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LATE-ONSET PREECLAMPSIA IS ASSOCIATED WITH AN IMBALANCE OF ANGIOGENIC AND ANTI-ANGIOGENIC FACTORS IN PATIENTS WITH AND WITHOUT PLACENTAL LESIONS CONSISTENT WITH MATERNAL UNDERPERFUSION

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Abstract

Objective—An imbalance between maternal angiogenic/anti-angiogenic factors concentrations has been observed in preeclampsia (PE) and other obstetrical syndromes. However, the frequency of pathologic findings in the placenta and the changes in maternal plasma angiogenic/anti-angiogenic factor concentrations differ between late-and early-onset PE. The aim of this study was to determine if the maternal plasma concentrations of placental growth factor (PlGF), soluble endoglin (sEng), and soluble vascular endothelial growth factor receptor-1 and 2 (sVEGFR-1 and sVEGFR-2) are different in late-onset PE with and without placental pathologic findings consistent with maternal underperfusion.

Study design—A cross-sectional study was conducted including 64 uncomplicated women and 66 women with late-onset PE (>34 weeks) who had blood samples and placenta available for pathologic examination. Patients with late-onset PE were divided into those with and without placental histologic findings consistent with maternal underperfusion as proposed by the Society for Pediatric Pathology. Maternal plasma concentrations of PlGF, sEng, sVEGFR-1 and sVEGFR-2 were determined by ELISA. Non-parametric statistics were used for analysis.

Results—1) the prevalence of placental histological findings consistent with maternal underperfusion among women with late-onset PE was higher than that of those with an uncomplicated pregnancy (47% (31/66) vs. 7.8% (5/64) respectively; $p<0.01$); 2) patients with late-onset PE and histological findings consistent with maternal underperfusion had a significantly lower median plasma concentration of PlGF, plasma PlGF/sVEGFR-1 ratio and plasma PlGF/sEng ratio than those with late-onset PE without placental underperfusion lesions (each $p<0.05$); 3) the most common pathological findings in the placenta of patient with PE were lesions consistent with villous changes (77%, 24/31); and 4) isolated vascular lesions in the placenta were found only in 2 cases (6.5%), and the rest had a combination of villous and vascular lesions.

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Declaration of interest

Tinnakorn Chaiworapongsa is a consultant in the preeclampsia advisory board of Roche Diagnostics. This study was conducted without any support from Roche Diagnostics. The immunoassays used in this study were not acquired from Roche Diagnostics.

Conclusions—Nearly half of the patients with late-onset PE have placental lesions consistent with maternal underperfusion. These lesions are associated with an imbalance in the maternal concentration of angiogenic/anti-angiogenic factors. We propose that there is a link between maternal underperfusion and an anti-angiogenic state characterized by the changes in the concentrations of angiogenic and anti-angiogenic factors in women with late onset PE.

Keywords

Placental growth factor (PlGF); soluble endoglin (sEng); soluble vascular endothelial growth factor receptor-1 (sVEGFR-1); soluble vascular endothelial growth factor receptor-2 (sVEGFR-2); ischemic placenta

Introduction

Preeclampsia (PE) is one of the leading causes of perinatal and maternal mortality [1–6]. Despite extensive research, the pathophysiology of this syndrome is still unclear [7,8]. Accumulating evidence, however, indicates that a central feature in the pathophysiology of preeclampsia is failure of physiologic transformation of the spiral arteries [9–13]. Although the primary insults for these abnormalities remain elusive [14,15], it is postulated that the resulting poor placentation and reduced blood supply to the placenta in early pregnancy leads to the release of factors into the maternal circulation causing systemic endothelial cell dysfunction [16,17], metabolic changes [18–20], a pro-thrombotic state [21–26], complement activation [27–32], intravascular inflammation [33–38] and multiple organ damage [1,39,40]. Candidates for these unknown factors [7,41,42] are cytokines [43–45] syncytiotrophoblast microparticles [46,46,47] apoptotic products [48,49] reactive-oxygen species [50,51] activated leukocytes [52,53] angiotensin II type 1 receptor antibody [54–56], galactins [57–59], soluble vascular endothelial growth factor receptor (sVEGFR)-1 [60–64] and soluble endoglin (sEng) [65–67]. Recently, an anti-angiogenic state has been proposed to play a central role in the pathophysiology of PE [62–102].

An imbalance between circulating angiogenic factors [vascular endothelial growth factor (VEGF) and placental growth factor (PlGF)] and anti-angiogenic factors (sVEGFR-1, sVEGFR-2 and sEng) has been observed both prior to the clinical manifestation [62,67,72,73,82,86–88,90,95–97,103–106] and at the time of clinical diagnosis of PE [63,65,68,69,71,75,79,84,107,108]. The sources of the imbalance between angiogenic and antiangiogenic factors in the maternal circulation are thought to derive mainly from the ischemic or underperfused placenta [61,68,109,110]. Consistent with this hypothesis, increased impedance to blood flow in the uterine artery [75,86,87,96,111,112] or uterine artery ligation in pregnant animals [113–115] are associated with an imbalance in the concentrations of angiogenic/anti-angiogenic factors in maternal circulation.

Several investigators have proposed that early- and late-onset PE may have different pathophysiology and that these two phenotypes should be studied individually [116–118]. Early-onset PE (≤34 weeks) is associated with greater perinatal and maternal mortality and morbidity than late-onset disease (≥34 weeks) [119–121]. Thus, the former type of PE received much more attention from investigators than the latter. However, a recent study from South Africa reported a 30% rate of severe maternal complications, 13% of eclampsia and 1.9% of fetal deaths, in patients with late-onset PE [122]. Moreover, the prevalence of late-onset disease is much higher than that of early-onset PE [123]. Thus, late-onset PE remains a major cause of maternal morbidity/mortality and fetal death worldwide, especially in several developing countries [124–126].

Although the magnitude of the imbalance between angiogenic and antiangiogenic factor concentrations in maternal blood is greater in early-onset than in late-onset PE [62,71,75,90,112,127], and the presence of placental lesions such as decidual arteriolopathy, infarctions, hypermaturity of villi (which may be related to reduced uteroplacental blood flow) is more common in early-onset than in late-onset PE [128–130], a subset of patients with late-onset PE has been affected by an imbalance of angiogenic/anti-angiogenic factors in maternal circulation [71,75,97,112,131]. Interestingly, the relationship between pathologic lesions of the underperfused placenta and plasma angiogenic/anti-angiogneic factors concentrations in late-onset PE has never been studied.

To gain insight into the pathophysiology of late-onset PE, the aim of this study was to examine if there is a change in the maternal plasma concentrations of PlGF, sEng, sVEGFR-1 and sVEGFR-2 in patients with late-onset PE with and without placental lesions consistent with maternal underperfusion.

Material and Methods

This retrospective cross-sectional study was conducted by searching the clinical database and bank of biological samples of the Perinatology Research Branch of NICHD/NIH and included 66 patients with the diagnosis of late-onset PE (>34 weeks) and 64 women with uncomplicated pregnancies. All were enrolled at Hutzel Women's Hospital in Detroit, MI, USA between June 1999 to July 2002. The inclusion criteria for women with PE (cases) were: 1) singleton gestation; 2) absence of major fetal structural or chromosomal anomalies; 3) absence of chronic hypertension; and 4) blood samples available for assay of angiogenic and anti-angiogenic factors, and placental blocks available for pathological review. Patients with PE had venipuncture upon diagnosis at enrollment. The control group consisted of women who had a venipuncture at the time of admission to Labor and Delivery (in cases of scheduled Cesarean section) or at the antenatal clinic prior to delivery or the initiation of labor.

Clinical definitions

Preeclampsia was defined as new onset hypertension that developed after 20 weeks of gestation (systolic or diastolic blood pressure ≥140 and/or ≥90 mm Hg, respectively, measured on at least two occasions, 4 hours to 1 week apart) and proteinuria (≥300 mg in a 24-hour urine collection, or two random urine specimens obtained 4 hours to 1 week apart containing ≥1+ by dipstick [132]or one dipstick demonstrating ≥2+ protein) [133]. Severe PE was diagnosed as described previously [133]. Late-onset PE was defined as diagnosis of PE after 34 weeks of gestation [116]. An SGA neonate was defined by a birthweight below the 10^{th} percentile for gestational age using a reference range from Alexander et al [134].

A patient was considered to have an uncomplicated pregnancy if she met the following criteria: 1) singleton gestation; 2) no medical, obstetrical or surgical complications; 3) absence of labor at the time of venipuncture; and 4) delivery of a normal term infant (≥37 weeks) whose birth weight was between the 10^{th} and 90^{th} percentile for gestational age.

Histopathological examination of the placenta

Histopathological changes of the placenta were diagnosed according to the criteria proposed by the Perinatal Section of the Society for Pediatric Pathology [135], which included lesions consistent with maternal vascular underperfusion. Findings consistent with maternal underperfusion were classified as: 1) villous changes, further subdivided into abrupt onset (remote villous infarcts, recent villous infarcts), gradual onset with intermediate duration (increased syncytial knots, villous agglutination, increased intervillous fibrin), or gradual

onset with prolonged duration (distal villous hypoplasia); and 2) vascular lesions (persistent muscularization of basal plate arteries, mural hypertrophy of decidual arterioles, acute atherosis of basal plate arteries and/or decidual arterioles). The decreased placental weight/increased fetoplacental weight ratio, which is part of the villous changes of prolonged duration in the classification, was not included because this information was not uniformly available. The presence of findings consistent with maternal underperfusion was defined by the presence of at least one pathologic lesion consistent with the above classification.

Maternal plasma concentrations of angiogenic and anti-angiogenic factors

After venipuncture was performed, the blood was collected into tubes containing EDTA, centrifuged and stored at −70°C. Maternal plasma concentrations of PlGF, sEng, sVEGFR-1 and sVEGFR-2 were determined by sensitive and specific immunoassays obtained from R&D Systems (Minneapolis, MN). All four immunoassays utilized the quantitative sandwich enzyme immunoassay technique and their concentrations in maternal plasma were determined by interpolation from the standard curves. The results of plasma PlGF, sEng, sVEGFR-1 and sVEGFR-2 concentrations have been previously reported in a study that evaluated the relationship between angiogenic/antiangiogenic factors and Doppler studies [62,111,112]. The inter- and intra-assay coefficients of variation obtained were: PlGF: 6.02% and 4.8%, respectively; sEng: 2.3% and 4.6% respectively; sVEGFR-1: 1.4% and 3.9%, respectively and sVEGFR-2: 2% and 4%, respectively. The sensitivity of the assays was: PlGF: 9.52 pg/ml, sEng: 0.08 ng/ml, sVEGFR-1: 16.97 pg/ml and sVEGFR-2: 19.01 pg/ml.

Placental histopathologic examinations

Placental tissue samples were taken by systematic random sampling [136], and subsequently fixed in 10% neutral-buffered formalin overnight, and embedded in paraffin. Five 3m-thick paraffin sections were stained with hematoxylin and eosin, and examined using bright-field light microscopy. Histopathologic examinations were performed by anatomic pathologists who were blinded to the clinical diagnosis.

Patients were divided into those with and without placental histologic findings consistent with maternal underperfusion [135]. The maternal plasma concentrations of PlGF, sEng, sVEGFR-1 and -2, the ratios of PlGFs/VEGFR-1 and PlGF/sEng in late-onset PE were compared between patients with and without these lesions.

All women provided written informed consent prior to the collection of samples. The collection of samples was approved by the Human Investigation Committees and its utilization for research purposes by the Institutional Review Boards of both, Wayne State University and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, DHHS.

Statistical Analysis—The normality of the data was tested using the Shapiro-Wilktest. Kruskal Wallis and post-hoc Mann-Whitney U tests were utilized for comparison of continuous variables among and between groups. Adjustment for multiple comparisons was performed with the Holm method. The Pearson's chi-square test was used to compare the proportion of placental lesions in the two groups. Analysis was conducted with SPSS V.15 (SPSS Inc., Chicago, IL). A p value <0.05 was considered significant.

Results

The clinical and obstetrical characteristics of women with an uncomplicated pregnancy (control) and that of those with late-onset PE, with and without underperfused placental

lesions, are displayed in Table I. Patients with late-onset PE (with or without evidence of underperfused placental lesions) had a lower median gestational age at delivery and birthweight than normal pregnant women (all $p<0.01$; Table I). There were no significant differences in the demographic characteristics between patients with late-onset PE with and without evidence of underperfused placental lesions. As expected, women with late-onset PE and evidence of underperfused placental lesions delivered a higher proportion of SGA neonates than those without evidence of these lesions (64.5% vs. 37.1%; $p<0.05$). There was no difference in the proportion of severe PE among patients with late-onset PE with and without underperfused placental lesions (83.9% vs. 88.6%; $p>0.05$).

Placental histologic findings

Patients with late-onset PE had a higher rate of placental lesions consistent with maternal underperfusion than those with uncomplicated pregnancies [47% (31/66) vs. 7.8% (5/64); $p<0.01$). Among patients with late-onset PE with underperfused placental lesions, 77.5% (24/31) had lesions consistent with villous changes, 6.5% (2/31) had isolated vascular lesions and 16% (5/31) had a combination of villous and vascular lesions. In contrast, all of the underperfused placental lesions observed in the control group consisted of villous changes.

To exclude the potential contribution of SGA to the frequency of underperfused placental lesions, a sub-analysis was performed excluding the women with PE who delivered an SGA neonate in the late-onset PE group. There were 33 patients with late-onset PE without SGA and 33% (11/33) of these cases had histologic lesions consistent with maternal underperfusion. After exclusion of patients with PE and SGA, the frequency of underperfused placental lesions was still more common in late-onset PE than in women with uncomplicated pregnancies [33.3% (11/33) vs. 7.8% (5/64); $p<0.05$].

Late-onset PE was associated with an imbalance of angiogenic/anti-angiogenic factors in maternal circulation

Women with late-onset PE, (either with or without underperfused placental lesions), had a higher median plasma concentration of sEng and sVEGFR-1 and lower median plasma concentrations of PlGF, PlGF/sVEGFR-1 ratio and PlGF/sEng ratio than women with an uncomplicated pregnancy (all $p<0.001$; see Figures 1–5 and Table II). In addition, the median plasma concentration of sVEGFR-2 was significantly lower in women with PE without underperfused placental lesions than that of uncomplicated pregnancies ($p=0.001$; see Figure 6 and Table II).

Patients with late-onset PE with underperfused placental lesions had a higher magnitude of an imbalance of angiogenic/anti-angiogenic factors than those without these lesions

Among women with late-onset PE, those with histological findings consistent with maternal underperfusion had a lower median plasma concentration of PlGF, PlGF/sVEGFR-1 ratio and PlGF/sEng ratio than those without these lesions; (all $p<0.05$; Figure 1–3 and Table II). The median plasma concentration of sEng and sVEGFR-1 was higher in patients with PE and evidence of underperfused placental lesions than that of those without these lesions. However, the difference did not reach statistical significance ($p=0.1$ for each; Figure 4 and 5; Table II). In contrast, there was no significant difference in the median plasma concentration of sVEGR-2 between the 2 groups ($p= 0.3$; Figure 6 and Table II).

Discussion

Principal findings of the study

1) A subset of patients with late-onset PE had an imbalance of angiogenic/anti-angiogenic factor concentrations in maternal circulation; these patients also had a higher frequency of histologic findings consistent with maternal underperfusion than that of women with a normal pregnancy; 2) among women with late-onset PE, the most common placental lesion associated with maternal underperfusion is villous changes (77%); and 3) the plasma concentrations of PlGF, PlGF/sVEGFR1 ratio and PlGF/sEng ratio, markers of angiogenic forces, were lower in patients with late-onset PE with underperfused placental lesions compared to those without these lesions.

Late-onset PE is associated with an imbalance of angiogenic/antiangiogenic factors

The finding that women with late-onset PE had significantly lower plasma concentrations of PlGF, sVEGFR-2, PlGF/sEng ratio and PlGF/sVEGFR-1 ratio and higher sVEGFR-1 and sEng compared to normal pregnant women extended our observations from a previous study in which we reported the changes of maternal plasma concentrations of angiogenic/anti-angiogenic factor in late-onset PE compared to normal pregnancy in a Hispanic population [62,67,71]. Although the mean plasma concentrations of PlGF and sVEGFR-1 has been reported to be different between Caucasians and Hispanics [137], evidence of an imbalance of angiogenic/antiangiogenic factors concentrations in PE has consistently been observed in women of Hispanic, Caucasian, Asian, African and African-American ethnic origin, and therefore, appears to be a consistent finding of the disorder [79,94,137–141]. Additional findings from the current study are that patients with late-onset PE, either with or without underperfused placental lesions, also experienced perturbation of these angiogenic/anti-angiogenic factors in their circulation.

Late-onset PE with underperfused placental lesions

The observation that patients with late-onset PE had a higher frequency of placental lesions consistent with maternal underperfusion than those with uncomplicated pregnancies is consistent with our observation in a Hispanic population [142]. A nested case-control study that included 8,307 women with singleton pregnancies reported that the prevalence of placental findings suggestive of maternal underperfusion on patients with PE decreased gradually with gestational age [142]. For example, the prevalence of histological lesions of placental underperfusion, using similar criteria, in PE decreased from approximately 75% before 32 weeks of gestation to about 50% after 34 weeks, and to 30% at term gestation [142]. In the current study, almost half of women with late-onset PE had evidence of histologic placental lesions consistent with maternal underperfusion.

Erez et al. have reported that women with PE had a higher proportion of underperfusion placental lesions than women who had an SGA neonate without PE [55.6% (65/117) vs. 32.7% (16/49)] [24]. In addition, syncytial knots was the lesion most commonly observed in women with PE [24]. Such findings are consistent with those observed in this study. In contrast, in a small histomorphometric study, placenta from women with PE at term without growth restriction were described to be similar to those from uncomplicated pregnant women at term regarding weight, parenchymal and cellular content, and surface areas of exchange between the mother and the fetus [143]. The prevalence of placental lesions indicative of underperfusion in the current study was 33% after exclusion of patients with PE and SGA, one of the most severe forms of late-onset PE. Possible explanations for these discrepant findings are the differences in histological criteria used to evaluate the placentas and the higher proportion of patients with severe PE included in the current study. While abnormal morphology of the villous tree is frequently observed in early-onset IUGR

(elongated maldeveloped villi) and PE (excessive branching villi) [144–147], Egbor et al reported that late-onset PE had a minimal influence on placental villous and vascular morphology compared with gestational age-matched controls [148]. The current study did not evaluate anatomical or morphometric changes of the villous tree.

Relationship between underperfused placental lesions and an imbalance of angiogenic/antiangiogenic factors among patients with late-onset PE

Patients with late-onset PE without placental lesions of underperfusion had lower plasma concentrations of PlGF and higher sVEGFR-1, sEng than uncomplicated pregnant women. However, patients with late-onset PE who had placental lesions of underperfusion had a phigher magnitude of an imbalance of angiogenic/anti-angiogenic factors concentration than those without placental lesions as demonstrated by significantly lower PlGF, PlGF/sVEGFR-1 ratio, and PlGF/sEng ratio. This perturbation is mainly driven by lower concentrations of the angiogenic factor PlGF, rather than an increase in anti-angiogenic factors as observed in early-onset disease [63,71,75,112,131].

In fact, *in vitro* studies have demonstrated that hypoxia may regulate the expression of PlGF, as demonstrated in isolated human term syncytiotrophoblast under hypoxic conditions (e.g. reduced mRNA PlGF expression) [149]. Similarly, hypoxia reduced the PlGF concentrations in the supernatant of primary cytotrophoblast cultures [150]. Thus, it is possible that chronic uteroplacental ischemia may account for the low maternal plasma concentration of PlGF in this subgroup of patients. However, a primary deficiency in PlGF cannot be excluded. The changes of sVEGFR-1 and sEng, which can also be induced by hypoxia, were modest and did not reach statistical significance in this study.

Imbalance of angiogenic factor in patients with late-onset PE without placental lesions of underperfusion

It is noteworthy that plasma sVEGFR-2 concentrations in late-onset PE are significantly lower than that of uncomplicated, pregnant women only in patients without evidence of an underperfused placenta. We interpret our results as suggesting that this subgroup of patients may have evidence of systemic inflammation without placental involvement [33–35]. Low plasma concentrations of sVEGFR-2 have been observed in patients with systemic inflammation, such as pyelonephritis during pregnancy [151]. Non-placental sources of angiogenic/antiangiogenic factors are activated monocytes, platelets and endothelial cells which may be responsible for the increase of anti-angiogenic factors in this subgroup of patients [152]. This interpretation would be consistent with the hypothesis that other factors (i.e. maternal systemic inflammation), rather than unique placenta factors, may play a significant role in the pathogenesis of late-onset PE [34,153].

Strengths and limitations of the study

This study is the first to examine the relationship between placental histologic findings and several maternal plasma angiogenic/antiangiogenic factors implicated in the pathophysiology of late-onset PE. Moreover, the histologic criteria used in this study were derived from a research and consensus study in which the pathological findings are reproducible [135,154]. Three limitations of this study are: 1) the inclusion criteria of this study required that every patient had placenta and plasma samples collected; therefore, a limited number of patients were included; 2) the criteria used to define lesions of placenta underperfusion may be too broad and the prevalence of these lesions could be decreased if more than two subclasses of lesions were required for the diagnosis; and 3) the prevalence of severe PE was high in this study. This may represent the nature of the patients admitted to a single tertiary care center.

Conclusion

A subset of patients with late-onset PE has an imbalance of angiogenic/anti-angiogenic factors concentration in maternal plasma. These patients also have a higher frequency of placental histological findings consistent with maternal underperfusion than uncomplicated pregnancies. Of note, the imbalance between angiogenic and antiangiogenic factors is predominantly due to low concentrations of the angiogenic factor PlGF.

Since late-onset PE is more common than early-onset PE, serious efforts to understand the pathophysiology and placental pathology of this condition must be undertaken. It is often overlooked that most women with eclampsia are patients with late-onset PE. Thus, the recent focus on early-onset PE should not diminish the clinical, epidemiologic, scientific, and public health importance of late-onset PE. Our study is an effort to understand late-onset PE.

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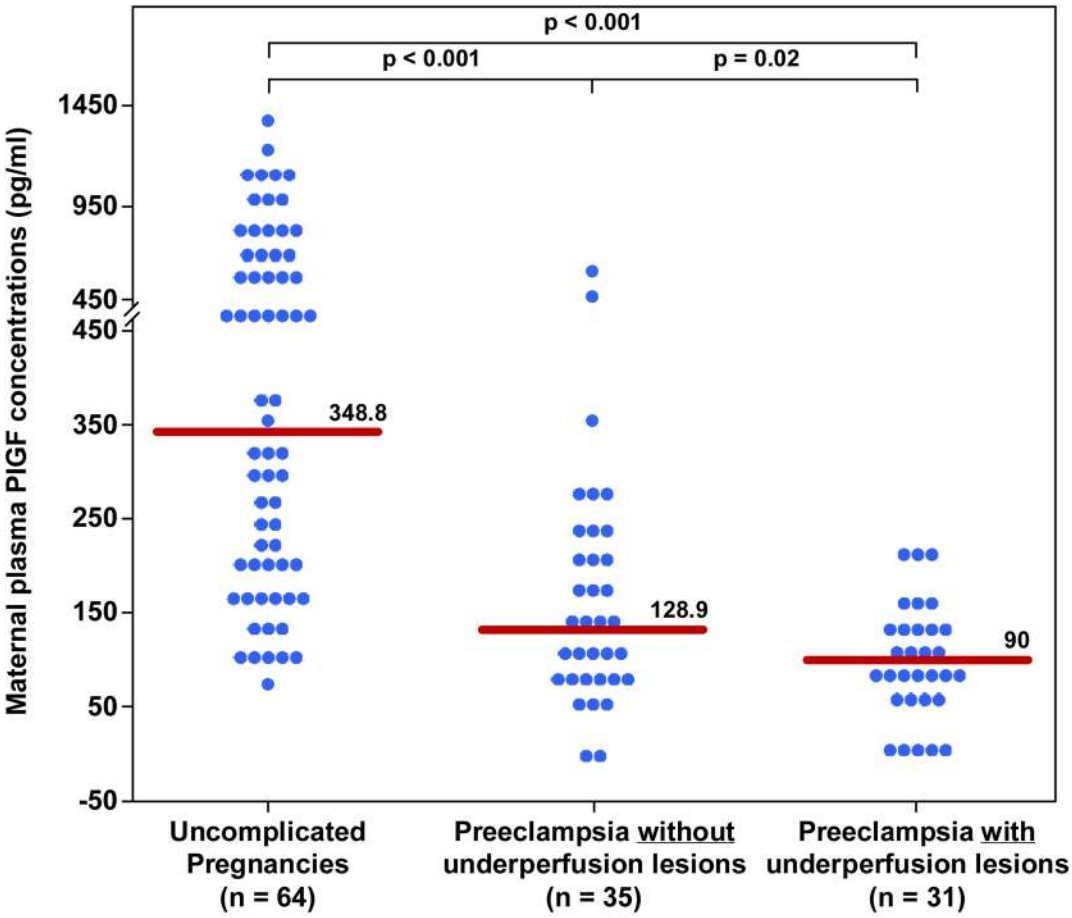

Figure 1. Maternal plasma concentration of PlGF between women with an uncomplicated pregnancy and women with late-onset PE with and without underperfused placental lesions

Women with late-onset PE without underperfused placental lesions had a lower median plasma PlGF concentration than women with uncomplicated pregnancies. Similarly, women with late-onset PE with underperfused placental lesions had a lower median plasma PlGF concentration than women with uncomplicated pregnancies. Among women with late-onset PE those who had underperfused placental lesions had a lower median plasma PlGF concentration than those without these lesions.

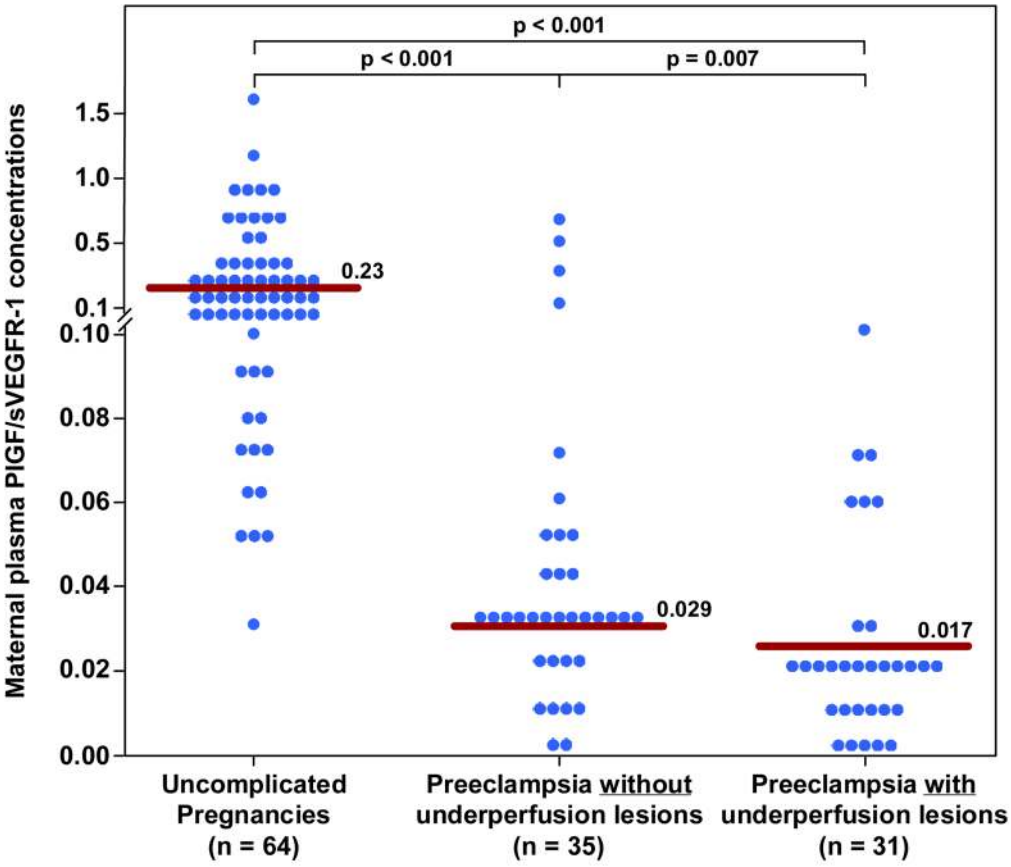

Figure 2. Maternal plasma PlGF/sVEGFR-1 ratio between women with an uncomplicated pregnancy and women with late-onset PE with and without underperfused placental lesions

Women with late-onset PE without underperfused placental lesion had lower median plasma PlGF/sVEGFR-1 ratio than women with uncomplicated pregnancies. Similarly, women with late-onset PE with underperfused placental lesions had a lower median plasma PlGF/sVEGFR-1 ratio than women with uncomplicated pregnancies. Among women with late-onset PE those with underperfused placental lesions had a lower median plasma PlGF/sVEGFR-1 ratio than women with late- onset PE without evidence of underperfused placental lesions.

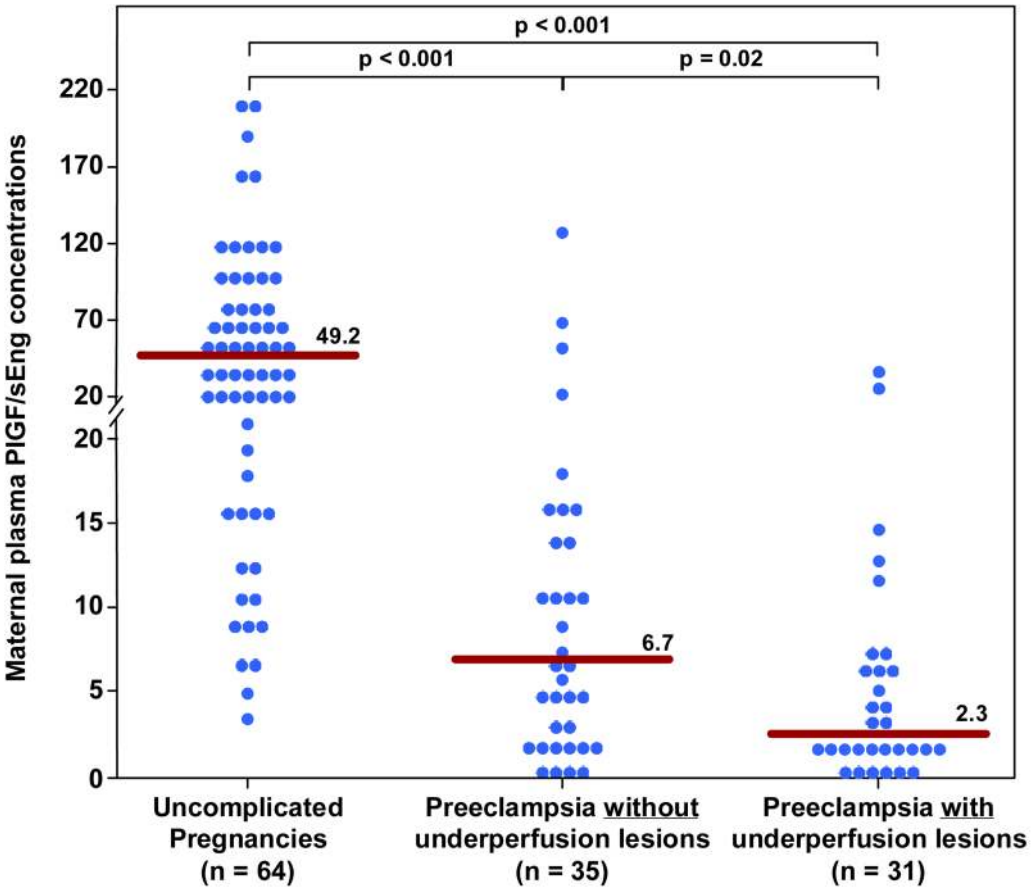

Figure 3. Maternal plasma PlGF/s-Eng ratio between women with an uncomplicated pregnancy and women with late-onset PE with and without underperfused placental lesions

Women with late-onset PE without underperfused placental lesion had lower median plasma PlGF/s-Eng ratio than women with uncomplicated pregnancies. Similarly, women with late-onset PE with underperfused placental lesions had a lower median plasma PlGF/s-Eng ratio than women with uncomplicated pregnancies. Among women with late-onset PE those with underperfused placental lesions had a lower median plasma PlGF/s-Eng ratio than women with late-onset PE without evidence of underperfused placental lesions.

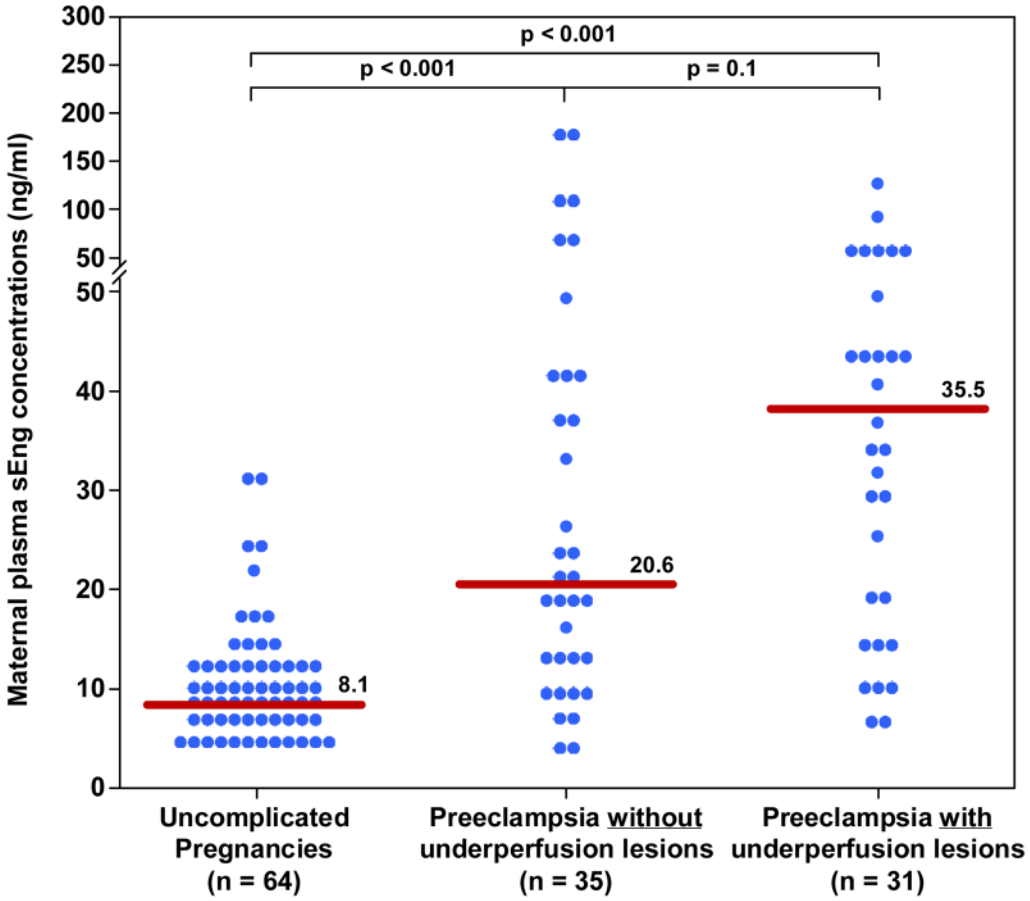

Figure 4. Maternal median plasma concentration of s-Eng between women with an uncomplicated pregnancy and women with late-onset PE with and without underperfused placental lesions

Women with late-onset PE without underperfused placental lesions had a higher median plasma s-Eng than women with uncomplicated pregnancies. Similarly, women with late-onset PE with underperfused placental lesions had a higher median plasma s-Eng than women with uncomplicated pregnancies. In contrast, there was no difference in the median plasma s-Eng between women with late-onset PE with or without underperfused placental lesions.

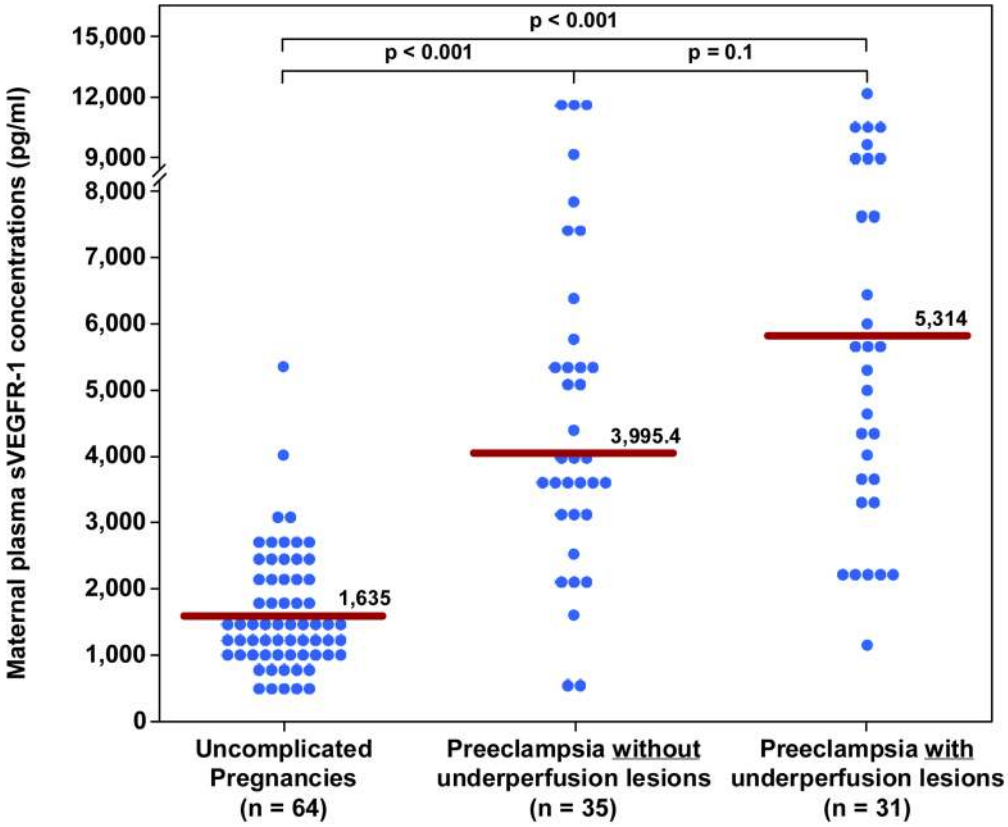

Figure 5. Maternal median plasma concentration of sVEGFR-1 between women with an uncomplicated pregnancy and women with late-onset PE with and without underperfused placental lesions

Women with late-onset PE without underperfused placental lesions had a higher median plasma sVEGFR-1 than women with uncomplicated pregnancies. Similarly, women with late-onset PE with underperfused placental lesions had higher median plasma sVEGFR-1 than women with uncomplicated pregnancies. In contrast, there was no difference in the median plasma sVEGFR-1 between women with late-onset PE with or without underperfused placental lesion.

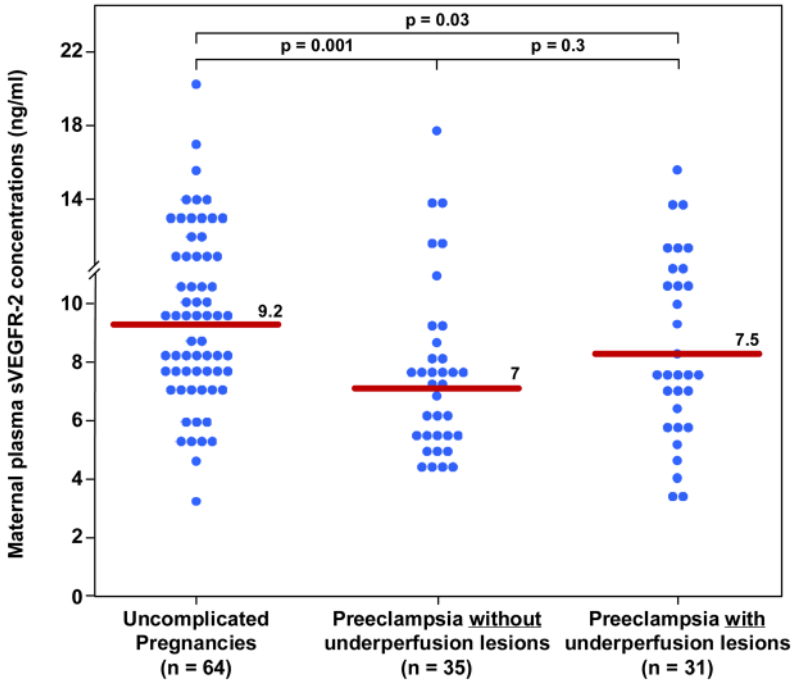

Figure 6. Maternal median plasma concentration of sVEGFR-2 between women with uncomplicated pregnancy and women with late-onset PE with and without underperfused placental lesions

Women with late-onset PE without underperfused placental lesion had higher median plasma sVEGFR-2 than women with uncomplicated pregnancies. In contrast, there was no difference in the median plasma concentration of sVEGFR-2 between women with late-onset PE with underperfused placental lesions women with uncomplicated pregnancies. There was no difference in the median plasma sVEGFR-2 between women with late-onset PE with or without underperfused placental lesion.

Table I

Clinical and obstetrical characteristics of the study population

	Uncomplicated Pregnancy (n = 64)	Preeclampsia without placental lesions of underperfusion (n = 35)	Preeclampsia with placental lesions of underperfusion (n = 31)
Maternal age (y)	27 (22 – 30)	21 (18 – 27) *	24 (20–30)
Nulliparity	11 (17.2)	21 (60)	20 (64.5)
Smoking	14 (21.9)	5 (14.3)	6 (19.4)
Gestational age at venipuncture (wks)	39.1 (38.3 – 39.4)	37.7 (36.5 – 39) *	38.4 (36 – 39.8)
Severe preeclampsia	0	31 (88.6)	26 (83.9)
Gestational age at delivery (wks)	39.1 (38.8 – 39.8)	37.8 (36.5 – 39) *	38.5 (36 – 39.8) *
Birthweight (g)	3342 (3152 – 3622)	2790 (2380 – 3210) *μ	2650 (2060 – 2880) *μ
SGA (BW <10%)	0	13 (37.1)	20 (64.5)
Male neonates	35 (54.7)	18 (51.4)	13 (41.9)

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

* p<0.05 when compared to normal pregnancy

μ p<0.05 when compared to late-onset preeclampsia without underperfusion placental lesions

SGA: Small for gestational age; BW: Birthweight

Table II

Maternal plasma concentration of angiongenic and antiangiogenic factors in the study population

	Uncomplicated Pregnancy (n=64)	Preeclampsia without placental lesions of underperfusion (n= 35)	Preeclampsia with placental lesions of underperfusion (n=31)
PlGF(pg/ml)	348.8 (196.3–729.3)	128.9 (85–212) †	90 (68–137) *†
PlGF/sVEGFR-1	0.23 (0.11–0.43)	0.029 (0.020–0.048) †	0.017 (0.10–0.26) *†
PlGF/sEng	49.2 (17.2–96)	6.7 (1.9–13.1) †	2.3 (1.5–6) *†
sEng(ng/ml)	8.1 (6.1–12.5)	20.6 (12–40.7) †	35.5 (15–49.2) †
sVEGFR-1(pg/ml)	1635 (1150–2138)	3995 (3058–5679) †	5314 (3404–8231) †
sVEGFR-2(ng/ml)	9.2 (7.4–11.2)	7 (5.4–8.5) †	7.5 (5.6–10.5)

Values expressed as median (interquartile range)

PE: Preeclampsia; PlGF: placental growth factor; sEng: soluble endoglin;

sVEGFR-1: soluble vascular endothelial growth factor receptor 1

sVEGFR-2: soluble vascular endothelial growth factor receptor 2

* p-value <0.05 when compared to late-onset PE without placental lesions of underperfusion.

† p-value <0.01 when compared to normal pregnancy