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High Sflt-1 Levels in Preeclampsia Patients Indicate Renal Impairment

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1. Abstract

1.1. Background: To study the values of the soluble FMS-like tyrosine kinase-1 (sFlt-1) in patients with preeclampsia, and its predictive values for clinical manifestation and prognosis of pregnancy outcome.

1.2. Methods: Thirty-four pregnant women with preeclampsia and twenty-eight pregnant healthy controls who attended antenatal care and delivered in our hospital from July 2017 to June 2018 were included in this study. The serum sFlt-1 levels were measured and compared between the two groups, and the correlation of the serum sFlt-1 values with the clinical indicators and prognosis were analyzed in patients with preeclampsia.

1.3. Results: Serum sFlt-1 values were higher in preeclampsia group than in control group and the difference was statistically significant ($P<0.05$). Dividing the preeclampsia group into early-oneset and late-onset subgroups, serum sFlt-1 values were higher in early-onset subgroup than in late-onset subgroup, and the difference was statistically significant ($P<0.05$). Dividing the pre-eclampsia group into severe and non-severe subgroups, serum sFlt-1 values were significantly higher in severe subgroup than in non-severe subgroup ($P<0.05$). Preeclampsia patients with high serum sFlt-1 exhibited higher values of creatinine, uric acid and urinary proteins, and the differences were statistically significant ($P<0.05$). Multiple logistic regression analysis showed that creatinine was an independent risk factor that influence the serum sFlt-1 in pregnant women with preeclampsia (OR=1.178, 95%CI 1.006-1.380).

1.4. Conclusions: Compared with pregnant healthy controls, serum sFlt-1 levels are higher in pregnant women with preeclampsia, among which serum sFlt-1 levels are higher in early-onset patients than in late-onset ones and higher in severe patients than in non-severe ones, especially correlated with indicators of renal function impairment.

2. Introduction

Preeclampsia (PE), one of the Hypertensive Disorders of Pregnancy (HDP), is a pregnancy specific disease. It causes about 70 thousand maternal deaths and 500 thousand neonatal deaths each year worldwide [1]. The principal pathological change of PE is systemic arteriolar spasm, manifested as lesions in multiple organs including kidney, liver, nervous system and blood system. In addition to hypertension, proteinuria and progressive renal dysfunction are the main and earlier occurring renal impairment of PE [2].

The pathogenesis of PE is complex, and the imbalance between placental-derived pro-angiogenic factors and anti-angiogenic factors is considered to be the important cause of PE [3]. Soluble FMS-like tyrosine kinase-1 (sFlt-1) is a splice variant of the transmembrane receptor for Vascular Endothelial Growth Factor (VEGF). It has a strong anti-angiogenesis effect and can cause endothelial cell dysfunction and vasoconstriction, leading to the emergence of clinical symptoms, such as hypertension and proteinuria [4, 5]. Previous studies have shown that sFlt-1 levels are significantly higher in patients with PE than those in patients without PE [6], and higher sFlt-1 levels may be associated with cardiovascular dysfunction during pregnancy and after delivery [7]. It has also been shown that sFlt-1 induced VEGF inhibition ultimately promotes the development of alternative, glomerular-centered pathways to escape the inhibition, which may be a direct cause of renal dysfunction associated with PE [2].

Due to the characteristics of multifactorial pathogenesis, PE is classified into distinct clinical subtypes such as early-onset and late-onset, and individual patients also have distinct clinical manifestations with different organ damage and different prognosis. Previous studies have suggested that serum sFlt-1 levels during early and middle stages of pregnancy are predictive of the onset of PE but of low value. However, the predictive values of sFlt-1 for different clinical subtypes and prognosis have been rarely reported. The aim of this study is to explore the predictive values of serum sFlt-1 for clinical manifestations and prognosis of PE by analyzing the correlation between serum sFlt-1 levels of patients with PE and their clinical manifestations and prognosis of pregnancy outcome.

3. Materials and Methods

3.1 Subjects

A total of 34 pregnant women with PE undergoing prenatal examination and delivery in our hospital from July 2017 to June 2018 were included in the study, and 28 normal pregnant women at the same gestational age but without metabolic diseases such as hypertension, nephropathy and diabetes were used as controls. For pregnant women who were first diagnosed as PE and normal controls at the same gestational age, maternal serum sFLT-1 levels were measured. Meanwhile, clinical indicators that impact prognosis were recorded, such as maternal age, gestational age at PE onset, Mean Arterial Pressure (MAP), serum albumin, urinary protein, Alanine Aminotransferase (ALT), creatinine, uric acid, hemoglobin, platelets, C Response Protein (CRP), and fibrinogen. The pregnancy outcomes, including gestational age at delivery, birth weight, Apgar score, with/without Fetal Growth Restriction (FGR) and other complications, were also recorded. This study was approved by the Ethics Committee of Hangzhou Obstetrics and Gynecology Hospital.

According to the [Diagnosis and treatment guideline of hypertensive disorders in pregnancy (2015)] issued by the Hypertensive Disorders in Pregnancy Subgroup, Chinese Society of Obstetrics and Gynecology, Chinese Medical Association in 2015, the diagnostic criteria for PE are as follows: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure≥ 90 mmHg after 20 weeks of gestation with any of the following situations: 1) proteinuria ≥ 0.3 g/24 h; 2) urinary protein/creatinine ratio≥ 0.3; 3) random urinary protein ≥ (+); 4) no proteinuria but accompanied by any organ or system involvement: abnormal changes in the heart, lung, liver, kidney and other vital organs, or blood system, digestive system, nerve system, placenta-fetal involvement, and others.

Severe preeclampsia includes: 1) sustained elevations in blood pressure: systolic blood pressure≥ 160 mmHg and/or diastolic blood pressure≥ 110 mmHg; 2) persistent headache, visual impairment, or other Central Nervous System(CNS) abnormalities; 3) persistent upper abdominal pain and subhepatic envelope hematoma or liver rupture; 4) abnormal liver enzymes: elevated levels of blood ALT or Aspartate Transaminase (AST); 5) impaired renal function: proteinuria ＞ 2.0 g/24 h, oliguria (urine output less than 400 ml/24 h or 17 ml/h), or blood creatinine > 106 μmol/L; 6) hypoproteinemia accompanied by ascites, pleural fluid or pericardial effusion; 7) hematic abnormalities: platelet count decreased consistently and below 100 × 109/L microintravascular hemolysis [presenting with anemia, jaundice, or elevated levels of blood Lactate Dehydrogenase (LDH)]; 8) cardiac failure; 9) pneumonedema; 10) Fetal Growth Restriction (FGR), or oligohydramnios, fetal death in utero, placental abruption, etc. FGR is defined as an estimated fetal weight less than the 10th percentile for gestational age by prenatal ultrasound evaluation

3.2 Specimen Collection and Detection

5 ml venous blood was collected and was let stand at room temperature for 30 min and then centrifuged at 3 000 r/min for 10 min. The upper serum was collected and stored in the refrigerator for examination. Serum sFlt-1 was detected using Enzyme-Linked Immunosorbent Assay (ELISA) kits produced at R&D Systems following manufacturer's instructions.

3.3 Statistical Analysis

Statistical analysis was performed using SPSS statistical package version 25.0 (IBM SPSS Inc., New York, NY, USA). Continuous variables (maternal age, gestational age at PE onset, gestational age at delivery, MAP, serum albumin, urinary protein, ALT, creatinine, uric acid, hemoglobin, platelets, CRP, fibrinogen, and sFlt-1) were subjected to normality test before statistical analysis. Data that follow normal distribution were compared using the Student t test and other data were compared using the Mann-Whitney U test. Categorical variables were analyzed using Chi-squared test and Fisher's exact test was used when the total frequency was less than 40. Finally, multiple logistic regression analysis was used to understand the relationship of sFlt-1 and related variables. $P < 0.05$ was considered statistically significant.

4.Results

4.1 Clinical and Biochemical Characteristics of PE and Control Groups

The clinical and biochemical characteristics of PE and control groups were compared, and statistically significant differences were detected in uric acid, birth weight, MAP, gestational age at delivery, urinary protein, serum albumin, serum sFlt-1, with/without complications and FGR ($P < 0.05$) (Table 1).

Table 1: Clinical and biochemical characteristics of PE and control groups

Characteristics	PE (n = 34[#])	Control (n = 28[#])	t-value/Z-value/chi-square value	*p*-Value
Age (years)	30.62 ± 4.86	29.42 ± 3.39	1.093	0.297
Uric acid (μmol/L)	423.97 ± 110.00	263.65 ± 64.22	7.147	<0.001
Hemoglobin (g/L)	116.29 ± 19.16	120.25 ± 8.12	1.091	0.281
Platelets (10^9/L)	167.26 ± 58.93	172.79 ± 42.47	0.415	0.68
Fibrinogen (g/L)	4.52 ± 1.01	4.81 ± 0.80	1.235	0.222
Birth weight (g)	2083.75 ± 927.64	3392.00 ± 421.23	7.096	<0.001
MAP (mmHg)	118.35(108.78,125.98)	86.67(81.84,90.17)	6.636	<0.001
Gestational age at Delivery (weeks)	34(31,36)	39(38,40)	6.196	<0.001
Urinary protein (mg/24h)	5.80(0.65,7.73)	0(0,0)	6.729	<0.001
Serum albumin (g/L)	29.55(26.50,35.08)	36.45(34.15,37.48)	4.655	<0.001
ALT (U/L)	15.00(10.25,22.00)	10.00(9.00,17.75)	1.417	0.156
Creatinine (μmol/L)	69.45(60.00,76.40)	65.15(61.35,74.78)	0.212	0.832
CRP (mg/L)	5.10(2.00,10.02)	3.90(2.15,7.90)	0.665	0.506
Serum sFLT-1 (pg/mL)	2053.81(1328.90,3484.97)	261.10(187.97,401.02)	6.493	<0.001
Complications				
without	21(65.60%)	24(96.00%)	7.79	0.005
with	11(34.40%)	1(4.00%）		
One minute after birth				
Apgar score				
≥ 7	27(84.40%)	25（100.00%）	2.55	0.11
< 7	5(15.60%）	0(0.00%)		
FGR				
without	24(75.00%)	25（100.00%）	5.35	0.021
with	8(25.00%)	0(0.00%)		

Five cases were lost during the follow-up visit about the pregnancy outcomes, including 2 in the PE group and 3 in the control group

4.2 Clinical and Biochemical Characteristics of Early-Onset and Late-Onset PE Subgroups as Well as Severe and Non-Severe Subgroups

Based on the time of onset, PE group was divided into early-onset (< 34 gestational weeks) and late-onset subgroups (≥ 34 gestational weeks), and statistically significant differences were detected in uric acid, platelets, fibrinogen, birth weight, urinary protein, serum albumin, serum sFlt-1, and with/without complications (P < 0.05) (Table 2). Moreover, based on the presence or absence of severe symptoms, PE group was divided into severe and non-severe subgroups, and statistically significant differences were detected in gestational age at PE onset, gestational age at delivery, uric acid, platelets, serum sFlt-1, birth weight, urinary protein, and Apgar score at one minute after birth (P < 0.05) (Table 3).

Table 2: Clinical and biochemical characteristics of early-onset and late-onset PE subgroups

Characteristics	Early-onset PE (n = 23[#])	Late-onset PE (n = 11)	*t*-value/Z-value/ chi-square value	*p*-Value
Age (y)	29.00（27.00,33.00）	31.00（28.00,34.00）	0.426	0.67
Uric acid (μmol/L)	465.65 ± 101.61	336.82 ± 69.80	3.785	0.001
Hemoglobin (g/L)	114.22 ± 16.98	120.64 ± 23.37	0.912	0.369
Platelets (10^9/L)	146.48 ± 51.03	210.73 ± 51.59	3.423	0.002
Fibrinogen (g/L)	4.04(3.47,4.73)	5.09(4.49,5.66)	2.43	0.015
Birth weight (g)	1692.86 ± 823.30	2830.00 ± 615.22	4.019	<0.001
MAP (mmHg)	120.00(117.00,131.00)	109.30(104.33,121.00)	1.75	0.08
Urinary protein (mg/24h)	6.56(2.36,8.19)	0.49(0.12,1.57)	3.001	0.003
Serum albumin (g/L)	29.25 ± 3.83	33.19 ± 4.96	2.549	0.016
ALT (U/L)	16.00(10.00,22.00)	14.00(10.00,17.00)	0.829	0.407
Creatinine (μmol/L)	69.70 ± 15.73	64.81 ± 13.60	0.885	0.383
CRP (mg/L)	6.00(1.90,10.50)	4.80(2.00,10.20)	0.665	0.506
Serum sFLT-1 (pg/mL)	2463.45(1850.94,3647.55)	1212.80(937.05,2031.22)	3.147	0.002
Complications				
without	11(50.0%)	10(90.9%)	_	0.027*
with	11(50.0%)	1(9.1%)		
One minute after birth				
Apgar score				
≥ 7	16(76.2%)	11(100.0%)	_	0.138*
< 7	5(23.8%）	0(0.00%)		
FGR				
without	15(71.4%)	9(81.8%)	_	0.681*
with	6(28.6%)	2(18.2%)		

* Fisher's exact test

In the early-onset PE subgroup, one case was lost concerning the complications and two cases were lost concerning the outcomes of neonates.

Table 3: Clinical and biochemical characteristics of severe and non-severe PE subgroups

Characteristics	Non-severe PE (n = 21)	Severe PE (n = 12[#])	*t*-value/Z-value/ chi-square value	*p*-Value
Age (y)	30.57 ± 4.49	30.83 ± 5.83	0.145	0.886
Gestational age at PE onset (w)	32.86 ± 3.26	28.58 ± 3.53	3.517	0.001
Gestational age at Delivery (w)	35.00 ± 2.24	30.50 ± 3.50	4.517	<0.001
MAP (mmHg)	118.80 ± 13.66	121.92 ± 13.52	0.634	0.531
Serum albumin (g/L)	31.29 ± 5.11	28.93 ± 3.15	1.035	0.112
Creatinine (μmol/L)	66.11 ± 13.52	72.88 ± 17.14	1.253	0.219
Uric acid (μmol/L)	377.19 ± 87.32	519.67 ± 75.95	4.717	<0.001
Hemoglobin (g/L)	115.57 ± 21.70	118.17 ± 15.33	0.364	0.718
Platelets (10^9/L)	185.19 ± 52.91	127.58 ± 45.76	3.153	0.004
Fibrinogen (g/L)	4.76 ± 1.06	4.11 ± 0.87	0.406	0.082
Serum sFLT-1 (pg/mL)	1987.07 ± 1172.45	3851.18 ± 2235.17	2.686	0.017
Birth weight (g)	2472.86 ± 818.61	1340.91 ± 634.36	3.99	<0.001
Urinary protein (mg/24h)	1.00(0.31,6.59)	6.56(5.76,9.25)	2.508	0.012
ALT (U/L)	14.00(10.00,18.00)	22.00(15.00,43.00)	1.799	0.072
CRP (mg/L)	4.70(2.00,8.10)	7.90(1.70,15.30)	0.898	0.369
One minute after birth Apgar score				
≥ 7	20(95.2%)	7(63.6%)	_	0.037*
< 7	1(4.8%）	4(36.4%)		
FGR				
Without	17(81.0%)	7(63.6%)	_	0.397*
With	4(19.0%)	4(36.4%)		

4.3 Clinical and Biochemical Characteristics of High-Sflt-1 and Low-Sflt-1 PE Subgroups and Multiple Logistic Regression Analysis

Based on the median value of serum sFlt-1 (2053.81 pg/mL), PE group was divided into high-sFlt-1 and low-sFlt-1 PE subgroups, and statistically significant differences were detected in gestational age at PE onset, gestational age at delivery, serum albumin, creatinine, uric acid, platelets, fibrinogen, urinary protein, and with/without complications ($P < 0.05$) (Table 4). Multiple logistic regression equations were constructed with all indicators of $P < 0.05$, and results showed that the effect of creatinine abnormalities on serum sFlt-1 was statistically significant (OR=1.178, 95%CI 1.006-1.380) (Table 5).

Table 4: Clinical and biochemical characteristics of high-sFlt-1 and low-sFlt-1 PE subgroups

Characteristics	Low-sFlt-1 PE	High-sFlt-1 PE	*t*-value/Z-value/ chi-square value	*p*-Value
Age (y)	30.24 ± 5.60	31.00 ± 4.14	0.453	0.654
Gestational age at PE onset (w)	33.00 ± 3.37	29.47 ± 3.59	2.954	0.006
Gestational age at Delivery (w)	34.88 ± 2.87	31.71 ± 3.33	2.979	0.005
MAP (mmHg)	117.53 ± 12.54	121.75 ± 14.24	0.917	0.366
Serum albumin (g/L)	32.48 ± 5.03	28.58 ± 3.0.7	2.731	0.011
Creatinine (μmol/L)	61.36 ± 13.13	74.88 ± 14.04	2.9	0.007
Uric acid (μmol/L)	363.41 ± 98.52	484.53 ± 86.38	3.811	0.001
Hemoglobin (g/L)	120.29 ± 18.38	112.29 ± 19.62	1.227	0.229
Platelets (10^9/L)	191.29 ± 58.13	143.24 ± 50.58	2.572	0.015
Fibrinogen (g/L)	4.94 ± 1.15	4.11 ± 0.65	2.594	0.016
Birth weight (g)	2301.88 ± 789.53	1865.63 ± 1019.43	1.348	0.188
Urinary protein (mg/24h)	0.76(0.15,6.44)	6.50(2.28,8.99)	2.739	0.006
ALT (U/L)	14.00(10.00,18.50)	17.50(11.25,36.25)	1.276	0.202
CRP (mg/L)	4.60(2.00,8.80)	6.05(1.93,14.93)	0.827	0.408
Complications				
Without	14(87.5%)	7(41.2%)		0.010*
With	2(12.5%)	10(58.8%)	-	
One minute after birth Apgar score				
≥ 7	14(87.5%)	13(81.3%)	_	>0.999*
< 7	2(12.5%）	3(18.8%)		
FGR				
Without	12(75.0%)	12(75.0%)	_	>0.999*
With	4(25.0%)	4(25.0%)		

* Fisher's exact test

In the high-sFlt-1 PE subgroup, one case was lost concerning the pregnancy outcomes and in the low-sFlt-1 PE subgroup, one case was lost concerning the Apgar score and FGR.

Table 5: Multiple logistic regression analysis of the association between serum sFlt-1 and other factors

Characteristics	b-value	SE	wald	*P*-value	OR	95%CI
Gestational age at PE onset (w)	-0.611	0.343	3.164	0.075	0.543	0.277-1.064
Gestational age at delivery (w)	-0.206	0.315	0.429	0.512	0.814	0.439-1.507
Serum albumin (g/L)	-0.327	0.232	1.99	0.158	0.721	0.457-1.136
Urinary protein (mg/24h)	-0.051	0.177	0.081	0.775	0.951	0.672-1.346
Creatinine (μmol/L)	0.164	0.081	4.128	0.042	1.178	1.006-1.380
Uric acid (μmol/L)	0	0.009	0.001	0.975	1	0.982-1.019
Platelets (10^9/L)	0.025	0.021	1.478	0.224	1.026	0.985-1.069
Fibrinogen (g/L)	-0.83	0.741	1.255	0.263	0.436	0.102-1.863
Complications	3.274	2.62	1.562	0.211	26.43	0.155-4492.350

4. Discussion

sFlt-1, a natural VEGF inhibitor composed of seven extracellular immunoglobulin domains, a single transmembrane domain and an intracellular tyrosine kinase domain, is mainly synthesized by trophoblasts. It can bind to VEGF and Placental Growth Factor (PLGF) to block the transduction of both proangiogenic signaling pathways, thus causing systemic vasospasm, hypertension, proteinuria and other symptoms [8]. Results from previous studies show a significant increase in serum sFLT-1 levels in PE patients compared with normal pregnant women [9, 10], which is consistent with our data. In recent years, the therapeutic theories and means of restoring angiogenic balance have been intensively studied by reducing sFlt-1 levels in PE pregnant women and promoting trophoblast proliferation and invasion [11], and have been demonstrated to improve maternal and neonatal outcomes. Some scholars have used C57Bl/6 J mice to establish an improved Reduced Utero-Placental Perfusion (RUPP) model to test the efficacy of MZe786 as a potential inhibitor of sFlt-1 to treat preeclampsia. Results showed that Hydrogen Sulfide (H2S) released from MZe786 successfully prevented the development of preeclampsia and improved fetal outcome by inhibiting sFlt-1 levels [12].

Our results showed that serum sFlt-1 level was significantly higher in early-onset PE patients than in late-onset ones, and it was also significantly higher in severe PE patients than in non-severe ones, indicating that serum sFlt-1 level is not only related to the onset time of PE, but also related to the severity of the disease. This conclusion has been consistently confirmed in recent relevant studies. A prospective cohort study in Spain that examined serum sFlt-1 levels in PE patients both at admission and before delivery found that serum sFlt-1 levels varied greatly in patients with comorbidities [13]. Aldika Akbar M.I. and colleagues showed that serum sFlt-1 levels were higher in early-onset PE patients than in late-onset PE patients, and higher sFlt-1 levels predicted an adverse pregnancy outcome [14]. It has also been suggested that the cause of elevated sFlt-1 in PE patients, especially early-onset ones, may be associated with placental is chemia caused by insufficient maternal spiral artery remodeling, which increased Hypoxia-Inducing Factor (HIF), a transcription factor acting on the transcription of target genes including sFlt-1 [15]. This explains the higher serum sFlt-1 levels in patients with early-onset PE.

Through further analysis, we found that high-sFlt-1 subgroup of PE patients showed earlier gestational age at PE onset, earlier gestational age at delivery and higher incidence of maternal delivery complications, which were associated with clinical indicators of poor prognosis. Multiple logistic analysis revealed that abnormally elevated creatinine was an independent risk factor for high sFlt-1 level, which is statistically significant. During non-pathological pregnancy, increased blood volume and glomerular filtration rate can facilitate the decrease in serum creatinine, and they decrease systemic vascular resistance via changes in Renin-Angiotensin-Aldosterone System (RAAS) and ultimately result in decreased blood pressure [16]. However, sFlt-1 may damage the glomerular filtration barrier by impairing endothelial cells and ultimately cause a decrease in serum creatinine clearance. The mechanism by which sFlt-1 causes endothelial dysfunction is unknown. It is possible to promote apoptosis in human umbilical vein endothelial cells by activation of the mitochondria-dependent pathway and thus induce the endothelial damage [17, 18]. sFlt-1 and soluble endoglin (sEng) was once injected into rats to induce hypertensive disorders of pregnancy and kidney injury evaluated by renal histopathology, Glomerular Filtration Rate (GFR) and T cell infiltration showed that Acute Kidney Injury (AKI) during pregnancy induced by sFlt-1 and sEng caused elevated blood pressure and elevated biochemical indicators of HELLP syndrome [19].

6. Conclusions

The results of this study suggest a significant increase of sFlt-1 in PE patients and serum sFLT-1 is significantly elevated in early-onset and severe PE patients with complications, especially correlated with indicators of renal function impairment. Therefore, maternal serum sFlt-1 level is more valuable as a predictor for the onset and progression of early-onset PE, especially for the degree of renal function impairment and the prognosis.

7. Author Contributions: Liming Yu and Caihe Wen contributed equally to this study; Liming Yu contributed to study design, execution, analysis and critical discussion. Caihe Wen contributed to experiments conduct, study design, analysis and manuscript drafting. Tengfei Luo contributed to analysis and critical discussion. Min Zhang and Yuanwei Liu contributed to experiments conduct and analysis. Yun Chai designed the experiments and critically reviewed the manuscript. All authors reviewed the manuscript.

8. Ethics Approval and Consent to Participate: The ethics committee of Hangzhou Women's Hospital approved the study. This

article has not been published and will not be submitted for publication elsewhere during the period of reviews. All participants signed a digital informed consent form.

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Data Availability: The datasets that support the findings of this study are available from the corresponding author upon reasonable written request.

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