Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2022**; 49(9): 211
https://doi.org/10.31083/j.ceog4909211

Original Research

Predictive Value Analysis of Serum sFlt-1 and PLGF Levels/Ratio in Preeclampsia

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Academic Editor: Michael H. Dahan
Submitted: 29 April 2022 Revised: 11 May 2022 Accepted: 19 May 2022 Published: 7 September 2022

Abstract

Background: This study is to explore the clinical significance of serum sFlt-1, and placental growth factor (PLGF) contents, as well as sFlt-1/PLGF ratio in predicting and diagnosing preeclampsia. **Methods**: Peripheral venous blood was collected from all pregnant women at 11–33^{+6} weeks for biomarker detection. Totally 105 patients with preeclampsia and 57 patients with severe preeclampsia were included. Serum sFlt-1 and PLGF levels were determined, and sFlt-1/PLGF ratio was calculated. Correlation between sFlt-1, PLGF, sFlt-1/PLGF ratio and serum total cholesterol, triglyceride, lactate dehydrogenase and calcium content levels were analyzed. receiver operating characteristic (ROC) analysis was used to evaluate values of sFlt-1, PLGF and sFlt-1/PLGF ratios in disease diagnosis and prediction. **Results**: Serum sFlt-1 content and sFlt-1/PLGF ratio in Preeclampsia (PE) patients were significantly higher than control. Serum sFlt-1 content and sFlt-1/PLGF ratio of the severe PE group were significantly higher than the PE group. Serum PLGF contents of the PE and severe PE group were significantly lower than control, and the difference in PLGF content between the severe and PE groups was not significant. There was a moderate correlation between the sFlt-1 content and the lactate dehydrogenase level. There was a low-level correlation between the sFlt-1/PLGF ratio and the lactate dehydrogenase level. The receiver ROC curve analysis showed that sFlt/PLGF had greater predictive value for preeclampsia, with a sensitivity of 98.1% and a specificity of 78.2%. **Conclusions**: Serum sFlt-1 level and sFlt-1/PlGF ratio have better predictive and diagnostic values, as well as better auxiliary efficiency for preeclampsia. The diagnostic efficiency of sFlt-1/PlGF ratio is better than sFlt-1 content alone.

Keywords: predictive value analysis; sFlt-1; PLGF; sFlt-1/PLGF ratio; preeclampsia (PE)

1. Introduction

Preeclampsia (PE) is a severe pregnancy-related comorbidity, which is one of the main causes of maternal death, with the global incidence of about 2–8% [1]. Patients with PE often report with proteinuria, hypertension, edema, and multiple organ dysfunction, possibly causing fetal growth restriction, fetal distress, and premature delivery, seriously endangering the health of pregnant women and fetuses [2]. At present, the pathogenesis of PE has not been fully elucidated, and there is still no effective predictive index for the evaluation of PE antenatally.

Usually, the symptomatic regimen would be used to treat patients after the appearance of clinical symptoms, resulting in poor prognosis, such as perinatal and maternal death [3]. Soluble vascular endothelial growth factor receptor-1 (sFlt-1) and placental growth factor (PLGF) have been widely used as common indicators in clinical evaluation of PE [4,5]. In this case-control study, the serum contents of sFlt-1 and PLGF were detected, and the sFlt-1/PLGF ratio was calculated and compared between the PE patients and control subjects. Moreover, the relationships between the sFlt-1/PLGF ratio and the serum levels of total cholesterol, triglyceride, lactate dehydrogenase and calcium were analyzed. The related significance in PE prediction and diagnosis was also investigated to provide evidence of early prevention and treatment for the disease.

2. Materials and Methods

2.1 Study Subjects

A total of 162 females with PE, who underwent routine prenatal examination and delivery at the Urumqi Maternal and Child Health Hospital, from January 2016 to June 2017, were included in this retrospective case-control study. Among these patients, there were 105 cases of PE and 57 cases of severe PE. Moreover, 200 pregnant females undergoing normal pregnancy and delivery were included as the control group. Exclusion criteria were as follows: (1) hypertension and chronic diseases caused by other factors; (2) glomerular diseases, liver and kidney diseases, heart failure, or proteinuria-related diseases; and (3) pregnancy complications such as gestational diabetes, or intrahepatic cholestasis.

2.2 General Data Collection

The general data of included subjects were collected by the physicians, who had been uniformly trained. The demographic data included maternal age, estimated gestational age, body mass index, as well as medical data in-

cluding maternal blood pressure, neonatal birth weight, and neonatal Apgar scores.

2.3 Detection of sFlt-1 and PLGF

Specimen collection included 4 mL of blood drawn from the antecubital vein. All subjects were under fasting condition. The blood sample was then centrifuged at 3000 rpm for 10 min, and the supernatant was collected, which was stored at –20 °C.

The contents of sFlt-1 and PLGF were detected with the Roche's Cobase 411 electrochemiluminescence automatic immunoassay system. The PLGF detection kit was the only prediction kit for PE in early pregnancy certified by the CE marked for *in vitro* diagnosis (CE-IVD).

2.4 Statistical Analysis

The SPSS 19.0 statistical software (IBM Corp, Chicago, IL, USA) was used for data analysis. One-way ANOVA was used for multiple group comparison with the pairwise test for variance homogeneity and Tamhane test for variance non-homogeneity. The ROC curve was used for predictive analysis and evaluation of PE diagnosis.

3. Results

3.1 Analysis of General Clinical Information and Data

The demographic and study data were presented in Table 1. Our analysis showed no significance in the average age of the control and study groups ($p > 0.05$). Significant differences were observed in the delivery gestational age, Blood pressure, neonatal birth weight, and Apgar scores between these groups (all $p < 0.05$). There were significant differences between the severe PE groups and the control group, as well as the and severe PE groups. The comparison of pre-pregnancy body mass index (BMI) showed that only the BMI of the severe PE group was significantly different from the control group. There was no statistically significant difference in the BMI between the PE group and the control group, or between the PE and severe PE groups.

The pre-pregnancy BMI of the enrolled pregnant women was divided into low weight (<18.5 kg/m^2), normal (18.5–24 kg/m^2), and overweight (≥24 kg/m^2), which were analyzed with the biomarkers (sFlt-1, PLGF, and sFlt-1/PLGF). Our results showed that sFlt-1 and PLGF had statistical differences between different pre-pregnancy BMIs ($F = 6.295$, $p = 0.002$; and $F = 3.742$, $p = 0.025$) (Table 2).

Results from the ROC analysis of PE (Fig. 1 and Table 3) showed the area under curve (AUC) value of the sFlt curve was 0.79. When the sFlt value was 4110.5 pg/mL, the Youden index had the largest value, with the corresponding sensitivity of 87.6% and specificity of 72.8%. Moreover, the AUC value for the sFlt/PLGF ratio was 0.819. When the sFlt/PLGF ratio was 37, the Youden index had the largest value, with the corresponding sensitivity of 98.1% and specificity of 78.2%. However, the AUC value for the PLGF was only 0.18, indicating no predictive value.

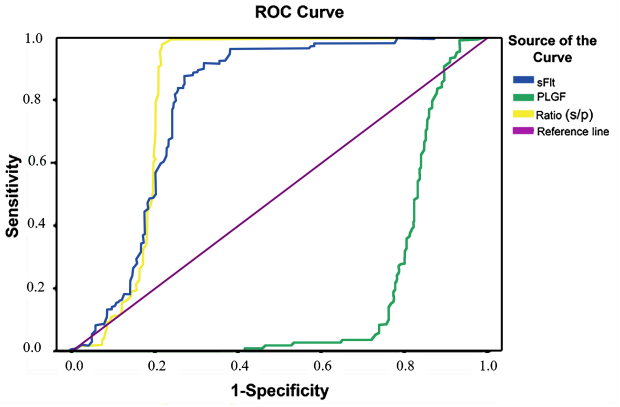

Fig. 1. ROC analyses of serum contents of sFlt-1, PLGF, and sFlt-1/PLGF ratio for diagnosing PE.

Results from the ROC analysis of severe PE (Fig. 2 and Table 4) showed that, the AUC value of the sFlt curve was 0.893. When the sFlt value was 5779.5 pg/mL, the Youden index had the largest value, with the corresponding sensitivity of 91.2% and specificity of 76.4%. Moreover, the AUC value for the sFlt/PLGF ratio was 0.92. When the sFlt/PLGF ratio was 58.5, the Youden index had the largest value, with the corresponding sensitivity of 89.5% and specificity of 82.3%. However, the AUC value for the PLGF was only 0.114, indicating no predictive value.

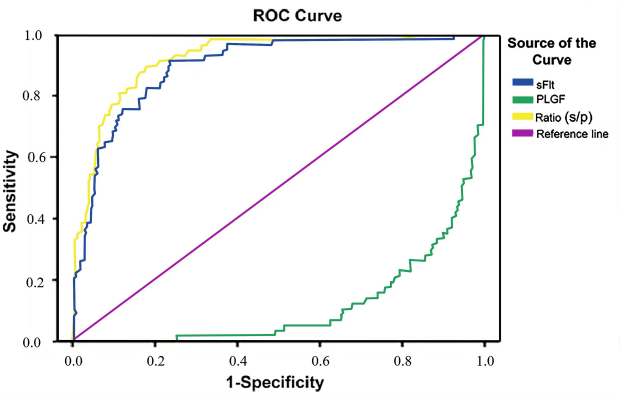

Fig. 2. ROC analyses of serum contents of sFlt-1, PLGF, and sFlt-1/PLGF ratio for diagnosing severe PE.

3.2 Comparison of Serum Contents of sFlt-1, PLGF, and sFlt-1/PLGF

The serum contents of sFlt-1, PLGF, and sFlt-1/PLGF were then analyzed and compared among the PE, severe PE, and control groups. As shown in Table 5, the serum sFlt-1 contents and sFlt-1/PLGF ratio for the and severe PE groups were significantly elevated compared with the control group. Moreover, the serum sFlt-1 contents and sFlt-1/PLGF ratio for the severe PE group were significantly elevated compared with the PE group. On the other

Table 1. General information of these three groups of pregnant females.

	Control group (n = 200)	PE group (n = 105)	Severe PE group (n = 57)
Age (yrs)	30.0 ± 4.4	30.3 ± 5.3	31.2 ± 6.1
Pregnancy	39.3 ± 1.4	38.3 ± 2.3^{a}	34.6 ± 3.6^{ab}
Pregnancy	22.1 ± 3.6	23.2 ± 4.1	24.5 ± 4.3^{a}
Pressure (mmHg)	118.4 ± 10.4	126.4 ± 13.7^{a}	152.8 ± 18.1^{ab}
Blood pressure (mmHg)	76.5 ± 7.4	82.9 ± 10.5^{a}	99.1 ± 12.7^{ab}
Weight (g)	3455.5 ± 472.3	3232.3 ± 652.8^{a}	2572.3 ± 915.0^{ab}
Score	9.7 ± 0.9	9.4 ± 0.7^{a}	8.4 ± 2.5^{ab}

Note: Compared with the control group, ^{a} $p < 0.05$; compared with the PE group, ^{b} $p < 0.05$.

Table 2. Analysis of BMI and sFlt-1, PLGF and sFlt-1 /PLGF before pregnancy.

	Low-body weight	Normal body weight	Overweight	F	p
sFlt-1	1987.7 ± 238.2	1408.4 ± 104.2	1029.6 ± 141.7	6.295	0.002
PLGF	3360.9 ± 4160.9	3877.2 ± 5310.4	5508.1 ± 6573.4	3.742	0.025
sFlt-1/PLGF	41.250 ± 24.707	70.612 ± 10.809	100.3 ± 14.7	2.477	0.085

Table 3. ROC analyses of the sFlt-1, PLGF, and sFlt-1/PLGF ratio in the diagnosis of PE.

	AUC	SE^{a}	Asymptotic Sig.^{b}	95% asymptotic CI	
				Lower limit	Upper limit
sFlt	0.79	0.024	0	0.743	0.837
PLGF	0.18	0.022	0	0.136	0.223
sFlt-1/PLGF ratio	0.819	0.023	0	0.774	0.863

Table 4. ROC analyses of the sFlt-1, PLGF, and sFlt-1/PLGF ratio in the diagnosis of severe PE.

	AUC	SE^{a}	Asymptotic Sig.^{b}	95% asymptotic CI	
				Lower limit	Upper limit
sFlt	0.893	0.023	0	0.849	0.937
PLGF	0.114	0.022	0	0.07	0.158
sFlt-1/PLGF ratio	0.92	0.019	0	0.882	0.957

Table 5. Comparison of serum sFlt-1, PLGF, and sFlt-1/PLGF ratio of three groups of pregnant women.

	Control group (n = 200)	PE group (n = 105)	Severe PE group (n = 57)
sFlt-1 (pg/mL)	2373.5 ± 1378.6	460.1 ± 273.4	7.3 ± 7.2
PLGF (pg/mL)	7612.2 ± 4597.3^{a}	105.4 ± 58.6^{a}	96.8 ± 121.9^{a}
sFlt-1/PLGF ratio	11857.6 ± 6048.1^{ab}	77.5 ± 75.0^{a}	282.6 ± 264.2^{b}

Note: Compared with the control group, ^{a} $p < 0.05$; compared with the PE group, ^{b} $p < 0.05$.

hand, the serum contents of PLGF in the and severe PE groups were significantly declined compared with the control group. Moreover, the serum PLGF contents of the severe PE group were lower than the PE group but not statistically significant.

3.3 Comparison of Serum Contents of Biochemical Indicators

The serum contents of biochemical indicators were analyzed and compared among the PE, severe PE, and control groups. As shown in Table 6, there was no significant difference in the serum levels of total cholesterol or triglyceride among these three groups. The serum levels of lactate dehydrogenase in the and severe PE groups were significantly higher than the control group. Moreover, the serum levels of lactate dehydrogenase in patients with severe PE were significantly higher than the PE group. Furthermore, the serum calcium contents in the severe PE group were significantly lower than the control group, and also significantly lower than the PE group. However, there were no significant differences in the serum calcium levels between the PE group and the control group.

3.4 Correlation Analysis between Serum Contents of sFlt-1, PLGF, sFlt-1/PLGF Ratio with Biochemical Indicators

Correlation between the serum contents of sFlt-1, PLGF, sFlt-1/PLGF ratio with biochemical indicators were analyzed. As shown in Table 7, slight correlations were

Table 6. Comparison of serum biochemical indexes of three groups of pregnant women.

	Control group (n = 200)	PE group (n = 105)	Severe PE group (n = 57)
Total cholesterol (mmol/L)	6.24 ± 1.26	6.08 ± 1.74	6.67 ± 1.46
Triglycerides (mmol/L)	3.57 ± 1.33	3.83 ± 1.82	4.19 ± 1.96
Lactate dehydrogenase (U/L)	173.38 ± 35.85	202.75 ± 45.31^{a}	237.49 ± 62.04^{ab}
Serum calcium (mmol/L)	2.23 ± 0.21	2.24 ± 0.21	2.12 ± 0.18^{ab}

Table 7. Correlation between serum sFlt-1, PLGF, sFlt-1/PLGF ratio and biochemical indicators.

		Total cholesterol (mmol/L)	Triglycerides (mmol/L)	Lactate dehydrogenase (U/L)	Serum calcium (mmol/L)
sFlt-1	r	0.073	0.111	0.517	–0.147
	p	0.167	0.035**	0.000*	0.005*
PLGF	r	0.063	–0.015	–0.296	0.072
	p	0.229	0.776	0.000*	0.173
sFlt-1/PLGF	r	0.093	0.045	0.451	–0.161
	p	0.078	0.392	0.000*	0.002*

Note: *$p < 0.01$, significant correlation at 0.01 level (two-sided); and **$p < 0.05$, significant correlation at 0.05 level (two-sided).

observed between the serum sFlt-1 content and the triglyceride/blood calcium contents, between the PLGF level and the lactate dehydrogenase level, between the sFlt-1/PLGF ratio and the serum calcium level ($p < 0.05$ or $p < 0.01$). Moreover, moderate correlation ($0.5 \leq |r| < 0.8$) was observed between the serum sFlt-1 levels and the lactate dehydrogenase levels. Furthermore, low correlation ($0.3 \leq |r| < 0.5$) was observed between the sFlt-1/PLGF ratio and the lactate dehydrogenase level.

3.5 ROC Analysis of Serum sFlt-1 and PLGF Contents, and sFlt-1/PLGF Ratio for PE Prediction

The ROC analysis results of preeclampsia is shown in Fig. 1 and Table 3. Our results showed that the area under curve (AUC) of sFlt was 0.79. When the sFlt value was 4110.5 pg/ml, the Youden index was the largest, with the corresponding sensitivity of 87.6% and specificity of 72.8%. The AUC of the sFlt/PLGF ratio was 0.819. When the sFlt/PLGF ratio was 37, the Youden index was the largest, with the corresponding sensitivity of 98.1% and specificity of 78.2%. The AUC of the PLGF curve was only 0.18, indicating no predictive value.

The ROC analysis of severe preeclampsia showed that the AUC of the sFlt was 0.893. When the sFlt value was 5779.5 pg/mL, the Youden index was the greatest, with the corresponding sensitivity of 91.2% and specificity of 76.4%. The AUC of sFlt/PLGF ratio was 0.92. When the sFlt/PLGF ratio was 58.5, the Youden index was the greatest, with corresponding sensitivity of 89.5% and specificity of 82.3%. The AUC of the PLGF was only 0.114, indicating no predictive value.

4. Discussion

There are many hypotheses concerning the disease process of PE including immune disorders, genetic factors, hyperlipidemia pathology, insulin resistance, calcium deficiency, oxidative stress, and environmental factors [6,7]. Since PE only occurs in the presence of the placenta, clinical symptoms should soon disappear after the placenta delivers [8]. Therefore, placental pathology has been widely accepted as the cause of PE. The placental ischemia theory states that PE is possibly due to placental insufficiency caused by poor infiltration of the embryonic trophoblastic cells into the dysplastic endometrium and intra-uterine muscular layer [9]. Furthermore, poor perfusion by the uterine artery causes ischemia and reperfusion of the developing placenta, leading to high placental oxidative Stress [10]. The ischemia-reperfusion injury of the placenta releases various vasoactive factors into maternal circulation through the villi space stimulating the production of inflammatory cytokines causing a systemic inflammatory response [11]. This response causes destruction of vascular endothelial cells and pathologic response of blood vessels causing the clinical symptoms of PE [12]. A number of studies [13] have shown that the occurrence of preeclampsia is related to pre-pregnancy overweight, obesity and excessive weight gain during pregnancy, among which high pre-pregnancy BMI (overweight/obesity) is an independent risk factor for the disease. It has been reported [14] that women with high BMI often have endocrine and metabolic disorders, which can easily lead to lipid and glucose metabolism disorders. Due to lipid metabolism disorder, atherosclerosis occurs in placental blood vessels, which leads to disease pathogenesis. Meanwhile, prostacyclin secretion decreases, peroxidase increases, vasoconstriction, platelet aggregation, and hemodynamic changes are induced, which can also lead to preeclampsia. Based on the presumed pathophysiology of PE, researchers are examining relevant biomarkers indicating the diagnosis and/or prediction of PE. Recent studies have shown obvious changes in serum contents of the sFlt-1, PLGF, soluble endoglin (sEng), placental protein 13 (PP13), and pregnancy-associated plasma protein A (PAPP-

A) beginning in early pregnancy [15]. These biomarkers, sFlt-1 and PLGF, produced by the maternal and placental tissue have been eliciting increasing attention.

The sFlt-1 gene is located on chromosome 13 and mainly secreted by the vascular endothelial cells, monocytes and placenta. In the placenta, sFlt-1 is mainly secreted by the syncytiotrophoblast [16]. Previous studies have found that the vascular endothelial growth factor (VEGF) in mice can regulate levels of sFlt-1 causing a self-secretory regulation of the vascular endothelial function [17]. It has been shown that sFlt-1 levels in PE patients are especially increased during early pregnancy. Animal studies have found that the over-expression of sFlt-1 in pregnant rats can induce clinical symptoms similar to PE [18]. It has also been found that when comparing pregnant women with PE and those without, sFlt-1 levels are significantly elevated in the placenta and serum samples of pregnant women with PE [19].

PLGF is a member of the vascular endothelial growth factor family, which is mainly expressed in the placenta [20]. It has an angiogenic effect on the placental circulation and supports the growth of trophoblasts [21]. PLGF is closely related to the maintenance of normal function of trophoblasts, apoptosis of endothelial cells, and angiogenesis. A number of studies have shown that PLGF has certain applicability in the occurrence of hypertension in pregnancy, especially in the diagnosis of preeclampsia [22]. It has also been shown that levels of vascular growth factors (including PLGF) were significantly lower in the serum samples and placenta tissues of PE patients compared with the normal pregnant patient [23–25]. Circulating angiogenic factors are thought to be important regulators in the pathogenesis of PE [26]. Elevated sFlt-1 could prevent endothelial dysfunction by preventing the binding of VEGF and PLGF to the corresponding receptors [27]. Recently, a multicenter, stepped-wedge cluster-randomized controlled trial showed that, in 11 maternity units in the UK in women with suspected pre-eclampsia, measurement of PLGF allowed for more rapid diagnosis of pre-eclampsia and significant reduction in adverse maternal outcomes [28].

In this study, our results showed significantly higher levels of sFlt-1 and lower levels of PLGF in PE patients compared to control subjects. As found in previous studies, our patients with severe PE had serum sFlt-1 levels significantly higher and PLGF significantly lower than our patients with PE [29,30]. The ROC analysis was performed to predict and analyze the occurrence of PE using serum sFlt-1 and PLGF levels. Our results confirmed previous study-results showing that sFlt-1 levels had greater predictive value and good sensitivity/specificity for or severe PE than PLGF levels alone [31]. Using the sFlt-1/PlGF ratio to assess PE can further improve the prediction sensitivity and specificity [32,33]. In a multi-center, prospective, observational study, 1050 pregnant women suspected of PE in 14 countries, were evaluated using the sFlt-1/PlGF ratio to predict whether the disease would occur in the short term [34]. Based on the analysis of 500 subjects, the cut-off value of 38 was determined. The cut-off value was then verified in a verification study of 550 subjects. Data analysis showed that the prediction value of the sFlt-1/PlGF ratio $\leq$38 successfully excluded the onset of PE within 1 week by 99.3% with significantly high sensitivity and specificity; while the prediction value of the sFlt-1/PlGF ratio >38 to predict the PE within 4 weeks was 36.7%, also high sensitivity and specificity [35]. Our results showed that the sFlt-1/PlGF ratio of PE patients was significantly higher than the control subjects, and the sFlt-1/PlGF ratio of severe PE was significantly higher than the PE. Our results from the ROC analysis showed the sFlt-1/PlGF ratio had good predictive and diagnostic value for and severe PE and higher sensitivity and specificity than using the sFlt-1 index alone. Similar to Zeisler *et al*. [34], results showed the cut-off value of PE was 37, and the cut-off value for severe PE was 58.5.

At 5–20 weeks of pregnancy, prior to PE symptoms, free fatty acid (FFA) in the blood would be elevated causing an increase in insulin resistance, induction of endothelial cell damage, and changes in production of vasoactive substances [36]. In Spracklen *et al*. [37], 74 studies were analyzed and found that, compared with normal pregnancy, PE subjects had significantly increased levels of total cholesterol (TC), non-high density lipoprotein cholesterol (non-HDL) and triglycerides (TG) in all stages of pregnancy; while HDL levels were always low in late pregnancy. Tang *et al*. [38] reported that serum levels of TG and TC were significantly higher in the PE group than the control group. Our results showed the average levels of TG in PE patients were higher than the control group, and the average levels of TG in the severe PE group were higher than the PE group, however, not statistically significant. Serum levels of TC in the PE patients showed no significant difference compared with the control group. Our correlation analysis showed no significant correlation between the sFlt-1, PlGF, sFlt-1/PlGF ratio and serum TG or TC levels [39].

Calcium supplementation during pregnancy can reduce the release of thyroid stimulating hormone, maintain normal plasma calcium levels, reduce the calcium influx, prevent the accumulation of intracellular calcium ions, enhance the role of magnesium ions, and inhibit the contraction of vascular smooth muscle. Calcium supplementation could also reduce the contraction of uterine smooth muscle, possibly preventing premature birth. Daily supplementation of 2 g calcium during pregnancy can possibly prevent the occurrence of PE, especially in females at high risk or with low calcium levels [39]. Meta analysis results of 13 studies with a total of 15,730 patients have shown that patients taking at least 1 g calcium daily during pregnancy have reduced risks of PE compared to control groups [40]. Results from 8 previous studies with a total of 10,678 patients with low calcium intake levels (<900 mg/d) indicated calcium supplementation had a significant effect on

reducing the risk of PE [28]. The WHO supports calcium supplementation during pregnancy stating that calcium supplementation could prevent PE and eclampsia, noting the benefits outweighing the risks [41]. In this study, our results showed that the mean serum calcium levels of patients with severe PE were significantly lower than the control group, which was also significantly lower than the PE group. However, there was no significant difference in the serum calcium levels between the PE group and the control group. The correlation analysis showed the sFlt-1, PlGF, sFlt-1/PlGF ratio and serum calcium levels were not significantly correlated.

Previous studies have shown that serum lactate dehydrogenase (LDH), as a biochemical indicator for hypertension in pregnancy, has a sensitivity of 71% and a specificity of 74%. The average LDH level of patients with eclampsia is statistically higher than those with severe PE [42]. Therefore, LDH might have certain clinical significance in assessing the progress and severity of hypertension during pregnancy [43]. In this study, our results showed that the mean content of serum lactate dehydrogenase in patients with severe PE was significantly higher than the control group, which was also significantly higher than the PE group. Moreover, the levels of lactate dehydrogenase in the PE group were significantly higher than the control group. Our correlation analysis showed that levels of sFlt-1 and lactate dehydrogenase had moderate correlation, and the sFlt-1/PlGF ratio had a low correlation with the lactate dehydrogenase.

5. Conclusions

In conclusion, our results showed that the angiogenesis factor markers, sFlt-1 and PlGF, had good auxiliary efficacy for diagnosis and prediction of PE. Moreover, the sFlt-1/PlGF ratio had good predictive and diagnostic values for both and severe PE, allowing for more informed decision-making for hospitalization of pregnant women suspected of PE. Further studies concerning the influence and role of conventional biochemical indicators used in diagnosis and prediction of PE are necessary.

Abbreviations

PE, preeclampsia; sFlt-1, Soluble vascular endothelial growth factor receptor-1; PLGF, placental growth factor.

Author Contributions

GFD designed the study. SYX, YF and WL performed the research and analyzed the data. SYX and YF wrote the manuscript. GFD provided help and advice on manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study was reviewed and approved by the Ethics Committee of the Urumqi Maternal and Child Health Hospital (No. XJFYLL2019005). These study subjects were informed and signed the informed consent.

Acknowledgment

Not applicable.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81960285), and Tianshan Innovation Team Plan (No. 2020D14010).

Conflict of Interest

The authors declare no conflict of interest.

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