ORIGINAL RESEARCH

Correlation of Serum IGF-1 and sFlt-1 Levels with Adverse Pregnancy Outcomes in Patients with Severe Preeclampsia

Yan Sun, MM; Chao Meng, MM; Limin Yu, MM

ABSTRACT

Objective • Our aim is to analyze the association of serum insulin-like growth factor 1 (IGF-1) and soluble fms-like tyrosine kinase 1 (sFlt-1) levels with adverse pregnancy outcomes in patients with severe preeclampsia (SPE).

Methods • A total of 108 patients with SPE who received treatment in Tianjin Medical University General Hospital in China from January 2017 to December 2019 were selected for the study. According to the presence or lack of presence of adverse pregnancy outcomes, the patients were divided into the occurrence group (n = 34) and the nonoccurrence group (n = 74). Before treatment, patient serum vitamin A (VA), vitamin E (VE), IGF-1 and sFlt-1 levels were measured. Logistic regression analysis was performed for the correlation of serum IGF-1 and sFlt-1 with adverse pregnancy outcomes in patients with severe SPE. In addition, a Receiver Operator Characteristic (ROC) curve was plotted to test the prediction value of patient serum VA, VE, IGF-1 and sFlt-1 levels.

Results • Compared with the nonoccurrence group, patients in the occurrence group had much lower serum VA, VE and IGF-1 levels and significantly higher sFlt-1 levels. Logistic regression analysis revealed that serum levels of VA, VE, IGF-1 and sFlt-1 before treatment were associated with adverse pregnancy outcomes in patients with SPE, and the ROC curve proved the accuracy of serum VA, VE, IGF-1 and sFlt-1 levels in predicting adverse pregnancy outcomes in patients with SPE.

Conclusion • Abnormal expression of serum IGF-1 and sFlt-1 before treatment in patients with SPE is correlated with adverse pregnancy outcomes. Clinically, the risk for adverse pregnancy outcomes can be predicted and intervention instituted by detecting pretreatment serum IGF-1 and sFlt-1 expression in patients with SPE. (*Altern Ther Health Med.* 2023;29(5):364-369).

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INTRODUCTION

Severe preeclampsia (SPE) is a common metabolic disease during pregnancy. Clinically, patients may suffer from symptoms such as elevation of blood pressure and proteinuria abnormalities.[1] These abnormal symptoms not only damage multiple organs like the heart, brain and liver, but also increase the risk for adverse pregnancy outcomes such as premature delivery, postpartum hemorrhage and intrauterine fetal death in patients with SPE.[2] Therefore, early and accurate prediction of the risk for adverse pregnancy outcomes in patients with SPE is particularly critical. Previous studies have confirmed that factors such as advanced age, multiple births and gestational diabetes can lead to adverse pregnancy outcomes in patients with SPE.[3,4] However, these factors cannot quantitatively analyze the risk for adverse pregnancy outcomes in patients with SPE at an early stage.[5]

Color Doppler has certain prediction value for the risk for adverse pregnancy outcomes in patients with SPE by detecting the hemodynamic changes in the cerebral artery of the fetus in the abdomens of expectant mothers with SPE.[6] However, because the hemodynamic changes in the cerebral artery in the fetus are confined to the early stage of fetal hypoxia, there are some limitations in clinical application.[6]

Insulin-like growth factor 1 (IGF-1) as a "growth promoting factor" is a polypeptide hormone similar to insulin in molecular structure that has a significant regulatory effect on cell division and proliferation.[7] Animal experiments have proven that IGF-1 is closely related to multiple fetal organs and can promote their growth and development.[8] Soluble fms-like tyrosine kinase 1 (sFlt-1), mainly generated by trophoblasts during pregnancy, is a common splice form of ms-like tyrosine kinase-1. As an angiogenesis suppressor, sFlt-1 has an inhibitory effect on placental angiogenesis.[9,10]

Based on these findings, we hypothesized that serum IGF-1 and sFlt-1 levels may have some correlation with adverse pregnancy outcomes in patients with SPE, but there is a lack of relevant research reports. In general, IGF-1 and sFlt-1 levels can be measured in blood, and the data can be obtained and quantitatively analyzed at an early stage. Therefore, this study provided a reference for predicting the risk for adverse pregnancy outcomes in patients with SPE in clinical practice by analyzing the association between serum IGF-1 and sFlt-1 levels and adverse pregnancy outcomes in patients with SPE.

METHODS

Study Participants

Patients with SPE who received treatment in Tianjin Medical University General Hospital in China from January 2017 to December 2019 were selected for the study. The patients were diagnosed as having severe preeclampsia according to the criteria of *Diagnosis and treatment of hypertension and pre-eclampsia in pregnancy: a clinical practice guideline in China (2015)*,[11] which includes the presence of severe hypertension, proteinuria and one or more of the following: thrombocytopenia, impaired liver function, progressive renal insufficiency, pulmonary edema or new-onset cerebral or visual disturbances. According to the inclusion and exclusion criteria, a total of 108 patients with SPE were screened as study participants.

This study was approved by the Ethics Committee of our hospital (IRB2016-267-02). The participants and their families were aware of the study and signed informed consent forms.

Inclusion criteria. Patients who (1) had SPE according to the relevant diagnostic criteria of *Diagnosis and treatment of hypertension and pre-eclampsia in pregnancy: a clinical practice guideline in China (2015)*;[11] (2) had a singleton pregnancy; (3) were admitted to the hospital; (4) had early-onset PE.

Exclusion criteria. Patients who had (1) heart, liver, kidney and other organ diseases; (2) other pregnancy complications (such as gestational diabetes, gestational hyperparathyroidism or hypoparathyroidism); (3) a history of hypertension before pregnancy; (4) thyroid disease; (5) who did not deliver a baby at our hospital.

Study participants' pregnancy outcomes were recorded, and patients were divided into the occurrence group (n=34) and the non-occurrence group (n=74) according to the presence or absence of adverse pregnancy outcomes. Referring to *Obstetrics and Gynecology* (8th edition),[12] adverse pregnancy outcomes included:

(1) **Severe fetal growth restriction**. Fetal growth was monitored by ultrasound, and measured data included head circumference, abdominal circumference and femur length. After measurement, the estimated fetal weight or abdominal circumference was below the 10th percentile for the corresponding gestational age.
(2) **Intrauterine fetal death**. The pregnant woman felt no fetal movement, and during ultrasound examination, the fetal heart rate could not be heard, the uterus stopped growing and the size of the uterus was inconsistent with the weeks of menopause.
(3) **Placental abruption.** The symptom was diagnosed by ultrasound examination, electronic fetal heart monitoring and laboratory tests.
(4) **Asphyxia neonatorum**. The Apgar score was <7.

Maternal or fetal co-occurrence of adverse pregnancy outcome was considered 1 case rather than 2 cases.

Demographic Information

General information on the enrolled patients was collected, including age, primipara (yes/no), anemia (yes/no), family medical history (such as hypertension, diabetes, coronary heart disease, etc.), abnormal pregnancy history (such as abortion, malformation, stillbirth, etc.), folic acid administration, PE induction factors (abnormal lipid metabolism, obesity during pregnancy, others) and gestational age at delivery.

Serum Index Measurements

On the morning of receiving treatment, 5 ml of fasting peripheral venous blood was drawn from the patients in both groups. The vitamin A (VA) and vitamin E (VE) content was determined by high performance liquid chromatography (Changsha Online Instrument and Equipment Co., Ltd., Model 1290, Changsha, China).

Later, the blood was centrifuged at 4000 r/min using TD5A-WS Intelligent Desktop Low-speed Centrifuge (Changsha Yingtai Instrument Co., Ltd.). After 10 minutes, the serum was collected. Subsequently, following the kit instructions (Lai Er Bio-Tech Co., Ltd., Hefei, China), enzyme-linked immunosorbent assay was applied to detect the IGF-1 and sFlt-1 levels. An ELISA assay was performed using a microplate reader (ThermoFisher Scientific, Waltham, Massachesetts, USA) at a wavelength of 450 nm. The concentrations of IGF-1 and sFlt-1 were calculated from standard curves generated with known concentrations of recombinant proteins. All samples were tested twice, and the mean value was used for analysis.

Statistical Analysis

Data processing was performed using Statistical Product and Service Solutions (SPSS) 24.0 software (IBM, Armonk, New York, USA). All measurement data were analyzed by Shapiro-Wilk normality test, skewed distribution was expressed as median interquartile range (M [P25, P75]) and the comparison between groups was checked by Mann-Whitney U test. Enumeration data were expressed as percentage (%) and χ^2 test was used for determination. Logistic regression was used to analyze the correlation of VA, VE, IGF-1 and sFlt-1 levels with adverse pregnancy outcomes in patients with SPE. A Receiver Operator Characteristic (ROC) curve was plotted for the analysis of the prediction value of serum VA, VE, IGF-1 and sFlt-1 levels. $P < .05$ indicated that the difference was statistically significant.

Table 1. Comparison of Baseline Data and Laboratory Indices Between Patients in the Occurrence and Nonoccurrence Groups

Factors n		Occurrence Group (n = 34)		Nonoccurrence Group (n = 74)		Statistic	*P* value
		%	n	%			
Age (years)		31(30.75, 31.21)		31 (31.75, 31.25)		$U = 0.000$	1.000
Primipara	Yes	25	73.53	48	64.86	$\chi^2 = 0.798$	.372
	No	9	26.47	26	35.14		
Anemia	Yes	16	47.06	40	54.05	$\chi^2 = 0.457$	.499
	No	18	52.94	34	45.95		
Family medical history	Yes	13	38.24	35	47.30	$\chi^2 = 0.775$	.379
	No	21	61.76	39	52.70		
Abnormal pregnancy history	Yes	16	47.06	37	50.00	$\chi^2 = 0.081$	.777
	No	18	52.94	37	50.00		
Folic acid administration	Yes	18	52.94	36	48.65	$\chi^2 = 0.172$	.679
	No	16	47.06	38	51.35		
PE induction factors	Abnormal lipid metabolism	16	47.06	32	43.24	$\chi^2 = 0.196$	.907
	Obesity during pregnancy	13	38.24	29	39.19		
	Others	5	14.70	13	17.57		
Menopause (weeks)		32 (31.00, 33.00)		32 (32.00, 32.00)		$U = 0.329$	.742
VA (mg/L)		0.13 (0.12,0.15)		0.28 (0.23, 0.33)		$U = 5.034$	<.001
VE (mg/L)		3.156 (2.74,3.47)		4.98 (4.24, 5.61)		$U = 5.252$	<.001
IGF-1 (μg/ml)		126.09 (116.81,130.80)		144.33 (134.46,150.34)		$U = 5.464$	<.001
sFlt-1 (ng/L)		4079.87 (4026.83,4150.60)		3118.60 (3061.00, 3154.03)		$U = 5.080$	<.001

Note: Measurement data were presented as n and percentage (%), and skewed distribution data were presented as [M (P25, P75)].

Abbreviations: IGF-1, insulin-like growth factor 1; PE, preeclampsia; sFlt-1 soluble, fms-like tyrosine kinase 1; VA, vitamin A; VE, vitamin E.

Table 2. Logistic Regression Analysis for the Correlation Between Laboratory Parameters and Adverse Pregnancy Outcomes in Patients with SPE

Variable	*B*	*S.E*	*Wals*	*P value*	*OR*	95% CI	
						Upper bound	Lower bound
Constant	25.319	0.138	9.679	.002	30.154	-	-
VA	15.585	0.002	9.708	.002	58.346	4.114	71.061
VE	1.567	0.488	10.323	.001	4.790	1.842	12.457
IGF-1	0.126	0.035	13.058	<.001	1.135	1.059	1.215
sFlt-1	1.536	0.533	12.012	<.001	2.315	1.674	4.569

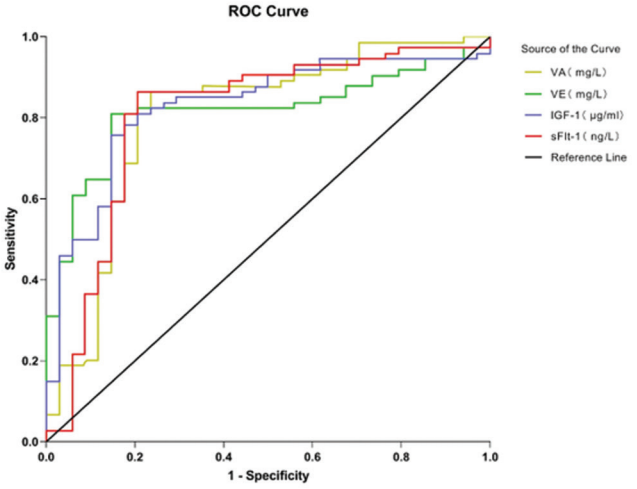
Abbreviations: IGF-1, insulin-like growth factor 1; sFlt-1 soluble, fms-like tyrosine kinase 1; VA, vitamin A; VE, vitamin E.

Table 3. Power Analysis of Laboratory Parameters Predicting the Risk for Adverse Pregnancy Outcomes in Patients with Severe Preeclampsia

Parameters	AUC	95% CI of the AUC	Standard error	*P* value	Cut-off value	Specificity	Sensitivity	Youden index
VA	0.802	0.703-0.902	0.051	<.001	0.182 mg/L	0.794	0.824	0.618
VE	0.816	0.734-0.897	0.042	<.001	3.782 mg/L	0.853	0.811	0.664
IGF-1	0.880	0.745-0.911	0.042	<.001	132.444μg/ml	0.794	0.811	0.605
sFlt-1	0.805	0.705-0.906	0.051	<.001	3171.155 ng/L	0.794	0.811	0.605

Abbreviations: AUC, area under the curve; CI, confidence interval; IGF-1, insulin-like growth factor 1; sFLT-a, soluble fms-like tyrosine kinase 1; VA, vitamin A; VE, vitamin E.

Figure. Receiver Operator Characteristic (ROC) curve for laboratory parameters predicting the risk for adverse pregnancy outcomes in patients with severe preeclampsia.



Abbreviations: IGF-1, insulin-like growth factor 1; sFlt-1 soluble, fms-like tyrosine kinase 1; VA, vitamin A; VE, vitamin E.

RESULTS

Patient Demographics

Of 108 patients with SPE, 34 had adverse pregnancy outcomes, including 15 cases of severe fetal growth restriction, 4 cases of intrauterine fetal death, 3 cases of placental abruption and 12 cases of asphyxia neonatorum; the incidence of adverse pregnancy outcomes reached 31.48% (34/108). A total of 74 patients did not have adverse pregnancy outcomes, and the non-incidence was 68.52% (74/108).

There was no statistical difference in age, primipara (yes/no), anemia (yes/no), family medical history, abnormal pregnancy history, folic acid administration, SPE induction factors or gestational age at delivery between the 2 groups ($P > .05$). Serum VA, VE and IGF-1 levels were lower and sFlt-1 levels were higher in the occurrence group than in the nonoccurrence group, and the differences were statistically significant ($P < .05$). The specific outcomes are shown in Table 1.

Logistic Regression Analysis of the Relationship Between Laboratory Parameters and Adverse Pregnancy Outcomes in Patients with Severe Preeclampsia

Risk factors for adverse pregnancy outcomes in patients with SPE were further analyzed by logistic regression analysis. The results are shown in Table 2. Before treatment, there was an obvious association of serum VA (odds ratio [OR] = 58.346; 95% CI, 4.114-71.061; $P = .002$), VE (OR = 4.790; 95% CI, 1.842-12.457; $P = .001$), IGF-1 (OR = 1.135; 95% CI, 1.059-1.215; $P < .001$) and sFlt-1 levels (OR = 2.315; 95% CI, 1.674-4.569; $P < .001$) with adverse pregnancy outcomes in patients with SPE.

Power Analysis of Laboratory Parameters Predicting the Risk for Adverse Pregnancy Outcomes in Patients with Severe Preeclampsia

ROC curves were plotted with serum VA, VE, IGF-1 and sFlt-1 levels as test variables and the occurrence of adverse pregnancy outcomes as state variables (1 = occurrence, 0 = nonoccurrence) in patients with SPE (Figure). The outcomes revealed a high accuracy of serum VA (area under the curve [AUC]=0.802; 95% CI, 0.703-0.902), VE (AUC=0.816; 95% CI, 0.734-0.897), IGF-1 (AUC=0.880; 95% CI, 0.745-0.911) and sFlt-1 (AUC=0.805; 95% CI, 0.705-0.906) in predicting the occurrence of adverse pregnancy outcomes in patients with SPE (Table 3).

DISCUSSION

SPE not only can induce cardiovascular and cerebrovascular accidents by damaging patient organ function, but can also cause systemic arterial spasm, induce insufficient placental blood supply, affect fetal growth and development and increase the risk for adverse pregnancy outcomes.[13] Therefore, early prediction of the risk for adverse pregnancy outcomes in patients with SPE is particularly important for the development of rational intervention programs and the improvement of pregnancy outcomes in patients.

Zhang Chao, et al.[14] pointed out that approximately 23.1% to 53.3% of patients with SPE developed adverse pregnancy outcomes after treatment. Among the 108 study patients with SPE, 34 had adverse pregnancy outcomes; the incidence was 31.48%. Specifically, there were 15 cases of severe fetal growth restriction, 4 of intrauterine fetal death, 3 of placental abruption and 12 of asphyxia neonatorum. These findings indicated that patients with severe PE were at high risk for adverse pregnancy outcomes. Therefore, this study focused on the analysis of laboratory parameters that may be related to adverse pregnancy outcomes in patients with SPE.

In recent years, some studies have claimed that the abnormal expression of VA and VE is the main factor causing PE.[15] Also, abnormal VA and VE expression in this study was demonstrated to be associated with adverse pregnancy outcomes in patients with SPE. The mechanism of abnormal VA and VE expression affecting adverse pregnancy outcomes in patients with SPE may be achieved by the promoting effects of VA and VE on epithelial tissue structure stability, epithelial cell glycoprotein synthesis, as well as fetal growth and development.[16] To be specific, low VA expression in patients with SPE is not conducive to the formation of the placenta and even affects the growth and development of the fetus and then increases the risk for adverse pregnancy outcomes. As for VE, low expression induces overexpressed free radicals in the body, ages the placenta, further aggravates the degree of placental vascular endothelial damage, increases the risk for fetal membrane cell injury and finally results in adverse pregnancy outcomes.[17] Of note, the accuracy of VA and VE test results is easily affected by various factors such as patients' hormone levels, physical nutritional status and food

and drug supplementation, so there are limitations to their application value.

IGF-1 is an active substance that regulates the growth of body tissues and cells. In general, IGF-1 can not only relax blood vessels, decrease vascular resistance and increase blood flow in placental tissues,[18] but also stimulate cell growth, allow cell differentiation and proliferation and contribute to nerve signal transduction.[19] As a vascular endothelial growth factor receptor, sFlt-1 can be released from the placenta and enter the maternal blood circulation when hypoxia, ischemia or dysfunction occurs in placental tissue. And by the same process, sFlt-1 inhibits the generation of new blood vessels and the survival of endothelial cells.[20] In our study, the serum IGF-1 level was lower in the nonoccurrence group, while the sFlt-1 level was higher in the occurrence group. We preliminarily speculated that abnormal serum IGF-1 and sFlt-1 expression may be involved in the development of adverse pregnancy outcomes in patients with SPE, and our speculation was proven by logistic regression analysis. Based on logistic regression analysis, the possible mechanisms of abnormal expression of serum IGF-1 and sFlt-1 involved in adverse pregnancy outcomes in patients were shown to be as follows.

First, IGF-1 has anti-inflammatory ability and the function of protecting microcirculation, which can stabilize vascular endothelial cells, reduce reactive oxygen species (ROS) content in the body and promote vascular regeneration.[21] In addition, IGF-1 can bind to IGF-1 receptor (IGF-1R), induce intracellular-related signaling and then prevent vascular endothelial cell apoptosis due to ischemia and hypoxia in the body.[22] Moreover, the binding of IGF-1 and IGF-1R exert repair functions in vascular endothelial cells and play a protective role in placental tissues.[23] And low expression of IGF-1 in patients with SPE accelerates the rate of apoptosis of placental vascular endothelial cells, aggravates placental tissue damage and thus increases the risk for adverse pregnancy outcomes.

Studies have shown that IGF-1 plays a critical role in fetal growth and development, and low levels of IGF-1 have been associated with impaired fetal growth and increased risk for preeclampsia.[24,25] On the other hand, sFlt-1, a soluble form of the vascular endothelial growth factor (VEGF) receptor, has been found to be elevated in preeclampsia and is thought to contribute to the development of the disease by inhibiting the angiogenic effects of VEGF, leading to endothelial dysfunction and hypertension.

As for sFlt-1, it has a variety of biological activities, and most important, significantly inhibits the physiological function of VEGF and placental growth factors. Specifically, sFlt-1 can cause angiogenesis disorders and induce impaired integrity and permeability of the placental vascular wall by reducing the expression VEGF and placental growth factors. Given this, sFlt-1 affects the nutritional supply of the fetus, and then results in fetal growth restriction, impaired organ function and poor prognosis.[26,27] In addition, the increase of sFlt-1 expression can accelerate the rate of apoptosis of placental vascular endothelial cells, aggravate the ischemia and hypoxia of placental tissue, affect the normal nutrient supply for fetal growth and development and thus increase the risk for adverse pregnancy outcomes.[27] Studies have suggested that sFlt-1 may inhibit the actions of IGF-1 in the placenta, leading to reduced fetal growth and increased risk for preeclampsia.[28,29]

Finally, an ROC curve was plotted, and serum IGF-1 and sFlt-1 levels were found to have high accuracy in predicting adverse pregnancy outcomes in patients with SPE. This finding indicated that serum IGF-1 and sFlt-1 were not only risk factors for adverse pregnancy outcomes, but also served as key markers for predicting the risk for adverse pregnancy outcomes in patients with PE before treatment. Therefore, in clinical practice, early detection and reasonable intervention in abnormal serum IGF-1 and sFlt-1 expression before treatment may have positive significance in reducing the risk for adverse pregnancy outcomes in patients with PE.

Study Limitations

In our study, due to condition constraints, the sample size was small and the plotted prediction model only enrolled the predictive analysis of serum VA, VE, IGF-1 and sFlt-1 for the risk for adverse pregnancy outcomes in patients with SPE rather than including other high risk factors. In future studies, the sample size needs to be increased and more high risk factors for adverse pregnancy outcomes must be included. Also, future studies could investigate the effects of interventions, such as supplementation or pharmacological treatments, on IGF-1 and sFlt-1 levels in patients with severe preeclampsia. These studies could then examine the impact of interventions on pregnancy outcomes, such as preterm delivery or neonatal complications. In addition, we only measured vitamin levels at 1 time point, which may not have fully captured the potential impact of these vitamins on the development of severe preeclampsia.

Moving forward, future research could examine the impact of longitudinal measurements of vitamin levels on the development of severe preeclampsia. In addition, it would be beneficial to conduct larger multicenter studies to confirm our findings and explore the impact of other potential risk factors for severe preeclampsia, such as lifestyle and environmental factors.

CONCLUSION

In conclusion, abnormal serum IGF-1 and sFlt-1 expression before treatment in patients with SPE is associated with the occurrence of adverse pregnancy outcomes. Simply speaking, low expression of IGF-1 and overexpression of sFlt-1 may indicate a high risk for adverse pregnancy outcomes in patients with SPE. In clinical practice, detection of serum IGF-1 and sFlt-1 expression in patients with SPE before treatment can be considered predictors of the risk for adverse pregnancy outcomes and guide the intervention. Furthermore, the ROC curve results of vitamin E and vitamin A were promising in predicting adverse pregnancy outcomes in patients with severe PE.

CONFLICT OF INTEREST

None.

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None.

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