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Evidence supporting that the excess of the sVEGFR-1 concentration in maternal plasma in preeclampsia has a uterine origin

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Abstract

Background. Preeclampsia has been considered an anti-angiogenic state. Two factors have been implicated in the genesis of this state: soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) and placental growth factor (PlGF). Indeed, the concentrations of PlGF, an angiogenic factor, are lower in preeclampsia than in normal pregnancy, while the opposite is the case for the anti-angiogenic factor, sVEGFR-1. The source of the excess sVEGFR-1 has not yet been determined. Since the placenta could be a source of sVEGFR-1, we conducted a study to determine whether there is a gradient in the plasma concentration of sVEGFR-1 and PlGF between the uterine vein and the antecubital vein in both patients with preeclampsia and normal pregnant women.

Methods. A cross-sectional study was performed to determine the plasma concentrations of sVEGFR-1 and PlGF in the uterine and antecubital vein of patients with preeclampsia ($n = 9$) and normal pregnant women at term ($n = 9$). Plasma samples were collected from antecubital and uterine veins at the time of cesarean section. The concentrations of sVEGFR-1 and PlGF were determined using specific enzyme-linked immunoassays. The differences of plasma concentrations of sVEGFR-1 and PlGF between uterine and antecubital veins in both groups were compared by paired *t*-tests.

Results. Patients with preeclampsia had a significantly higher mean plasma concentration of sVEGFR-1 in the uterine vein than in the antecubital vein (uterine vein: mean 13,675 $\pm$ 5,684 pg/ml vs. antecubital vein: mean 10,234 $\pm$ 4,700 pg/ml; paired *t*-tests, $p = 0.04$). In contrast, among normal pregnant women at term, there was no significant difference in plasma concentrations of sVEGFR-1 between the uterine and antecubital veins (uterine vein: mean 1,918 $\pm$ 665 pg/ml vs. antecubital vein: mean 1,750 $\pm$ 475 pg/ml; paired *t*-tests, $p = 0.1$). The mean plasma concentration of sVEGFR-1, either in the antecubital or uterine vein, was significantly higher in preeclampsia than in normal pregnancy (unpaired *t*-tests; both $p < 0.001$). There was no significant difference in the mean plasma concentration of PlGF between the uterine and the antecubital veins in both the preeclamptic (uterine vein, mean $\pm$ SD: 129 $\pm$ 106 pg/ml vs. antecubital vein, mean $\pm$ SD: 82 $\pm$ 43 pg/ml; paired *t*-tests, $p = 0.2$) and normal pregnancy groups (uterine vein, mean $\pm$ SD: 331 $\pm$ 254 pg/ml vs. antecubital vein, mean $\pm$ SD: 319 $\pm$ 259 pg/ml; paired *t*-tests, $p = 0.4$). The mean plasma concentration of PlGF, either in the uterine or antecubital vein, was lower in preeclampsia than in normal pregnancy (unpaired *t*-tests; $p = 0.008$ and 0.02 respectively).

Conclusions. Plasma concentration of sVEGFR-1 was higher in the uterine vein than in the antecubital vein in women with preeclampsia. This provides evidence supporting the concept that the uterus is a potential source of the excess circulating sVEGFR-1 concentration in preeclamptic women.

Keywords: *Preeclampsia, soluble vascular endothelial growth factor receptor-1 (sVEGFR-1), placental growth factor (PlGF), uterine vein, angiogenesis*

Introduction

Preeclampsia, one of 'the great obstetrical syndromes' [1], is a leading cause of maternal and perinatal morbidity and mortality [2]. This syndrome is unique to pregnancy and is diagnosed in the presence of hypertension and proteinuria in the second or third trimester. The precise mechanisms of disease responsible for the development of this syndrome have not yet been elucidated [3–5]. However, a role for uteroplacental ischemia [6–11] increased trophoblast apoptosis/necrosis [12–18], endothelial cell dysfunction [19–21], and an exaggerated maternal inflammatory response [22–26] to deported trophoblast [27–31] have been proposed.

Nearly a century ago, preeclampsia was attributed to the presence of a circulating 'toxin' in maternal blood [32]. Hence the term 'toxemia of pregnancy'

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which is still used in clinical obstetrics. The placenta (but not the fetus) is required for the development of this disorder, as patients with classic 'hydatidiform moles' (without a fetus) can develop preeclampsia [33], and delivery of the placenta is the only effective means of curing the disease.

Accumulating evidence suggests that preeclampsia exhibits an anti-angiogenic state [34]. Angiogenesis is regulated by a balance between pro-angiogenic and anti-angiogenic factors. Vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), angiogenic factors produced by the placenta, are key for vasculogenesis, angiogenesis, and placental development [35–40]. VEGF can promote proliferation, migration [41] and survival of endothelial cells [42]. PlGF potentiates the angiogenic response of VEGF. VEGF exerts its biologic effect through two high-affinity receptor tyrosine kinases: VEGFR-1 (VEGF receptor-1 or flt-1) and VEGFR-2 (or KDR/Flk-1). Whereas VEGFR-2 is the major mediator of the mitogenic, angiogenic, permeability-enhancing, and endothelial survival [42] effects of VEGF, the precise function of VEGFR-1 is still subject to debate, the point of contention being whether it is a decoy or functioning receptor [41]. Other than the transmembrane isoform, VEGFR-1 has another isoform, which is a soluble form. This isoform binds VEGF or PlGF and inhibits their biological activities [40,41,43].

Several lines of evidence implicate sVEGFR-1 in the pathophysiology of preeclampsia. First, patients with preeclampsia at the time of clinical diagnosis have higher plasma concentrations of sVEGFR-1 than normal pregnant women [44–48]. Second, administration of sVEGFR-1 to pregnant animals induces the clinical characteristics of preeclampsia, including hypertension, proteinuria, and glomerular endotheliosis [34]. Third, serum from preeclamptic patients inhibits endothelial tube formation *in vitro*, and this effect could be restored by adding VEGF and PlGF [34]. Fourth, the anti-angiogenic effect of serum from women with preeclampsia disappeared after delivery, suggesting that the factor(s) may be produced by the placenta [34]. Indeed, Clark et al. proposed that sVEGFR-1 was produced by the human placenta and released into maternal circulation [49,50]. The sVEGFR-1 concentrations in cytotrophoblast-conditioned medium were higher in preeclamptic patients than in those without this condition [35]. The mRNA and protein expression of sVEGFR-1 was higher in the placentas of preeclamptic patients than those from normal pregnancies [34,47]. Collectively, these observations suggest that the placenta is a potential source of the elevation of sVEGFR-1 in peripheral blood of patients with preeclampsia.

This study was conducted to determine whether there is a gradient in plasma concentration of sVEGFR-1 and PlGF between the uterine and antecubital vein in patients with preeclampsia and those with normal pregnancy.

Patients and methods

Study design

A cross-sectional study was performed by including patients with preeclampsia and normal pregnant women at term who were admitted to Hutzel Hospital in Detroit, Michigan. Preeclampsia was defined as hypertension (systolic blood pressure $\geqslant 140$ mmHg or diastolic blood pressure $\geqslant 90$ mmHg on at least two occasions, 4 h to 1 week apart) and proteinuria ($\geqslant 300$ milligrams in a 24 h urine collection or one dipstick measurement $\geqslant 2+$) [51]. Severe preeclampsia was defined as either severe hypertension (diastolic blood pressure $\geqslant 110$ mm Hg) and proteinuria, or mild hypertension and severe proteinuria (a 24-h urine sample containing 3.5 grams protein or urine specimen $\geqslant 3+$ protein by dipstick measurement) [51]. Patients with normal pregnancies were included if they met the following criteria: (1) no medical, obstetrical or surgical complications; (2) cesarean section at term ($\geqslant 37$ weeks); and (3) delivery of a normal infant whose birthweight was between 10th to 90th percentile for gestational age [52]. Plasma samples were collected simultaneously from the antecubital and uterine veins at the time of cesarean section, before the uterine incision was performed. All women provided written informed consent prior to the collection of plasma samples. The collection and utilization of the samples were approved by both the Human Investigation Committee of Wayne State University and the IRB of the National Institute of Child Health and Human Development.

Human sVEGFR-1 and human PlGF immunoassays

Blood was collected into tubes containing an anticoagulant (Ethylene diamine tetra acetic acid; EDTA). The specimens were centrifuged immediately, and the supernatant was aliquotted and stored at -70° C. The concentrations of plasma sVEGFR-1 and PlGF were measured using specific and sensitive enzyme-linked immunosorbent assays (ELISA; R&D Systems, Minneapolis, MN). The assays employed the quantitative sandwich immunoassay technique. Briefly, recombinant human VEGFR-1 or PlGF standards and maternal plasma specimens were incubated in duplicate wells of the microtiter plates pre-coated with monoclonal antibodies specific for VEGFR-1 or PlGF. During this incubation, the immobilized antibodies in the microtiter plate bound

the VEGFR-1 or PlGF in both the standards and samples. After washing unbound substances, polyclonal antibodies to human VEGFR-1 or PlGF conjugated to an enzyme (horseradish peroxidase) were added to the assay wells. Once the incubation period was completed, the assay plates were washed to remove unbound antibody-enzyme reagents. Upon addition of a substrate solution (tetramethylbenzidine), color developed in the assay plates proportionally to the amount of VEGFR-1 or PlGF bound in the initial step. The microtiter plates were read with a programmable spectrophotometer (Ceres 900 Microplate Workstation, Bio-Tek Instruments, Winooski, VT). For sVEGFR-1, the inter- and intra-assay coefficients of variation (CVs) were 4.8% and 6.9%, respectively. The detection limit (sensitivity) was 17.8 pg/ml. The corresponding numbers for PlGF were 6.62%, 2.86% and 10.84 pg/ml, respectively.

Statistical analysis

Shapiro-Wilk tests were used to test for normal distribution of the data. After logarithmic transformation of the data, the differences of plasma concentration of sVEGFR-1 and PlGF in the uterine and antecubital veins were compared by paired *t*-tests. Unpaired *t*-tests were utilized to determine the differences of the mean plasma concentrations of sVEGFR-1 and PlGF between groups. The statistical package used was SPSS V.12 (SPSS Inc., Chicago, IL). A *p*-value of < 0.05 was considered statistically significant.

Results

This study included nine patients with preeclampsia and nine normal pregnant women at term. Clinical characteristics of the study population are displayed in Table I. As expected, patients with preeclampsia delivered earlier (33 ± 5 vs. 39 ± 0.9 weeks; $p = 0.01$) and their neonatal birthweights were lower than those with normal pregnancy ($1{,}653 \pm 1{,}057$ vs. $3{,}265 \pm 253$ grams; $p = 0.002$). Clinical and laboratory characteristics of patients with preeclampsia are displayed in Table II. Five (56%) patients were diagnosed as having severe preeclampsia. Four (44%) underwent induction of labor before delivery by cesarean section.

Patients with preeclampsia had a mean plasma sVEGFR-1 concentration significantly higher in the uterine vein than in the antecubital vein (uterine vein, mean $\pm$ SD: $13{,}675 \pm 5{,}684$ pg/ml vs. antecubital vein, mean $\pm$ SD: $10{,}234 \pm 4{,}700$ pg/ml; paired *t*-tests, $p = 0.036$; Figure 1). This difference remained significant even when the analysis was performed after exclusion of patients who underwent induction of labor (uterine vein, mean $\pm$ SD: $14{,}740 \pm 3{,}261$ pg/ml vs. antecubital vein, mean $\pm$ SD: $13{,}016 \pm 3{,}547$ pg/ml; paired *t*-tests, $p = 0.046$). In contrast, among normal pregnant women at term, there was no significant difference in the gradient of plasma concentrations of sVEGFR-1 between the uterine and antecubital veins (uterine vein, mean $\pm$ SD: $1{,}918 \pm 665$ pg/ml vs. antecubital vein, mean $\pm$ SD: $1{,}750 \pm 475$ pg/ml; paired *t*-tests, $p = 0.1$; Figure 1). All preeclamptic patients had higher plasma sVEGFR-1 concentrations in the uterine vein than in the antecubital vein (see Figure 1). The mean plasma concentration of sVEGFR-1 in either uterine or antecubital vein was significantly higher in preeclampsia than in normal pregnancy at term (unpaired *t*-tests; both $p < 0.001$).

There was no significant difference in the gradient of plasma concentration of PlGF between the uterine and antecubital veins in either women with preeclampsia (uterine vein, mean $\pm$ SD: 129 ± 106 pg/ml vs. antecubital vein, mean $\pm$ SD: 82 ± 43 pg/ml; paired *t*-tests, $p = 0.2$; Figure 2) or normal pregnancy at term (uterine vein, mean $\pm$ SD: 331 ± 254 pg/ml vs. antecubital vein, mean $\pm$ SD: 319 ± 259 pg/ml; paired *t*-tests, $p = 0.4$; Figure 2). The mean plasma concentration of PlGF in either the uterine or antecubital veins was significantly lower in preeclampsia than in normal pregnancy (unpaired *t*-tests; $p = 0.008$ and $p = 0.02$ respectively).

Table I. Clinical characteristics of the study population.

	Normal pregnancy $n = 9$	Preeclampsia $n = 9$	*p*
Age (y)	26 ± 5	30 ± 7	0.3
Nulliparous	0	4 (44%)	0.08
Smoking	1 (11%)	2 (22%)	1.0
Gestational age at diagnosis (weeks)	–	32 ± 5	–
Gestational age at delivery (weeks)	39 ± 0.9	33 ± 5	0.01*
Birthweight (grams)	$3{,}265 \pm 253$	$1{,}653 \pm 1{,}057$	0.002*

Value expressed as mean $\pm$ SD or number (%). *Statistically significant, $p < 0.05$.

Discussion

Our findings demonstrate that preeclampsia, but not normal pregnancy at term, was associated with a significantly higher difference in plasma sVEGFR-1 concentrations between the uterine and antecubital veins. Moreover, plasma concentrations of sVEGFR-1 were higher in both the uterine and antecubital veins of patients with preeclampsia than in normal pregnant women at term, while plasma concentrations of PlGF were lower.

Table II. Clinical and laboratory characteristics of patients with preeclampsia.

Blood pressure (mmHg)	
Systolic	159 ± 10
Diastolic	99 ± 11
Mean arterial pressure	119 ± 10
Urine protein (+ dipstick) Mean ± SD	2.5 ± 0.5
Median (range)	3 (2–3)
Aspartate aminotransferase (SGOT) (U/L)	95 ± 156
Platelet count (x10^3) (μ/L)	190 ± 55
Birthweight < 10th percentile	6 (67%)
Severe preeclampsia	5 (56%)

Value expressed as mean ± SD or number (%).

As early as 1915, Williams hypothesized the presence of toxic factors in the blood of women with the clinical syndrome of 'toxemia' or preeclampsia [32]. A number of subsequent studies, aimed at determining whether blood from pregnant women or placental extracts contained a factor responsible for hypertension, yielded contradictory results [53,54]. Tatum and Mule reported that whole blood collected from patients with severe preeclampsia could induce transient hypertension when transfused to the same patients in the postpartum period [55]. Similar observations were described by Pirani and MacGillivray [56] after the injection of plasma from preeclamptic women 6 days after delivery. Since the increase in blood pressure could not be elicited by retransfusion at 6 weeks postpartum, the authors concluded that patients with preeclampsia had increased sensitivity to pressor agents lasting about 1 week after delivery, but not as long as 6 weeks. Thereafter, considerable effort was devoted to the identification of the pressor agents responsible for

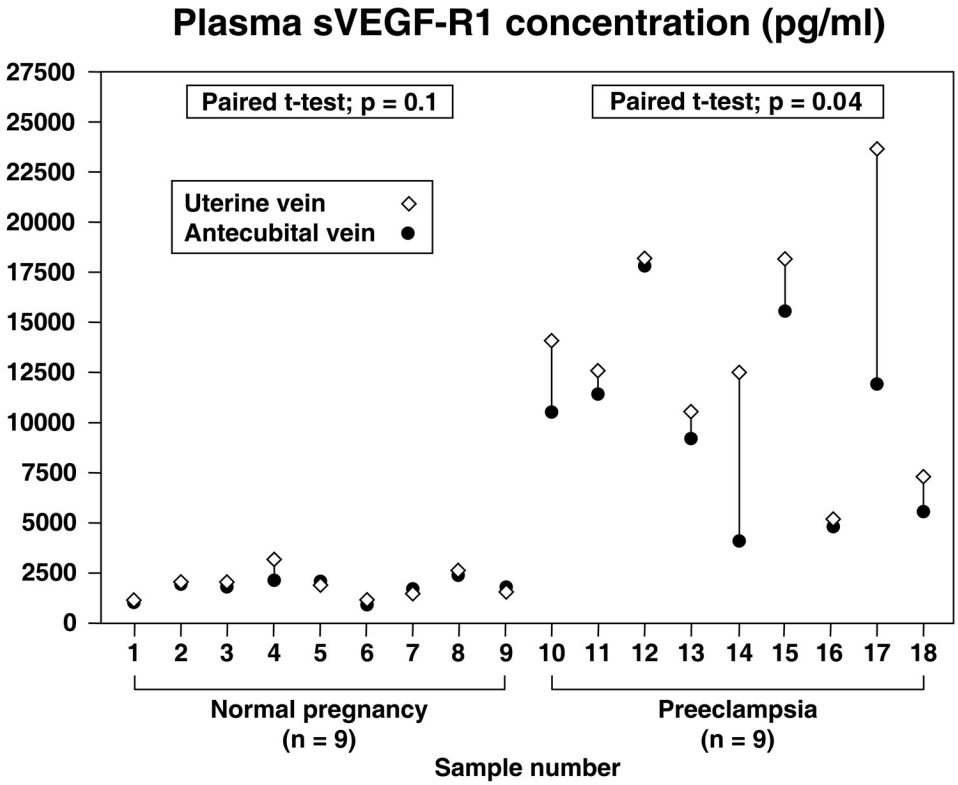

Figure 1. Plasma concentrations of sVEGFR-1 in the antecubital (circle) and uterine veins (diamond) of normal pregnant women at term and patients with preeclampsia. Patients with preeclampsia had a higher mean plasma concentration of sVEGFR-1 in the uterine vein than in the antecubital vein (uterine vein, mean ± SD: 13,675 ± 5,684 pg/ml vs. antecubital vein, mean ± SD: 10,234 ± 4,700 pg/ml; paired *t*-test, $p = 0.036$). In contrast, among normal pregnant women, there was no significant difference in the mean plasma concentrations of sVEGFR-1 between the uterine and antecubital veins (uterine vein, mean ± SD: 1,918 ± 665 pg/ml vs. antecubital vein, mean ± SD: 1,750 ± 475 pg/ml; paired *t*-test, $p = 0.1$). All patients with preeclampsia had plasma sVEGFR-1 concentrations higher in the uterine vein than in the antecubital vein. The mean plasma concentration of sVEGFR-1 in either uterine or antecubital vein was significantly higher in preeclampsia than in normal pregnancy at term (unpaired *t*-test; both $p < 0.001$).

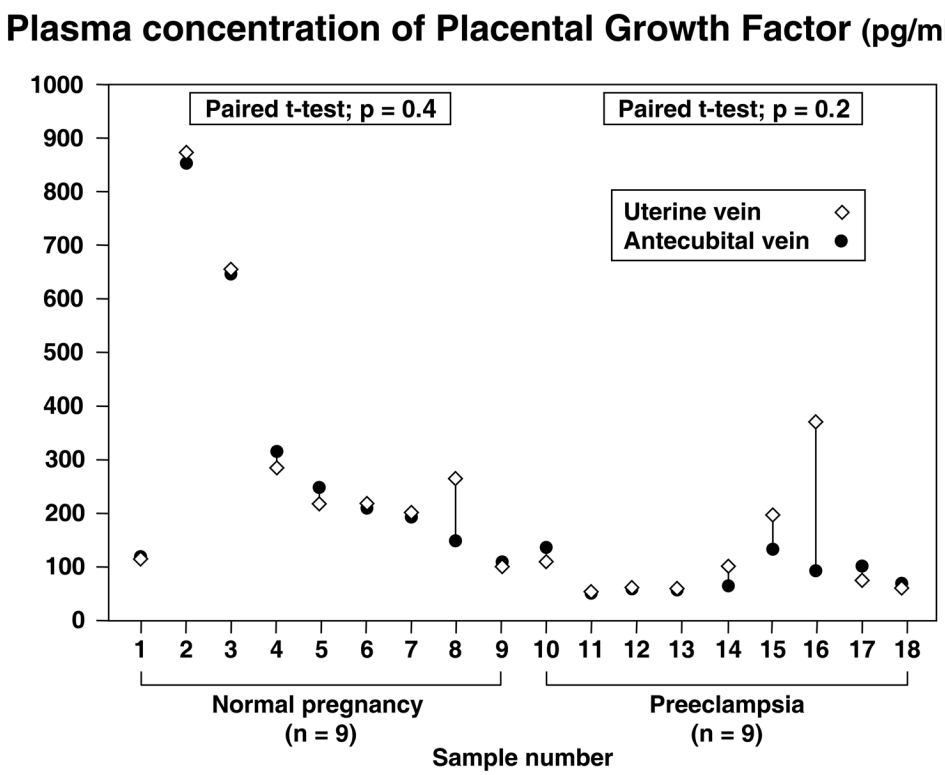

Figure 2. Plasma concentrations of PlGF in the antecubital (circle) and uterine veins (diamond) of normal pregnant women at term and patients with preeclampsia. There was no significant difference in the gradient of plasma concentration of PlGF between the uterine vein and antecubital vein in either preeclampsia (uterine vein, mean ± SD: 129 ± 106 pg/ml vs. antecubital vein, mean ± SD: 82 ± 43 pg/ml; paired *t*-test, $p = 0.2$) or normal pregnancy at term (uterine vein, mean ± SD: 331 ± 254 pg/ml vs. antecubital vein, mean ± SD: 319 ± 259 pg/ml; paired *t*-test, $p = 0.4$). The mean plasma concentration of PlGF in either the uterine or antecubital vein was lower in preeclampsia than in normal pregnancy (unpaired *t*-test; $p = 0.008$ and $p = 0.02$ respectively).

this biological effect in the maternal circulation, and the focus over the years has encompassed the renin-angiotensin system [57–61], norepinephrine [62,63], vasopressin [64], prostaglandins [65], endothelin [20], cytokines [7], and others [66]. Since many investigators believed that the placenta is the source of the pressor agents, some studies also explored the concentration of numerous candidate mediators for 'toxic factors' of preeclampsia in the uterine vein, which represents blood exiting the uterus before gaining access to the peripheral circulation.

Previous studies have examined plasma/serum concentrations of cytokines, nitric oxide metabolites, hemostatic factors, and soluble/cell adhesion molecules in the uterine vein of patients with preeclampsia and women with normal pregnancies [67–71]. Plasma concentrations of TNF-alpha [70], nitrites [71] and soluble vascular cell adhesion molecule-1 (sVCAM-1) [68] are higher in both the uterine and antecubital veins of preeclamptic patients than in normal pregnant women. However, there is no concentration gradient between the two compartments for all these analytes. Although Higgins et al. reported higher plasma concentrations of thrombin anti-thrombin III (TAT) complex as well as fibrin degradation product (FDP) in the uterine vein than in the antecubital vein of patients with preeclampsia, there was no significant difference in plasma concentrations of TAT complex and FDP in the antecubital vein between mothers with pre-eclampsia and those with normal pregnancy in that study [67]. Other than changes in the expression of cell surface markers that suggest cell activation of neutrophils (CD 11a, CD11b, CD11c) and monocytes (CD11a, CD11c and CD49d) [69], only plasma sVEGFR-1 concentration has been found to have a higher concentration in the uterine vein than in the antecubital vein from the same patient (paired *t*-test) with preeclampsia.

The gradient between the uterine and antecubital veins of plasma sVEGFR-1 concentration in preeclampsia observed herein would suggest a uterine origin for the excess VEGFR-1 in the peripheral blood for preeclamptic patients. Since previous observations have demonstrated an increased expression of sVEGFR-1 mRNA and protein in the placenta of preeclamptic patients [34,47], this organ is the most likely source of elevated sVEGFR-1 concentrations in preeclampsia.

The mechanisms responsible for the elevation of plasma sVEGFR-1 concentration in the uterine vein of patients with preeclampsia remain to be determined. Since hypoxia can stimulate VEGFR-1 expression by trophoblasts [72–74], it is possible that an ischemic placenta could induce expression and release of sVEGFR-1 from villous trophoblasts, which is in direct contact with maternal blood in the intervillous space. Evidence in support of this is the presence of an increased mRNA expression for both membrane and soluble forms of VEGFR-1 in syncytiotrophoblasts of hypoxic/ischemic villi of preeclamptic patients [75]. Alternatively, since VEGFR-1 and its ligands (VEGF and PlGF) are involved in angiogenesis and trophoblast proliferation/differentiation [37,38,40,76–82], it is possible that the increased expression of VEGFR-1 in trophoblasts may relate to the remodeling process of the villous tree in response to chronic uteroplacental insufficiency.

It is noteworthy to emphasize that our observations do not preclude the placenta from being a source of sVEGFR-1 and PlGF in the peripheral circulation of normal pregnancy. In normal pregnant women at term, the mean plasma sVEGFR-1 and PlGF concentrations tend to be higher in the uterine vein than in the antecubital vein. However, the magnitude of the increase in plasma sVEGFR-1 concentration is much lower in normal pregnancy than in preeclampsia. For example, the increase in the mean plasma concentration of sVEGFR-1 in the uterine vein compared to that of the antecubital vein is approximately 30% in preeclampsia (13,675 pg/ml vs.10,234 pg/ml), while it is only 10% in normal pregnant women at term (1,918 pg/ml vs. 1,750 pg/ml).

In the peripheral circulation, VEGF exerts its biological effect on the endothelium through two receptor tyrosine kinases: VEGFR-1 (or flt-1) and VEGFR-2 (or KDR/Flk-1) [41]. Binding of VEGF to VEGFR-2 mediates mitogenic, angiogenic, and permeability-enhancing functions [41], as well as maintaining endothelial cell survival [42,83]. In contrast, binding of VEGF to VEGFR-1 or its soluble form inhibits VEGF activities. Similarly, binding of PlGF to VEGFR-1 is thought to potentiate an angiogenic response of VEGF, while binding of PlGF to the soluble form of VEGFR-1 inhibits PlGF activities. Maynard et al. proposed that the placenta of preeclamptic patients releases sVEGFR-1, which binds free VEGF and PlGF [34]. As a result, the normal vasculature in the kidney, brain and other organs is deprived of the essential factors maintaining endothelial function. Moreover, the increased availability of sVEGFR-1 in preeclampsia may counteract the prostacycline and nitric oxide-induced vasodilatation effect of VEGF [84,85], resulting in the elevation of maternal blood pressure.

In conclusion, our observations suggest that the excess plasma concentrations of sVEGFR-1 in women with preeclampsia are due to an increased uterine production of this soluble receptor.

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