; soluble vascular endothelial growth factor receptor-1; sVEGFR-1

INTRODUCTION

Preeclampsia, one of the "great obstetrical syndromes,"[1;2] complicates about 2 to 7% of pregnancies,[3] and is a major contributor to maternal and neonatal morbidity and mortality worldwide.[4-8] In recent years, an imbalance between circulating angiogenic and anti-angiogenic factors has emerged as a potential key pathway in the pathophysiology of preeclampsia.[9-69] Specifically, patients with preeclampsia have a higher circulating concentration of anti-angiogenic factors [i.e., soluble vascular endothelial growth factor receptor-1 (sVEGFR-1, also called soluble fms-like tyrosine kinase 1 (sFlt1))[15-17;20-22;25;31-33;37;39;41;42;45;48-50;57;58;60;69;70] and soluble endoglin (sEng)][34;35;49;51;52;57;60;63;69;70] and a lower maternal circulating concentration of free angiogenic factors [i.e., vascular endothelial growth factor (VEGF)[15;71] and placental growth factor (PlGF)][11;12;14;15;19;20;23;39;41;48;50;53;54;56-58;60;61;68;71;72] than patients with a normal pregnancy. These findings have been demonstrated both at the time of the clinical diagnosis of preeclampsia and also prior to the clinical manifestation of the disease.[12;14;19;20;23;25;44;47;48;50;51;59;60;63;68;72-78]

In addition, the degree of the angiogenic/anti-angiogenic imbalance in preeclampsia has been associated with disease severity. Indeed, Venkatesha et al.[35] reported that serum sEng concentrations were three-, five- and ten-fold higher in individuals with mild preeclampsia, severe preeclampsia and HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, respectively, compared to gestational age-matched controls. Therefore, sEng has been suggested to be a marker for severity of disease.[35]

Eclampsia, defined as the occurrence of new-onset grand mal seizures or unexplained coma in a woman with preeclampsia,[6;79] is a serious and life-threatening complication of pregnancy with an incidence of about 1 in 2000 pregnancies.[80;81] In approximately two-thirds of cases the onset of seizures is during pregnancy (antepartum or intrapartum); however, eclampsia can occur in the post-partum period in about one-third of cases (range 11% to 44%).[79;81-84] One of the signs characterizing women as having severe preeclampsia is the eclamptic seizures. However, the classical diagnostic signs of preeclampsia (i.e., hypertension and proteinuria) may not precede the eclamptic seizures in more than one-third of the cases,[81;82] and hypertension may be absent in about 20% of cases.[85;86] Katz et al.[82] analyzed a series of 53 cases of eclampsia and found that seizures were the first signs of preeclampsia in 60% of cases. The authors concluded that eclampsia seems not to be a progression from severe preeclampsia.[82]

The underlying pathophysiologic process predisposing pregnant women to eclamptic seizures is not clear. Several mechanism of disease have been implicated in the pathogenesis of eclampsia including hypertensive encephalopathy, cerebral edema, infarction, or hemorrhage, endothelial dysfunction, and others.[79;87-94] To our knowledge, there is no data regarding the concentrations of angiogenic/anti-angiogenic factors in serum from patients with eclampsia, and whether the concentrations of angiogenic and anti-angiogenic factors in these patients differ from those of patients with severe preeclampsia. Thus, the aim of this study was to compare the profile of circulating angiogenic (i.e., PlGF) and anti-angiogenic (i.e. sVEGFR-1 and sEng) factors in patients with eclampsia and those with severe preeclampsia.

PATIENTS AND METHODS

Study design

A cross-sectional study was conducted by searching our clinical database and bank of biologic samples, and included 100 pregnant women in the following groups: 1) normal pregnancy (n=40); 2) severe preeclampsia (n=40); and 3) eclampsia (n=20). Women with multiple pregnancies, fetuses with chromosomal and / or congenital anomalies, as well as women with HELLP syndrome or in which eclampsia occurred after the delivery of the placenta were excluded.

All participants provided written informed consent prior to the collection of blood samples. The collection of blood and its utilization for research purposes was approved by the Institutional Review Boards of Wayne State University. Many of these samples have been previously used to study the biology of inflammation, hemostasis, angiogenesis regulation and growth factor concentrations in normal pregnant women and those with pregnancy complications.

Clinical definitions

Women with a normal pregnancy were defined as those without medical, obstetrical, or surgical complications at the time of the study and who subsequently delivered an appropriate-for-gestational age infant at term (≥37 weeks of gestation)95 without neonatal complications. Preeclampsia was defined as the onset of hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg on at least two occasions, 4 hours to 1 week apart) after 20 weeks of gestation with proteinuria (≥300 mg in a 24-hour urine collection or at least one dipstick measurement ≥2+).6;96 Severe preeclampsia was diagnosed according to the criteria proposed by the American College of Obstetricians and Gynecologists (ACOG) committee6 as systolic blood pressure ≥160mmHg and/or diastolic blood pressure ≥110mmHg and/or proteinuria greater than 5g in a 24h collection or ≥3+ protein on dipstick, or in the presence of multi-organ involvement.3;6 HELLP syndrome was defined as hemolysis (serum LDH >600IU/l; bilirubin >1.2mg/dl; presence of schistocytes in peripheral blood), elevated liver enzymes (serum ALT and/or AST >70IU/l) and thrombocytopenia (platelet count <100,000/mm^3).[97] Eclampsia was defined as the occurrence of convulsions in pregnant women who had preexisting gestational hypertension or preeclampsia or as new-onset convulsions in women without a previously known hypertensive or seizure disorder, however in whom hypertension (systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg) was part of the clinical presentation.

Blood sample collection and determination of PlGF, sVEGFR-1 and sEng in maternal serum

Maternal blood samples were obtained from normal pregnant women either during an antenatal clinic visit or before a scheduled cesarean section, and from women with preeclampsia or eclampsia at the time of diagnosis. Samples of peripheral blood were obtained by venipuncture, centrifuged at 1300 × g for 10 min at 4°C, and stored at −70°C until assayed.

Concentrations of PlGF, sVEGFR-1 and sEng in maternal serum were determined using specific and sensitive immunoassays (R&D Systems, Minneapolis, MN, USA). All three immunoassays utilized the quantitative sandwich enzyme immunoassay technique. Immunoassays were carried out according to the manufacturer's recommendations. The calculated inter-assay coefficients of variation (CV) for PlGF, sVEGFR-1 and sEng immunoassays in our laboratory were 5.7%, 6.2% and 3.8%. Calculated intra-assay CVs for

PlGF, sVEGFR-1 and sEng were 4.4%, 2.2% and 2.8%. The calculated detection limit (sensitivity) for PlGF, sVEGFR-1 and sEng assays were 9.2 pg/ml, 16.8 pg/ml, and 0.11 ng/ml, respectively.

Statistical analysis

Kolmogorov–Smirnov tests were used to test for normal distribution of the data. Since maternal serum concentrations of PlGF, sVEGFR-1, and sEng were not normally distributed, Kruskal-Wallis test with *post-hoc* Mann-Whitney U test were used for comparisons of continuous variables among and between groups. Comparison of proportions was performed using Fisher's exact test. Correlations between continuous variables were examined using Spearman's rank correlation test. A multivariable logistic regression analysis was applied to determine the association between serum concentrations of PlGF, sVEGFR-1, and sEng (and their ratios) and eclampsia while adjusting for maternal age and gestational age at blood drawn among patients with severe preeclampsia and those with eclampsia (pooled together). A p-value <0.05 was considered statistically significant. Analysis was performed with SPSS, version 12 (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographic and clinical characteristics

The demographic and clinical characteristics of the study population are shown in Table 1. There were no significant differences among the study groups in the medians of any of the demographic characteristics, as well as in the median gestational age at blood drawn. As expected, patients with severe preeclampsia or eclampsia had significantly higher medians of maximal systolic and diastolic blood pressure and lower medians of gestational age at delivery and neonatal birthweight than women with a normal pregnancy. None of these variables differ significantly between patients with severe preeclampsia and those with eclampsia.

Maternal serum concentration of PlGF in women with a normal pregnancy, severe preeclampsia, or eclampsia

The median maternal serum PlGF concentration was lower in patients with severe preeclampsia (190 pg/mL, interquartile range (IQR) 63.1-190.0) or eclampsia (84.3 pg/mL, IQR 44.9-145.9) than that of women with a normal pregnancy (335.6 pg/mL, IQR 220.6-646.0; p<0.001 for both comparisons) (Figure 1). The median maternal serum concentration of PlGF was not significantly different between patients with severe preeclampsia and those with eclampsia (p=0.3). The association between maternal serum concentrations of PlGF and eclampsia remained non-significant after adjusting for maternal age and gestational age at blood drawn (OR 1.002, 95% CI 0.998-1.005; p=0.37).

Maternal serum concentration of sVEGFR-1 in women with a normal pregnancy, severe preeclampsia, or eclampsia

The median maternal serum sVEGFR-1 concentration was higher in patients with severe preeclampsia (19,070.6 pg/mL, interquartile range (IQR) 12,425.9-35,456.5) or eclampsia (28,527.9 pg/mL, IQR 14,441.1-53,197.3) than that of women with a normal pregnancy (6,483.3 pg/mL, IQR 3,464-8,585.5; p<0.001 for both comparisons) (Figure 2). The median maternal serum concentration of sVEGFR-1 was not significantly different between patients with severe preeclampsia and those with eclampsia (p=0.2). The association between maternal serum concentrations of sVEGFR-1 and eclampsia remained non-significant after adjusting for maternal age and gestational age at blood drawn (OR 1.000, 95% CI 1.000-1.000; p=0.5).

Maternal serum concentration of sEng in women with a normal pregnancy, severe preeclampsia, or eclampsia

The median maternal serum sEng concentration was higher in patients with severe preeclampsia (37.2 pg/mL, interquartile range (IQR) 21.9-47.8) or eclampsia (46.7 pg/mL, IQR 25.6-107.6) than that of women with a normal pregnancy (12.7 pg/mL, IQR 8.8-19.6; $p<0.001$ for both comparisons) (Figure 3). The median maternal serum concentration of sEng was not significantly different between patients with severe preeclampsia and those with eclampsia ($p=0.2$). The association between maternal serum concentrations of sEng (pg/mL) and eclampsia remained non-significant after adjusting for maternal age and gestational age at blood drawn (OR 1.013, 95% CI 0.998-1.029; $p=0.08$).

The ratios between PlGF, VEGFR-1, and sEng in women with a normal pregnancy, severe preeclampsia, or eclampsia

The ratios of PlGF/sVEGFR-1, PlGF/sEng, PlGF/(sEng X VEGFR-1), and PlGF/(sEng +VEGFR-1)[68] were all significantly lower in patients with severe preeclampsia or eclampsia than patients with a normal pregnancy ($p<0.001$ for all comparisons; Table 2). However, these ratios did not differ significantly between patients with severe preeclampsia and those with eclampsia (Table 2). In addition, the different ratios were not significantly associated with eclampsia after adjusting for maternal age and gestational age at blood drawn (data not shown).

COMMENT

Principal findings of the study

1) At the time of diagnosis, the median maternal serum concentrations of sVEGFR-1 and sEng were significantly higher and those of PlGF significantly lower in patients with severe preeclampsia or eclampsia than in women with a normal pregnancy; 2) Similarly, the ratios PlGF/sVEGFR-1, PlGF/sEng, PlGF/(sEng × sVEGFR-1), and PlGF/(sEng + sVEGFR-1) were significantly lower in patients with severe preeclampsia or eclampsia than those with a normal pregnancy; 3) In contrast, all 3 analytes and their ratios were comparable at the time of diagnosis in maternal circulation of patients with severe preeclampsia and those with eclampsia.

A large body of evidence supports the notion that an imbalance between angiogenic and anti-angiogenic factors in maternal circulation plays a critical role in the pathogenesis of preeclampsia. Increased concentrations of placental-derived anti-angiogenic factors (i.e., sVEGFR-1 and sEng) and decreased concentrations of free angiogenic factors (i.e., VEGF and PlGF) have been reported in maternal blood at the time of the clinical diagnosis of preeclampsia.[9-11;13;15-17;21;22;24;26-46;49;52-56;58;65-67;70;71] Levine et al.[20] reported that the concentrations of sVEGFR-1 begin to increase about five weeks prior to the manifestation of preeclampsia with a parallel decrease in free PlGF and free VEGF concentrations. Moreover, the authors reported that the degree of angiogenic/anti-angiogenic imbalance was associated with disease severity. Indeed, women with preterm preeclampsia or preeclampsia with a small-for-gestational (SGA) neonate had a more severe imbalance between these angiogenic/anti-angiogenic factors than women with term preeclampsia of preeclampsia without SGA.[20] A correlation between severity of preeclampsia and elevated concentrations of anti-angiogenic factors has been also demonstrated by others.[22;35;39;67] Venkatesha et al.35 reported that the concentrations of sEng were three-, five-, and tenfold higher in women with mild preeclampsia, severe preeclampsia and HELLP syndrome, respectively, than gestational-age matched normal pregnant women. Similarly, Chaiworapongsa et al.22 (sVEGFR-1), Masuyama at al.39 (sVEGFR-1 and sEng), and Kim et al.67 (sEng) reported an association between elevated circulating concentrations of anti-

angiogenic factors and severity of preeclampsia. However, to our knowledge, this is the first study that was specifically design to determine the concentration of angiogenic and anti-angiogenic factors in patients with eclampsia.

Eclampsia, the ultimate life-threatening complication of preeclampsia, is characterized by the occurrence of seizures in association with signs and symptoms of preeclampsia; yet, seizures as the first clinical manifestation of this complication of pregnancy is not an infrequent event.[79;81;82;86] The eclamptic seizures are commonly attributed to hypertensive encephalopathy,[79] and indeed, frequent findings in autopsy of women who died from eclampsia are cerebral edema and intracranial hemorrhage.[87;88] However, Schwartz et al.[91] reported that the baseline and maximal mean systolic and diastolic blood pressures were not significantly different between women with eclampsia with and without cerebral edema on MRI, and it has been proposed that the edema may be secondary to endothelial dysfunction.[64;91] The increased concentrations of anti-angiogenic factors in maternal circulation have been hypothesized to be related to the extensive endothelial dysfunction implicated in the pathogenesis of preeclampsia.[15] Indeed overexpression of sFlt1 and sEng in animals models have been associated not only with features of severe preeclampsia, but also cerebral edema that resembles what is noted in human eclampsia.[98]

In the present study, and consistent with previous reports, women with severe preeclampsia had a higher median serum concentration of sVEGFR-1 and sEng and a lower median PlGF concentration than normal pregnant women. Our study further demonstrates that women with eclampsia have a similar imbalance in angiogenic/anti-angiogenic factors as women with preeclampsia. However, there was no significant difference in the degree of angiogenic/anti-angiogenic imbalance (i.e., the median concentration of sVEGFR-1, sEng, PlGF, and their ratios) between women with severe preeclampsia and those with eclampsia. These findings suggest that the degree of angiogenic/anti-angiogenic imbalance *per se* is not associated with eclampsia. Thus, it seems that other factors rather than the maternal circulating concentration of angiogenic and anti-angiogenic factors may be involved in predisposing women to eclampsia.

Strength and limitation of the study—To our knowledge, this is the first study that specifically examines the changes in maternal serum concentrations of PlGF, sVEGFR-1, and sEng in patients with antepartum eclampsia. This is not the first report regarding angiogenic/anti angiogenic factors in preeclampsia to include patients with eclampsia; however, previous studies included such patients as part of the severe preeclampsia group.[20;25] Furthermore, we excluded patients with HELLP syndrome or post-partum eclampsia from this study, because both HELLP syndrome35 and the delivery of the placenta69;99 have been previously shown to be associated with changes in angiogenic/ anti-angiogenic factors. Thus, one of the limitations of this study relies on the relative small number of subjects with antepartum eclampsia without concomitant HELLP syndrome. Indeed, there was a trend toward higher median concentrations of sVEGFR-1 and sEng and a lower median concentration of PlGF in patients with eclampsia than in those with severe preeclampsia. It is possible that a higher sample size would reveal significant difference between these two entities. Another limitation is the fact that some patients with eclampsia were in active labor at the time of seizures and blood drawn. To date, the only study to examine the effect of the process of labor on anti-angiogenic factors concentration demonstrated a higher concentration of sVEGFR-1 (but not of sEng) in women with pre-eclampsia at full-dilatation compared to the pre-labor concentration.[69] The small sample size and different gestational age at blood drawn of the current study preclude us from determining whether labor itself could have influence our results.

In conclusion, our findings suggest that, similar to patients with severe preeclampsia, patients with eclampsia have increased maternal circulating concentration of the anti-angiogenic factors, sVEGFR-1 and sEng, and decreased concentrations of the angiogenic factor PlGF compared to women with a normal pregnancy. However, the concentrations of these 3 analytes and their ratios could not differentiate between patients with severe preeclampsia and those who experienced eclampsia during pregnancy. Collectively, these findings suggest that the severity of the angiogenic imbalance is not associated (at least not independently) with the presence of eclampsia. Further studies may be warranted, with a larger sample size as well as with a longitudinal design in order to determine whether one, or more, of the angiogenic/anti-angiogenic factors have a predictive value and a role in the pathophysiology of eclampsia.

CONDENSATION

Eclampsia, similar to severe preeclampsia, is associated with maternal circulating concentration of sVEGFR-1 and sEng and lower concentrations of PlGF than normal pregnant women.

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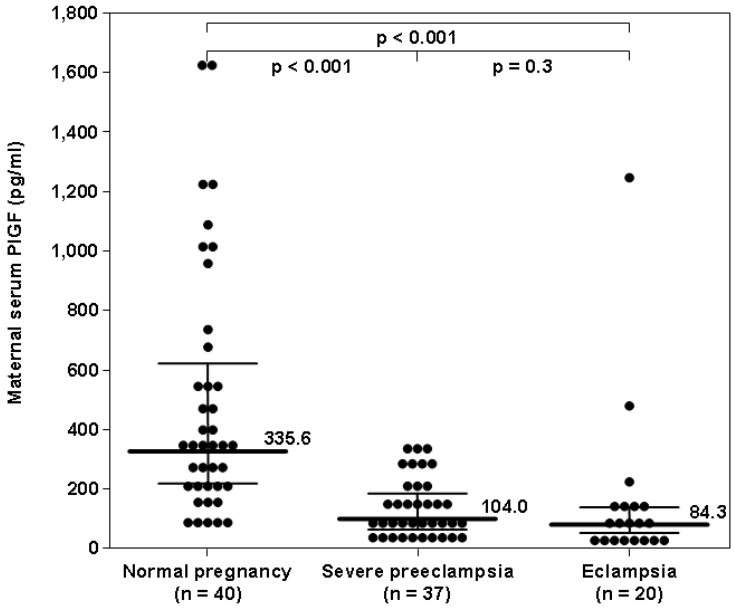

Figure 1. Comparison of serum concentration of placental growth factor (PlGF) between women with a normal pregnancy, severe preeclampsia, or eclampsia

The median maternal serum PlGF concentration was lower in patients with severe preeclampsia (190 pg/mL, interquartile range (IQR) 63.1-190.0) or eclampsia (84.3 pg/mL, IQR 44.9-145.9) than that of women with a normal pregnancy (335.6 pg/mL, IQR 220.6-646.0; $p<0.001$ for both comparisons). The median maternal serum concentration of PlGF was not significantly different between patients with severe preeclampsia and those with eclampsia ($p=0.3$).

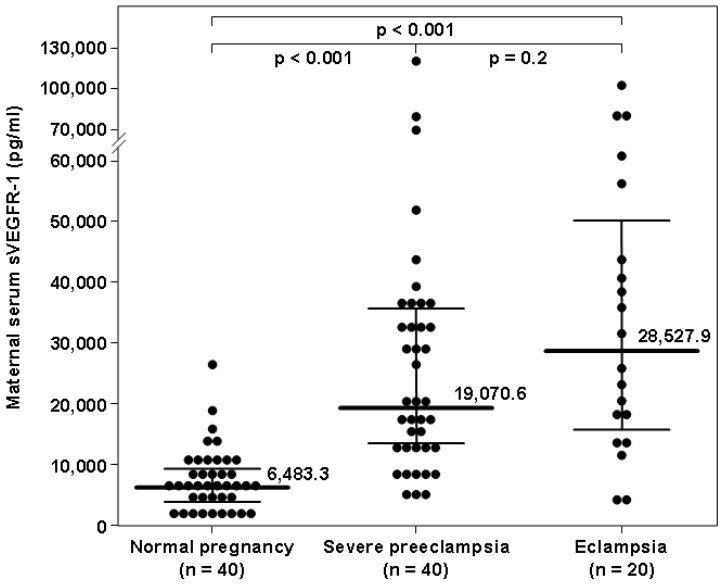

Figure 2. Comparison of serum concentration of soluble vascular endothelial growth factor receptor (sVEGFR)-1 between women with a normal pregnancy, severe preeclampsia, or eclampsia

The median maternal serum sVEGFR-1 concentration was higher in patients with severe preeclampsia (19,070.6 pg/mL, interquartile range (IQR) 12,425.9-35,456.5) or eclampsia (28,527.9 pg/mL, IQR 14,441.1-53,197.3) than that of women with a normal pregnancy (6,483.3 pg/mL, IQR 3,464-8,585.5; $p<0.001$ for both comparisons). The median maternal serum concentration of sVEGFR-1 was not significantly different between patients with severe preeclampsia and those with eclampsia ($p=0.2$).

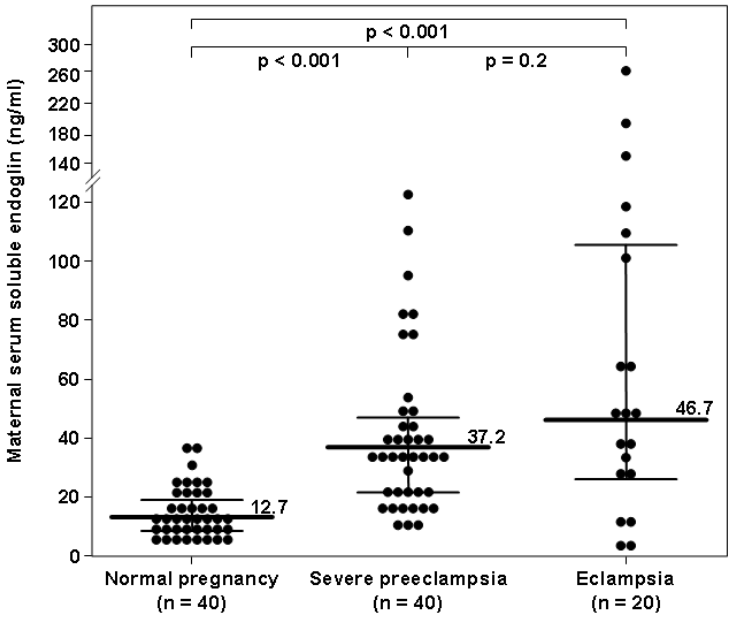

Figure 3. Comparison of serum concentration of soluble endoglin (sEng) between women with a normal pregnancy, severe preeclampsia, or eclampsia

*T*he median maternal serum sEng concentration was higher in patients with severe preeclampsia (37.2 pg/mL, interquartile range (IQR) 21.9-47.8) or eclampsia (46.7 pg/mL, IQR 25.6-107.6) than that of women with a normal pregnancy (12.7 pg/mL, IQR 8.8-19.6; p<0.001 for both comparisons). The median maternal serum concentration of sEng was not significantly different between patients with severe preeclampsia and those with eclampsia (p=0.2).

Table 1

Demographic and clinical characteristics of the study population

Variable	Normal pregnancy (n=40)	*p*[a]	Severe preeclampsia (n=40)	*p*[b]	Eclampsia (n=20)	*p*[c]
Maternal age (years) *	20 (19-23)	0.1	23.5 (18-27)	0.2	20 (17-25)	0.8
African American Ethnic origin	80 (32)	0.3	90 (36)	0.4	80 (16)	0.99
Nulliparity	87 (35)	0.005	57.5 (23)	0.3	75 (15)	0.3
Pre-pregnancy BMI (kg/m^2) *	25.8 (22.7-28.3)	0.3	27.6 (21.7-36.6)	0.8	25.5 (24.0-29.3)	0.6
BMI at blood draw (kg/m^2)*	30.7 (27.6-35.2)	0.2	35.0 (27.6-44)	0.9	34.8 (30.2-37.3)	0.3
Delta BMI (kg/m^2)*	4.8 (3.2-8.2)	0.99	5.1 (3.0-9.0)	0.2	7.9 (5.1-12.2)	0.1
Maximum Systolic BP (mm Hg) †	120 (110-130)	<0.001	165 (151-180)	>0.99	159 (150-174)	<0.001
Maximum Diastolic BP (mm Hg) †	68 (60-72)	<0.001	99 (88-104)	>0.99	96 (85-107)	<0.001
Gestational age at blood sampling (weeks) **	38.6 (34.5-39.9)	0.1	36.7 (34.7-38.9)	0.6	36.5 (32.2-39)	0.2
Gestational age at delivery (weeks) †	39.9 (39.0-40.4)	<0.001	36.8 (34.9-38.9)	>0.99	37 (33.2-39.2)	<0.001
Birthweight (grams) †	3400 (3122-3674)	<0.001	2624 (2030-3062)	0.6	2569 (1546-3227)	<0.001
Sample starage time (years) ***	12.7 (11.5-13.4)	0.4	12.2 (11.5-13.1)	0.09	11.5 (9.8-12.8)	0.0

Values are expressed as median (interquartile range) or percent (number)

BMI, body mass index; BP, blood pressure

* Kruskal-Wallis, p = NS

** Kruskal-Wallis, $p < 0.001$

*** Kruskal-Wallis, $p = 0.04$

† ANOVA, $p < 0.001$

p^a: Normal pregnancy vs. Severe preeclampsia

p^b: Severe preeclampsia vs. Eclampsia

p^c: Normal pregnancy vs. Eclampsia

Table 2

Comparison of the ratios of PlGF, VEGFR-1, and sEng in normal pregnancy, severe preeclampsia and eclampsia.

Ratio	Normal pregnancy (n=40)	p^a	Severe preeclampsia (n=40)	p^b	Eclampsia (n=20)	p^c
PlGF/sVEGFR-1*	0.0580 (0.0240-0.167)	<0.001	0.0047 (0.0025-0.0161)	0.27	0.0043 (0.0011-0.008)	<0.001
PlGF/sEng*	29.59 (9.86-64.98)	<0.001	2.69 (1.30-9.45)	0.22	1.56 (0.46-5.73)	<0.001
PlGF/(sEng × sVEGFR-1)*	0.0048 (0.0011-0.021)	<0.001	0.0002 (0.0001-0.0007)	0.19	0.0001 (0.0000-0.0004	<0.001
PlGF/(sEng + sVEGFR-1)*	0.0578 (0.0239- 0.1669)	<0.001	0.0047 (0.0025-0.016)	0.27	0.0043 (0.0011-0.008)	<0.001

Values are expressed as median (interquartile range)

*Kruskal-Wallis, $p < 0.001$

p^a: Normal pregnancy vs. Severe preeclampsia

p^b: Severe preeclampsia vs. Eclampsia

p^c: Normal pregnancy vs. Eclampsia