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Elevated serum soluble vascular endothelial growth factor receptor 1 (sVEGFR-1) levels in women with preeclampsia

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Abstract Hoping to get more insight into a role of vascular endothelial growth factor (VEGF), a putative substance involved in the development of preeclampsia, we measured concentrations of soluble VEGF receptor-1 (sVEGFR-1), a natural antagonist of VEGF, in serum from women with (n = 31) and without (n = 52) preeclampsia. The concentrations of sVEGFR-1 in serum from women with preeclampsia (median 7791 pg/mL) were > 6-fold higher than those from control (1132 pg/mL, $p < 0.0001$). The levels of sVEGFR-1 decreased markedly after delivery in both groups. Serum sVEGFR-1 levels of non-preeclamptic women were positively correlated with gestational age($r = 0.570$, $p < 0.0001$), whereas those of preeclamptic women exhibited no correlation with gestational age ($r = -0.130$ $p = 0.476$). These findings may point to an involvement of sVEGFR-1 in the pathophysiology of preeclampsia possibly by antagonizing of VEGF effects on the formation of placental vasculature and maternal endothelial cell function.

Introduction

Preeclampsia remains one of the common causes of maternal death and a major contributor to both maternal and fetal morbidity. Although, the etiology of preeclampsia, at present, is not fully understood, the concept has been emerging that dysfunction in the maternal vascular endothelium may play a central role in the development of preeclampsia given clinical manifestation of preeclampsia, i.e., hypertension, proteinuria being explained by endothelial damage (1).

When looking at placentas from preeclamptic pregnancies, impaired trophoblast invasion into spiral arteries in the placental bed is one of the hallmarks of preeclampsia (2). Inadequate placental development may cause fetal growth restriction on one hand, and result in producing factor(s) responsible for maternal endothelial damage on the other hand. At any rate, dysregulation of the vascular system occurring at the fetomaternal interface and systemic maternal circulation is thought to lie in the center of the pathogenesis of preeclampsia.

Recently, a great attention has been focused on the role of vascular endothelial growth factor (VEGF) in the development of preeclampsia with inconsistent data on serum VEGF levels and the amounts of mRNA for VEGF in placentas in preeclampsia (3-7). To better define the role of VEGF, we envisioned that the involvement of VEGF should be considered in the context of the balance between VEGF and its naturally occurring antagonist, soluble VEGF receptor-1 (sVEGFR-1) in light of the presence of sVEGFR-1 in sera from pregnant women(8). Toward this end, we determined serum sVEGFR-1 levels from preeclamptic women versus control women.

Materials and methods

A total of 83 pregnant women with (n = 31) and without (n = 52) preeclampsia were included in this study. Their gestational ages ranged from 18 to 40 weeks. Preeclampsia was defined as persistent blood pressure of (>140 / 90 mmHg) with proteinurea of either >100 mg/dL by urine analysis or >300 mg in a 24-hour urine collection. None of the patients with preeclampsia had any prior history of hypertension or renal disease. Control subjects were collected randomly from women who had no hypertension, proteinuria nor edema. A subset of the subjects (n = 6 from each group) was recruited for an examination of postpartum period and the samples were taken at one week after delivery as well. The experimental procedures were approved by the Institutional Review Board, and signed informed consent was obtained from each woman.

Blood samples were collected from women with preeclampsia soon after the manifestation of the

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disease and before commencing any medication. Serum was separated by centrifugation and stored at −70C before use. Concentrations of sVEGFR-1 in serum were measured in duplicate, using a specific enzyme-linked immunosorbent assay (ELISA, R&D Systems, Inc., Minneapolis, MN) in a blind fashion. The mean minimum detectable dose of this kit was 5.01 pg / mL. The intra- and inter-assay coefficients of variation were less than 3.8% and 8.1%, respectively.

Gestational ages at the time of sampling and maternal ages between preeclamptic women and control women were compared using Student's *t* test. Serum sVEGFR-1 levels were compared using Mann-Whitney *U* test. The correlation between serum sVEGFR-1 levels and gestational age was analyzed by Spearman's test. *P* less than 0.05 was considered to be statistically significant.

Results

Table 1 shows the distribution of concentrations of sVEGFR-1 in serum from control and preeclamptic women. There were no significant differences in gestational ages at the time of sampling and maternal ages between the two groups. The concentrations of sVEGFR-1 in serum from women with preeclampsia (median 7791 pg/mL; interquartile range 5485-10448) were >6-fold higher than those from control (1132 pg/mL, 680-1964, $p < 0.0001$). In a subset of women whose postpartum sVEGFR-1 levels were also examined, the sVEGFR-1 levels decreased markedly in both preeclamptic (antepartum 4360 ± 467.3 postpartum 95.66 ± 24.87, mean ± SEM) and control (antepartum 1485 ± 311.2 postpartum 45.31 ± 17.99) women after delivery. As illustrated in Figure 1, serum sVEGFR-1 levels of non-preeclamptic women were positively correlated with gestational age ($r = 0.570$, $p < 0.0001$), whereas those of preeclamptic women exhibited no correlation with gestational age ($r = -0.130$, $p = 0.4760$).

Discussion

In the present study, we demonstrated that serum sVEGFR-1 levels were significantly elevated in preeclamptic women compared with controls across gestational ages. In addition, it is of note that sVEGFR-1 levels were positively correlated with gestational age in the controls, whereas no such correlation was observed in preeclamptic women.

Although VEGF has been suggested to play a role in the derangement of the vascular systems in preeclampsia, data on serum VEGF hitherto reported have been inconsistent. In view of an antagonistic role of sVEGFR-1 against VEGF, present findings that serum sVEGFR-1 levels in preeclamptic women were more than 6 fold over the control may imply that net VEGF function is diminished in preeclamptic women. A recent study demonstrated that treatment of cultured cytotrophoblasts with molecules that block the ligand binding to VEGFR reduced invasion of the cells and increased apoptosis of the cells (9). It also showed that the placentas of preeclamptic women produced higher levels of sVEGFR-1 in vitro as compared to controls (9). Therefore, it is plausible that sVEGFR-1 increased in the placentas from preeclamptic women may impair the placental vascularization by antagonizing VEGF, leading to reduced placental perfusion. Elevation of plasma sVEGFR-1 levels may also diminish the effect of VEGF and, therefore, perturb endothelial cell function in maternal circulation. These are possible explanations for pathogenesis of preeclampsia.

Observed increased circulating sVEGFR-1 levels in preeclamptic women may reflect enhanced production of sVEGFR-1 by the placenta. In support for this, serum sVEGFR-1 in pregnant women is thought to originate largely from the placenta (8), in addition to an increased capacity of placentas with severe preeclampsia to release sVEGFR-1(9).

Table 1. Clinical parameters and sVEGF serum levels in study groups

	Preeclampsia (n = 31)	Control (n = 52)	Statistical significance
Gestational age			
(week, mean ± SD)	34.0 ± 4.9	33.3 ± 5.6	NS
Maternal age			
(year, mean ± SD)	33.1 ± 4.0	31.4 ± 4.3	NS
sVEGFR (pg/ml)			
Median and IQR	7791 (5485 - 10448)	1132 (680 - 1964)	P < 0.0001
Mean ± SD	8788 ± 4527	1382 ± 833.5	

IQR: interquartile range

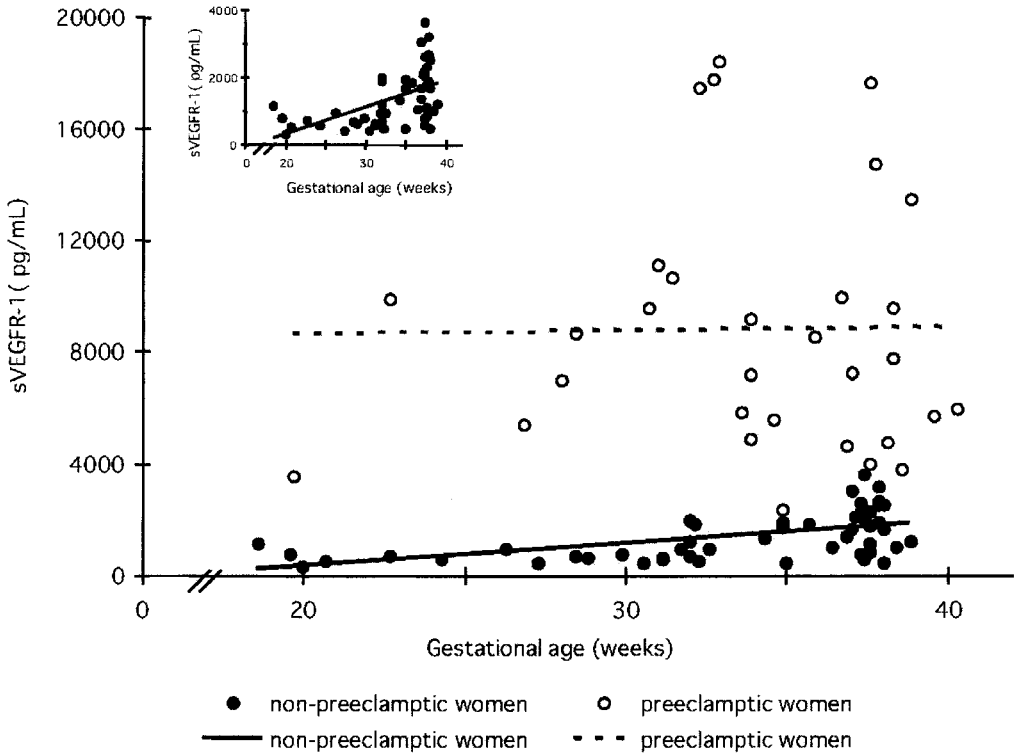

Fig 1. A scatter plot of the serum levels of soluble vascular endothelial growth factor receptor 1 (sVEGFR-1) versus gestational age in non-preeclamptic (closed circles) and preeclamptic (open circles) women. The *inset* is the same scatter plot of non-preeclamptic women with expanded scale on Y axis. A statistically significant positive correlation was found between the serum levels of sVEGFR-1 and gestational ages in non-preeclamptic women (unbroken line; $r = 0.570$, $p < 0.0001$), whereas no correlation was found between then in preeclamptic women (broken line; $r = -0.130$, $p = 0.476$).

In the present study, we demonstrated that the levels of sVEGFR-1 decreased markedly in both preeclamptic and control group in their postpartum periods, which suggests that a large fraction of serum sVEGFR-1 in both groups were derived from the placenta. However, in light of the association of essential hypertension with elevated sVEGFR-1(10), there is a possibility that sVEGFR-1 production may be augmented in tissues other than the placenta in preeclamptic women. The notion may be consistent with the fact that sVEGFR-1 levels were still higher in preeclamptic women as compared to normal controls in their postpartum period, although the levels were much lower than those during pregnancy. In either case, our data may imply clinical utility of sVEGFR-1 as a marker of preeclampsia, which warrants further study.

We also demonstrated that serum sVEGFR-1 levels of non-preeclamptic women positively correlated with gestational age, whereas those of preeclamptic women did not. In view of the finding that the expression of sVEGFR-1 mRNA increases with gestational age in mouse placenta (11), it can be inferred that gestational age-related increase of serum sVEGFR-1 levels in non-preeclamptic women may be due to the increase in placental production as well as placental mass. At present, we are far from understanding the reason for the lack of gestational age-related changes in sVEGFR-1 levels in preeclampsia. One possibility is that the production of sVEGFR-1 by the preeclamptic placenta may escape the physiological regulation and elevate irrespective of gestational ages. Another is that non-placental production of sVFGFR-1, if actually occurring in the setting of preeclampsia, may be unrelated to gestational age.

In summary, we demonstrated that serum sVEGFR-1 levels were significantly elevated in preeclamptic women compared with controls. This finding may point to an involvement of sVEGFR-1 in the pathophysiology of preeclampsia possibly through modulation of VEGF effects on the formation of placental vasculature and maternal endothelial cell function.

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