论著·临床医学

# 胎盘生长因子在子痫前期患者中的动态变化及对妊娠结局的预测效能

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［摘要］ **目的** 分析胎盘生长因子(placental growth factor,PLGF)水平在子痫前期(preeclampsia,PE)患者中的动态改变及对妊娠结局预测作用。**方法** 采用回顾性队列研究,选取2021年1月至2024年1月天津市北辰医院产科收治的198例患者,其中非重度PE有151例,重度PE有47例。同期于天津市北辰医院产科另纳入100位健康孕妇为对照组。对198例PE患者依据其妊娠的最终状况进行划分:不良结局组(88例)与良好结局组(110例)。采用局部加权回归散点平滑法(locally weighted scatterplot smoothing,LOWESS)分析血管内皮功能指标与PLGF浓度的关系;采用Logistic回归分析患者发生不良妊娠结局的影响因素;采用受试者操作特征曲线(receiver operating characteristic curve,ROC)分析PLGF浓度对非重度PE、重度PE患者不良妊娠结局的预测价值。**结果** 不同孕周PLGF水平呈峰形,孕28~29$^{+6}$周水平较低,随着孕周增加逐渐升高,孕30~31$^{+6}$周达高峰后逐渐下降($P$<0.05),对照组、非重度PE组、重度PE组PLGF逐渐降低($P$<0.05)。LOWESS方法分析结果显示,PLGF浓度与可溶性血管内皮生长因子受体-1(soluble fms-like tyrosine kinase receptor1,sFlt-1)、血管内皮生长因子(vascular endothelial growth factor,VEGF)、一氧化氮(nitric oxide,NO)、血栓调节蛋白(thrombomodulin,TM)、血栓素A2(thromboxane A2,TXA2)以及血管假性血友病因子(von willebrand factor,VwF)均具有一定的非线性关系。Logistic回归分析结果显示,逐步排除共线性混杂因素并校正各协变量后,28~29$^{+6}$孕周PLGF水平与妊娠结局仍存在独立相关性($OR$=0.593,95%$CI$:0.583~0.778,$P$<0.001);将PLGF水平转化为二分类变量后,PLGF高水平与妊娠结局存在独立相关性($OR$=0.773,95%$CI$:0.671~0.885,$P$<0.001);与PLGF最低的五分位数组(Q1)相比,随着PLGF水平逐渐升高(Q2~Q5组),相关性效应值分别为($OR$=0.765,95%$CI$:0.639~0.837,$P$=0.092)、($OR$=0.752,95%$CI$:0.624~0.818,$P$=0.056)、($OR$=0.696,95%$CI$:0.615~0.813,$P$=0.027)、($OR$=0.642,95%$CI$:0.591~0.733,$P$<0.001),且趋势性检验存在统计学意义($P_{趋势}$<0.001)。ROC曲线分析显示,28~29$^{+6}$孕周血清PLGF水平预测非重度PE患者不良妊娠结局的ROC曲线下面积为0.830(95%$CI$:0.635-0.917),最佳临界阈值为75.47 ng/L,敏感度为88.37%,特异度为71.30%,阳性预测值为55.07%,阴性预测值为93.90%;预测重度PE患者不良妊娠结局的ROC曲线下面积为0.874(95%$CI$:0.677-0.923),最佳临界阈值为38.53 ng/L,敏感度为88.89%,特异度为50.00%,阳性预测值为97.56%,阴性预测值为16.67%。**结论** 28~29$^{+6}$孕周PLGF与妊娠结局存在独立相关性且对非重度PE和重度PE患者不良妊娠结局的预测性能良好。

［关键词］ 胎盘生长因子;子痫前期;病情程度;妊娠结局;预测价值
［中图法分类号］ R181.32;R341;R714.245 ［文献标志码］ A

# Dynamic change in placental growth factor in patients with preeclampsia and its predictive efficay for pregnancy outcomes

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［**Abstract**］ **Objective** To analyze the dynamic change in placental growth factor (PLGF) level in

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patients with preeclampsia (PE) and its role in predicting pregnancy outcomes. **Methods** A retrospective cohort study was conducted on 198 PE patients admitted to Department of Obstetrics of Tianjin Beichen Hospital from January 2021 to January 2024. Among them, 151 cases were identified as non-severe PE and 47 cases as severe PE. During the same period, another 100 healthy pregnant women were included in the department and served as the control group. According to the final pregnancy status of the PE patients, they were divided into an adverse outcome group (88 cases) and a good outcome group (110 cases). Locally Weighted Scatterplot Smoothing (LOWESS) was used to analyze the relationship between vascular endothelial function indicators and PLGF level. Logistic regression was employed to identify the influencing factors for adverse pregnancy outcomes. Receiver operating characteristic (ROC) curve was plotted to evaluate the value of PLGF level for predicting adverse pregnancy outcomes in patients with non-severe PE and severe PE. **Results** The PLGF level was in a peak shape at different gestational weeks, relatively low at 28~29 $^{+6}$ weeks of gestation, gradually increasing with the increment of gestational weeks, reaching a peak at 30~31 $^{+6}$ weeks of gestation, and then gradually decreased ($P$<0.05). The PLGF level was gradually reduced in the control group, non-severe PE group, and severe PE group in turn ($P$<0.05). LOWESS analysis showed that the PLGF level exhibited certain nonlinear relationship with soluble fms-like tyrosine kinase receptor 1 (sFlt-1), vascular endothelial growth factor (VEGF), nitric oxide (NO), thrombomodulin (TM), thromboxane A2 (TXA2), and Von Willebrand factor (VwF). The results of logistic regression analysis indicated that after gradually eliminating collinearity confounding factors and adjusting for each covariate, there was still an independent correlation between the PLGF level at 28~29 $^{+6}$ gestational weeks and pregnancy outcome ($OR$=0.593, 95%$CI$: 0.583~0.778, $P$<0.001). After converting the PLGF level into a binary variable, there was an independent correlation between high PLGF level and pregnancy outcome ($OR$=0.773, 95%$CI$: 0.671~0.885, $P$<0.001). Compared with the quintile with the lowest PLGF (Q1), as the PLGF level gradually increased (Q2 to Q5), the correlation effect values were ($OR$=0.765, 95%$CI$: 0.639~0.837, $P$=0.092), ($OR$=0.752, 95%$CI$: 0.624~0.818, $P$=0.056), ($OR$=0.696, 95%$CI$: 0.615~0.813, $P$=0.027), and ($OR$=0.642, 95%$CI$: 0.591~0.733, $P$<0.001), and the trend test was statistically significant ($P_{trend}$<0.001). ROC curve analysis revealed that the area under the ROC curve (AUC) of serum PLGF level at 28-29$^{+6}$ gestational weeks in predicting adverse pregnancy outcomes in non-severe PE patients was 0.830 (95%$CI$: 0.635~0.917), the optimal critical threshold was 75.47 ng/L, the sensitivity was 88.37%, the specificity was 71.30%, the positive predictive value was 55.07%, and the negative predictive value was 93.90%. Its AUC value of the level for the prediction in patients with severe PE was 0.874 (95%$CI$: 0.677~0.923), the optimal critical threshold was 38.53 ng/L, the sensitivity was 88.89%, the specificity was 50.00%, the positive predictive value was 97.56%, and the negative predictive value was 16.67%. **Conclusion** At 28~29$^{+6}$ gestational weeks, PLGF has an independent correlation with pregnancy outcomes and shows a good predictive performance for adverse pregnancy outcomes in patients with non-severe PE and severe PE.

[**Key words**] placental growth factor; preeclampsia; disease severity; pregnancy outcomes; predictive value

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子痫前期(preeclampsia,PE)作为妊娠期高血压疾病中最严重的亚型,以妊娠20周后新发高血压合并蛋白尿或肝、肾、神经等多器官损害为特征,是导致孕产妇和围产儿发病及死亡的主要原因之一[1-2]。其病理生理机制复杂,涉及胎盘功能异常、血管内皮损伤、免疫失衡等多个环节,且病情进展迅速,严重威胁母婴健康。当前,应用于PE筛查的多种技术手段均面临单独使用时灵敏度或特异性不足,以及筛查时机选择存在争议等困难。现有筛查技术如孕妇风险因素评估、子宫动脉多普勒超声、部分生化指标检测等,单独应用时普遍存在灵敏度或特异性不足的问题,且对于最佳筛查时机的选择尚未达成共识,导致部分患者在明确诊断时已出现不可逆的母婴损害[3]。有研究报道,PE患者在典型临床症状显现前数周甚至数月,胎

盘及母体血管系统已发生病理改变,孕妇与胎儿的健康损害可能在此阶段即已启动[4]。因此,寻找能够早期识别PE风险、预测疾病进展及妊娠结局的生物学标志物,对于优化产前诊疗流程、实现PE的早防早治具有重要意义。胎盘生长因子(placental growth factor,PLGF),作为血管内皮生长因子(vascular endothelial growth factor,VEGF)家族成员,其主要由合体滋养层细胞所分泌。PLGF可促进胎盘血管的生成、螺旋动脉的重塑,以及滋养细胞的增殖与侵袭能力[5-6]。在妊娠早、中、晚期,患有PE的孕妇群体,其血清中PLGF的浓度均显著低于健康对照组[7]。PE更倾向于发生在具有高危因素的孕产妇中,包括高龄、高体质指数(body mass index,BMI)、既往高血压病史及糖尿病史等,但PLGF水平的下降往往先于高血压、蛋白尿等典型临床症状的出现,提前9~11周[8]。然而,当前关于PLGF的研究多集中于单一时间点的水平比较,对于其在不同严重程度PE患者中的动态变化规律,以及这种变化与具体妊娠结局的关联强度仍缺乏系统探讨。此外,PLGF与其他血管内皮功能指标的相互作用及其对预测效能的影响也有待深入分析。基于此,本研究旨在通过比较PLGF水平在不同严重程度PE患者中的动态变化,分析其对妊娠结果的预测能力,为PE防治提供理论依据。

## 1 资料与方法

### 1.1 研究对象

采用回顾性队列研究,选取2021年1月至2024年1月天津市北辰医院产科收治的198例患者,年龄22~40岁,平均(31.12±4.61)岁;孕龄28~40周,平均(31.64±7.83)周。非重度PE患者151例,妊娠20周后出现收缩压≥140 mmHg和(或)舒张压≥90 mmHg,且伴有下列任1项:24 h尿蛋白定量≥0.3 g,或尿蛋白/肌酐比值≥0.3,或随机尿蛋白≥(+)。重度PE患者47例,诊断标准为在子痫前期基础上伴有下面任何1种表现者:①收缩压≥160 mmHg和(或)舒张压≥110 mmHg;②血小板<$100\times10^9$/L;③肝功能损害(血清转氨酶水平为正常的2倍以上),持续性右上腹或上腹疼痛,不能用其它疾病解释;④肾功能受损(血肌酐水平>1.1 mg/dL或无其他肾脏疾病时肌酐浓度为正常值2倍以上);⑤肺水肿;⑥新发生的中枢神经系统异常或视觉障碍。对198例PE病例依据其妊娠的最终状况进行划分,出现胎盘早剥、产后出血、溶血、肝酶升高和血小板降低(hemolysis, elevated liver enzyme and low platelet, HELLP)综合征、胎儿生长受限、胎儿窘迫、早产、新生儿窒息的不良结局组(88例)与良好结局组(110例)。纳入标准:①符合PE的诊断标准[9];②单胞胎;③妊娠超过20周出现初发高血压(收缩压140 mmHg,舒张压90 mmHg),并于出生后12周随访;④病例资料完整。排除标准:①合并妊娠高血糖等并发症;②伴有重度感染性疾病;③妊娠前已有心、脑、肝、肾和其他脏器疾病;④患有血液系统疾病;⑤研究者认为不宜入选本次研究的其他情况,如患有严重精神疾病,难以配合完成本研究。同期于天津市北辰医院产科另取100位健康孕妇为对照组,年龄20~40岁,平均(31.46±4.14)岁;孕龄28到40周,平均(31.53±4.15)周。研究方案已获天津市北辰医院伦理委员会批准(KY2020082615),并已豁免知情同意。

### 1.2 方法

分别收集患者$28\sim29^{+6}$孕周、$30\sim31^{+6}$孕周、$32\sim34^{+6}$孕周的空腹中静脉血5 mL,处理血液样本可在20 ℃条件下,以2 000 r/min的转速进行离心操作,离心持续时间为20 min,并确保离心机的半径设定为10 cm。完成上述步骤后,分离出上层血清,并随后采用高度特异性的酶联免疫吸附试验方法,检测血清中PLGF、可溶性血管内皮生长因子受体-1(soluble fms-like tyrosine kinase receptor1,sFlt-1)、VEGF、血栓调节蛋白(thrombomodulin,TM)、血栓素A2(thromboxane A2,TXA2)、血管假性血友病因子(von willebrand factor,VwF);采用硝酸还原酶法测定检测血浆一氧化氮(nitric oxide,NO)。

### 1.3 观察指标

收集3组患者的一般指标,如年龄、产前BMI、高血压史、糖尿病史、不良情绪、产检情况、胎心异常、孕周、孕次、产次、流产、不良孕产史、剖宫产史、收缩压、舒张压以及分娩方式。血液指标:PLGF、sFlt-1、VEGF、NO、TM、TXA2、VwF。PLGF检测频次:分别于$28\sim29^{+6}$孕周、$30\sim31^{+6}$孕周、$32\sim34^{+6}$孕周进行3个时段PLGF的动态检测。

### 1.4 统计学分析

采用SPSS 22.0对数据进行统计分析。分类数据通过计数和比率(%)进行描述,组间比较运用$\chi^2$检验方法,有理论频数低于5时行Fisher's精确检验。连续型数据则以均值和标准差的形式表达,而2组间的比较则选择$t$检验,组间比较采用单因素方差分析(analysis of variance, ANOVA),事后两两比较使用LSD-$t$检验。在数据分析中,采用局部加权回归散点平滑法(locally weighted scatterplot smoothing, LOWESS)以探索连续变量间的二维曲线关系。运用多元

Logistic回归分析PE患者发生不良妊娠结局的关联。为了评估孕期血清中PLGF浓度对于预测非重度PE和重度PE患者不良妊娠结局的价值,采用受试者操作特征曲线(receiver operating characteristic curve,ROC)分析。$P<0.05$表示差异具有统计学意义。

## 2 结果

### 2.1 基线资料特征

基线资料特征比较,对照组、非重度PE组、重度PE组在产前BMI方面,三组呈现逐渐增高的趋势;高血压史占比同样依次升高($P<0.001$);收缩压和舒张压也随病情严重程度增加而逐渐增高($P$均$<0.001$);sFlt-1、TM、TXA2及VwF水平在三组中逐渐增高($P<0.001$),而VEGF、NO及PLGF则逐渐降低($P<0.001$,表1)。提示随着PE病情严重程度的增加,孕妇的身体基础状况、血压水平及血管内皮功能均呈现逐渐恶化的趋势,这些指标的变化可能与PE的发生发展密切相关。

### 2.2 不同孕周下的PLGF浓度比较

不同孕周PLGF水平的变化情况,对照组、非重度PE组、重度PE组孕妇不同孕周的PLGF水平呈现峰形变化,其中孕28~29$^{+6}$周时水平较低,随着孕周增加逐渐升高,至孕30~31$^{+6}$周达到高峰后又逐渐下降($P<0.05$);同时,在相同孕周下,对照组、非重度PE组、重度PE组的PLGF水平依次逐渐降低($P<0.05$,表2)。提示PLGF水平在孕期存在动态变化规律,且其水平高低与PE病情严重程度相关,病情越严重,PLGF水平越低。

### 2.3 血管内皮功能与PLGF浓度的相关性分析

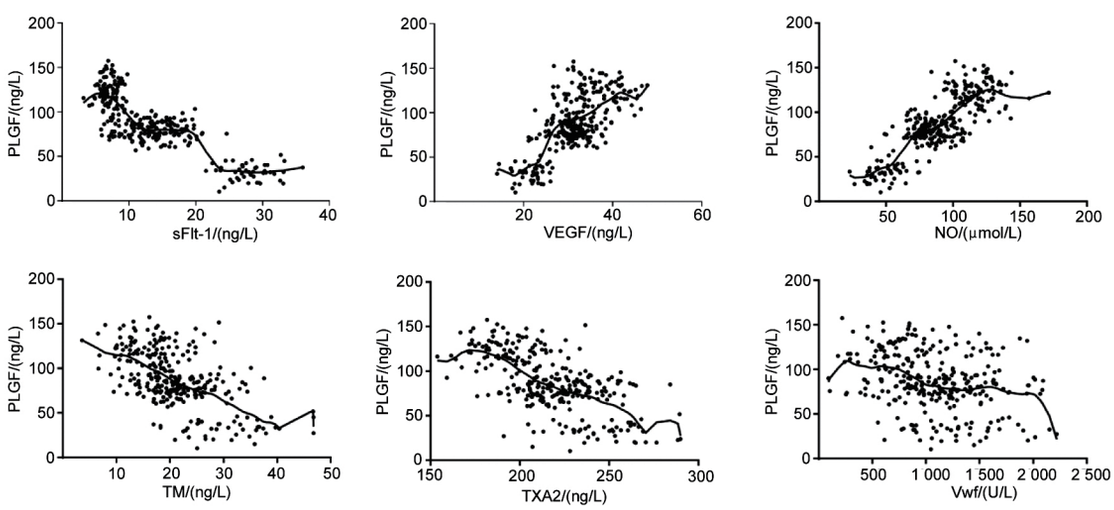
LOWESS方法分析28~29$^{+6}$孕周PLGF浓度与血管内皮功能指标的关系,以sFlt-1、VEGF、NO、TM、TXA2及VwF为自变量,以该孕周PLGF浓度为因变量进行分析。结果显示,28~29$^{+6}$孕周PLGF浓度与sFlt-1、VEGF、NO、TM、TXA2以及VwF均呈现出一定的非线性关系(图1)。提示在28~29$^{+6}$孕周,PLGF浓度与血管内皮功能指标的关系密切,这可能与该时期胎盘功能及血管内皮状态的动态变化有关。

### 2.4 不良妊娠结局发生率比较

不良妊娠结局比较,298名孕妇中共有100例(33.56%)发生不良妊娠结局;其中,PE患者的不良结局发生率为44.40%(88/198),明显高于对照组的12.00%(12/100);重度PE组的胎盘早剥、产后出血、HELLP综合征、胎儿生长受限、胎儿窘迫、早产、新生儿窒息的发生率均明显高于非重度PE组和对照组,尤其在早产、胎儿窘迫和新生儿窒息方面更为明显。提示随着PE病情加重,不良妊娠结局的发生风险显著增加($P$均$<0.05$,表3)。

### 2.5 妊娠不良结局组和良好结局组的临床资料比较

临床资料比较,不良结局组患者的产前BMI、高血压史占比、收缩压、舒张压、sFlt-1、TM、TXA2、VwF以及重度PE占比均高于良好结局组患者,而VEGF、NO以及PLGF则低于良好结局组患者,且上述差异均具




PLGF: Placental growth factor; sFlt-1: soluble fms-like tyrosine kinase receptor 1; VEGF: Vascular endothelial growth factor; NO: Nitric oxide; TM: Thrombomodulin; TXA2: Thromboxane A2; VwF: Von Willebrand factor

**图1 血管内皮功能指标与PLGF浓度的LOWESS分析**

**Figure 1 LOWESS analysis of vascular endothelial function indicators and PLGF concentration**

**表1 重度PE组、非重度PE组及对照组的临床基线资料比较[例(%),$\bar{x}\pm s$]**

**Table 1 Comparison of clinical baseline data among the severe PE group, the non-severe PE group and the control group [$n$(%), $\bar{x}\pm s$]**

| Item | Control group ($n$=100) | Non-severe PE group($n$=151) | Severe PE group($n$=47) | $F/\chi^2$ | $P$ |
|---|---|---|---|---|---|
| Age /years | 31.60±4.04 | 31.08±4.28 | 31.34±4.19 | 0.467 | 0.627 |
| Prenatal BMI/(kg/m$^2$) | 25.70±2.29 | 26.57±2.21[a] | 27.96±2.23[ab] | 16.431 | <0.001 |
| History of hypertension | | | | 15.250 | <0.001 |
| Yes | 18(18.00) | 49[a](32.45) | 23[ab](48.94) | | |
| No | 82(82.00) | 102[a](67.55) | 24[ab](51.06) | | |
| History of diabetes | | | | 0.984 | 0.611 |
| Yes | 15(15.00) | 24(15.89) | 10(21.28) | | |
| No | 85(85.00) | 127(84.11) | 37(78.72) | | |
| Negative emotions | | | | 0.869 | 0.648 |
| Yes | 17(17.00) | 30(19.87) | 11(23.40) | | |
| No | 83(83.00) | 121(80.13) | 36(76.60) | | |
| Prenatal checkup situation | | | | 0.180 | 0.914 |
| regular | 91(91.00) | 138(92.72) | 42(89.36) | | |
| Irregular | 9(9.00) | 13(7.28) | 5(10.64) | | |
| Abnormal fetal heart rate | | | | 2.150 | 0.341 |
| Yes | 12(12.00) | 23(15.23) | 10(21.28) | | |
| No | 88(88.00) | 128(84.77) | 37(78.72) | | |
| Pregnancy times /times | 1.70±0.54 | 1.70±0.50 | 1.77±0.48 | 0.372 | 0.670 |
| Birth time/times | 1.52±0.52 | 1.48±0.55 | 1.51±0.62 | 0.171 | 0.843 |
| Miscarriage/times | 0.18±0.39 | 0.22±0.43 | 0.26±0.44 | 0.628 | 0.534 |
| History of adverse pregnancy and childbirth | | | | 0.819 | 0.664 |
| Yes | 19(19.00) | 32(21.19) | 12(25.53) | | |
| No | 81(81.00) | 119(78.81) | 35(74.47) | | |
| History of cesarean section | | | | 0.261 | 0.878 |
| Yes | 34(34.00) | 53(35.10) | 18(38.30) | | |
| No | 66(66.00) | 98(64.90) | 29(61.70) | | |
| Systolic blood pressure/mmHg | 110.05±8.11 | 122.07±7.32[a] | 141.30±7.42[ab] | 272.265 | <0.001 |
| Diastolic blood pressure/mmHg | 70.77±7.11 | 80.29±6.65[a] | 94.85±8.89[ab] | 181.424 | <0.001 |
| sFlt-1/(ng/L) | 7.16±1.30 | 13.64±3.69[a] | 28.12±3.20[ab] | 773.053 | <0.001 |
| VEGF/(ng/L) | 36.30±5.24 | 30.85±3.53[a] | 21.50±2.95[ab] | 208.241 | <0.001 |
| NO/(μmol/L) | 116.58±14.95 | 83.72±12.89[a] | 50.14±12.73[ab] | 409.152 | <0.001 |
| TM/(ng/L) | 16.19±4.87 | 21.44±5.30[a] | 31.00±7.34[ab] | 114.749 | <0.001 |
| TXA2/(ng/L) | 194.56±16.56 | 223.07±19.11[a] | 245.53±22.73[ab] | 131.424 | <0.001 |
| VwF/(U/L) | 875.50±387.48 | 1 079.43±394.29[a] | 1 299.38±411.14[ab] | 19.56 | <0.001 |
| PLGF/(ng/L) | 122.91±14.58 | 79.93±10.02[a] | 32.31±8.96[ab] | 1 026.879 | <0.001 |
| Mode of delivery | | | | 1.669 | 0.434 |
| Natural delivery | 28(28.00) | 34(22.52) | 9(19.15) | | |
| Cesarean section | 72(72.00) | 117(77.48) | 38(80.85) | | |

PE: Preeclampsia; BMI: Body mass index; sFlt-1: soluble fms-like tyrosine kinase receptor 1; VEGF: Vascular endothelial growth factor; NO: Nitric oxide; TM: Thrombomodulin; TXA2: Thromboxane A2; VwF: Von Willebrand factor; PLGF: Placental growth factor. a: $P$<0.05, in comparison with the control group; b: $P$<0.05, in comparison with the non-severe PE group

表2 重度PE组、非重度PE组及对照组在不同孕周下的PLGF浓度比较($\bar{x}\pm s$,ng/L)

**Table 2 Comparison of PLGF concentrations in the severe PE group, the non-severe PE group PE group and the control group at different gestational weeks**($\bar{x}\pm s$,ng/L)

| Gestational weeks | Control group($n$=100) | Non-severe PE group($n$=151) | Severe PE group($n$=47) | $F$ | $P$ |
|---|---|---|---|---|---|
| 28~29$^{+6}$ | 79.49±9.15 | 51.34±6.37$^{a}$ | 23.85±7.72$^{ab}$ | 921.859 | <0.001 |
| 30~31$^{+6}$ | 122.91±14.58 | 79.93±10.02$^{a}$ | 32.31±8.96$^{ab}$ | 1026.879 | <0.001 |
| 32~34$^{+6}$ | 110.42±13.45 | 70.04±8.64$^{a}$ | 29.65±7.04$^{ab}$ | 1054.393 | <0.001 |
| $F$ | 185.032 | 164.747 | 22.107 | | |
| $P$ | <0.001 | <0.001 | <0.001 | | |

PLGF: Placental growth factor; PE: Preeclampsia. a: $P$<0.05, in comparison with the control group; b: $P$<0.05, in comparison with the non-severe PE group

表3 重度PE组、PE组及对照组的不良妊娠结局发生率比较[例(%)]

**Table 3 Comparison of the incidence of adverse pregnancy outcomes among the severe PE group, the PE group and the control group** [$n$(%)]

| Group | Pregnancy outcome of the parturient | | | The perinatal outcome | | | |
|---|---|---|---|---|---|---|---|
| | Placental abruption | Post-partum hemorrhage | HELLP syndrome | Fetal growth restriction | Fetal distress | Premature birth | Neonatal asphyxia |
| Control group($n$=100) | 1(1.00) | 1(1.00) | 1(1.00) | 1(1.00) | 2(2.00) | 5(5.00) | 1(1.00) |
| Non-severe PE group($n$=151) | 2(1.32) | 2(1.32) | 2(1.32) | 3(1.99) | 5(3.31) | 11(7.28) | 4(2.65) |
| Severe PE group($n$=47) | 4$^{b}$(8.51) | 4$^{b}$(8.51) | 4$^{b}$(8.51) | 5$^{ab}$(10.64) | 11$^{a}$(23.40) | 22$^{ab}$(46.81) | 9$^{a}$(19.15) |
| $\chi^2$ | 9.263 | 9.263 | 9.263 | 11.257 | 35.722 | 58.456 | 26.392 |
| $P$ | 0.010 | 0.010 | 0.010 | 0.004 | <0.001 | <0.001 | <0.001 |

PE: Preeclampsia; HELLP syndrome: A severe form of pre-eclampsia with haemolysis, elevated liver enzymes, and low platelets. a: $P$<0.05, in comparison with the control group; b: $P$<0.05, in comparison with the PE group

有统计学意义($P$<0.05,表4)。提示产前BMI、血压水平、血管内皮功能相关指标及PE严重程度可能与妊娠结局相关。

### 2.6 28~29$^{+6}$孕周PLGF与妊娠结局的关系

采用Logistic回归分析28~29$^{+6}$孕周PLGF水平与妊娠结局的独立相关性,逐步排除存在共线性的混杂因素,最终校正各协变量(模型5)后进行分析,同时将PLGF水平转化为二分类变量及五分位数组进行进一步分析。结果显示,校正各协变量后,28~29$^{+6}$孕周PLGF水平与妊娠结局仍存在独立相关性($OR$=0.593,95%$CI$:0.583~0.778,$P$<0.001);将PLGF水平转化为二分类变量后,PLGF高水平与妊娠结局存在独立相关性($OR$=0.773,95%$CI$:0.671~0.885,$P$<0.001);与PLGF最低的五分位数组(Q1)相比,随着PLGF水平逐渐升高(Q2~Q5组),相关性效应值分别为($OR$=0.765,95%$CI$:0.639~0.837,$P$=0.092)、($OR$=0.752,95%$CI$:0.624~0.818,$P$=0.056)、($OR$=0.696,95%$CI$:0.615~0.813,$P$=0.027)、($OR$=0.642,95%$CI$:0.591~0.733,$P$<0.001),且趋势性检验存在统计学意义($P_{趋势}$<0.001,表5)。提示28~29$^{+6}$孕周PLGF水平与妊娠结局存在独立相关性,且随着PLGF水平的升高,不良妊娠结局发生的风险逐渐降低,PLGF水平可作为预测妊娠结局的重要指标。

### 2.7 28~29$^{+6}$孕周血清PLGF水平对非重度PE和重度PE患者不良妊娠结局的预测价值

采用ROC分析28~29$^{+6}$孕周PLGF水平对非重度PE和重度PE患者不良妊娠结局的预测价值,结果显示,28~29$^{+6}$孕周血清PLGF水平预测非重度PE患者不良妊娠结局的ROC曲线下面积为0.830(95%$CI$:0.635~0.917),最佳临界阈值为75.47 ng/L,敏感度为88.37%,特异度为71.30%,阳性预测值为55.07%,阴性预测值为93.90%;预测重度PE患者不良妊娠结局的ROC曲线下面积为0.874(95%$CI$:0.677~0.923),最佳临界阈值为38.53 ng/L,敏感度为88.89%,特异度为50.00%,阳性预测值为97.56%,阴性预测值为16.67%(图2)。提示28~29$^{+6}$孕周血清PLGF水平对非重度PE和重度PE患者不良妊娠结局均具有一定的预测价值,可作为临床评估相关患者不良妊娠结局风险的参考指标。

表4 妊娠不良结局组和良好结局组的临床资料比较[例(%),$\bar{x}\pm s$]

**Table 4 Comparison of clinical data between the adverse pregnancy outcome group and the good pregnancy outcome group** [$n$(%),$\bar{x}\pm s$]

| Factors | Adverse outcome group($n$=88) | Good Outcome Group($n$=110) | $t/\chi^2$ | $P$ |
|---|---|---|---|---|
| Age/years | 31.17±4.32 | 31.38±4.52 | 0.331 | 0.741 |
| Prenatal BMI/(kg/m$^2$) | 27.74±2.19 | 25.89±2.48 | 5.491 | <0.001 |
| History of hypertension | | | 14.938 | <0.001 |
| Yes | 45(51.14) | 27(24.55) | | |
| No | 43(48.86) | 83(75.45) | | |
| History of diabetes | | | 0.002 | 0.966 |
| Yes | 15(17.05) | 19(17.27) | | |
| No | 73(82.95) | 91(82.73) | | |
| Negative emotions | | | 0.006 | 0.937 |
| Yes | 18(20.45) | 23(20.91) | | |
| No | 70(79.55) | 87(79.09) | | |
| Prenatal checkup situation | | | 0.248 | 0.619 |
| law | 81(92.05) | 99(90.00) | | |
| Irregular | 7(7.95) | 11(10.00) | | |
| Abnormal fetal heart rate | | | 1.636 | 0.201 |
| Yes | 18(20.45) | 15(13.64) | | |
| No | 70(79.55) | 95(86.36) | | |
| Gestational weeks/weeks | 31.62±3.89 | 31.39±4.18 | 0.397 | 0.692 |
| Pregnancy times | 1.71±0.34 | 1.69±0.45 | 0.345 | 0.730 |
| Birth time | 1.48±0.43 | 1.51±0.54 | 0.424 | 0.672 |
| Miscarriage | 1.01±0.25 | 0.99±0.27 | 0.535 | 0.593 |
| History of adverse pregnancy and childbirth | | | 0.037 | 0.848 |
| Yes | 19(21.59) | 25(22.73) | | |
| No | 69(78.41) | 85(77.27) | | |
| History of cesarean section | | | 0.018 | 0.895 |
| Yes | 32(36.36) | 39(35.45) | | |
| No | 56(63.64) | 71(64.55) | | |
| Systolic blood pressure/mmHg | 139.14±9.47 | 114.51±9.47 | 18.185 | <0.001 |
| Diastolic blood pressure/mmHg | 95.32±7.71 | 71.42±7.48 | 22.038 | <0.001 |
| sFlt-1/(ng/L) | 28.16±2.31 | 9.63±3.64 | 41.521 | <0.001 |
| VEGF/(ng/L) | 21.32±3.23 | 35.86±3.59 | 29.598 | <0.001 |
| NO/(μmol/L) | 51.57±12.84 | 114.71±15.84 | 30.270 | <0.001 |
| TM/(ng/L) | 31.09±5.84 | 19.47±7.37 | 12.065 | <0.001 |
| TXA2/(ng/L) | 245.53±18.54 | 210.04±23.15 | 11.690 | <0.001 |
| VwF/(U/L) | 1 310.54±384.87 | 994.17±455.12 | 5.200 | <0.001 |
| 28~29$^{+6}$ gestational weeks PLGF/(ng/L) | 33.92±11.54 | 99.94±15.07 | 33.901 | <0.001 |
| Mode of delivery | | | 0.536 | 0.464 |
| Natural delivery | 17(19.32) | 26(23.64) | | |
| Cesarean section | 71(80.68) | 84(76.36) | | |
| Degree of PE | | | 65.687 | <0.001 |
| Non-severe PE | 43(48.86) | 108(98.18) | | |
| Severe PE | 45(51.14) | 2(1.82) | | |

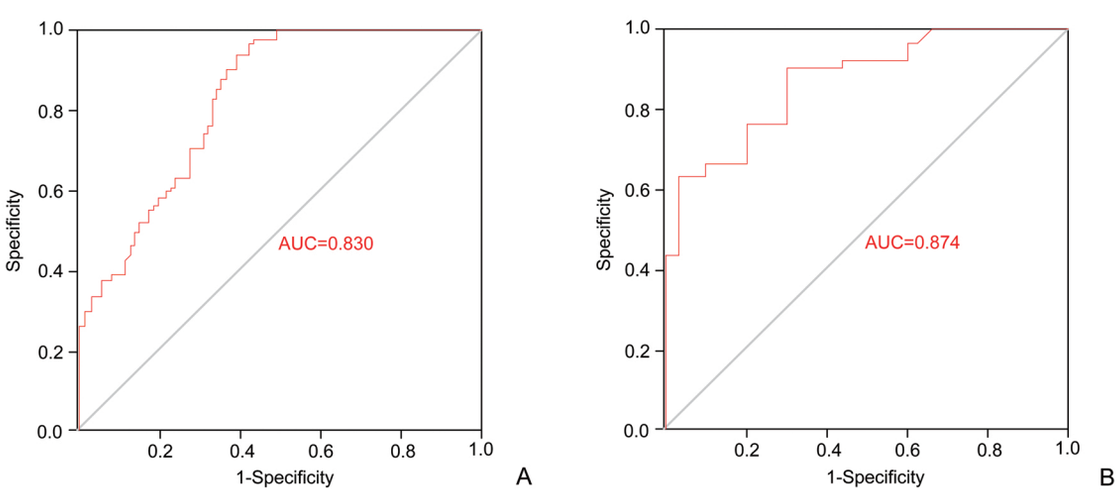
BMI: Body mass index; sFlt-1: soluble fms-like tyrosine kinase receptor 1; VEGF: Vascular endothelial growth factor; NO: Nitric oxide; TM: Thrombomodulin; TXA2: Thromboxane A2; VwF: Von Willebrand factor; PLGF: Placental growth factor; PE: Preeclampsia

表5 28~29$^{+6}$孕周PLGF与妊娠结局的独立相关性

Table 5 Independent correlation between PLGF at 28-29 $^{+6}$ gestational weeks and pregnancy outcomes

| Variables | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
|---|---|---|---|---|---|
| PLGF | 0.543(0.414~0.663) | 0.622(0.605~0.785) | 0.624(0.611~0.799) | 0.551(0.418~0.683) | 0.593(0.583~0.778) |
| PLGF binary classification | | | | | |
| Low expression(≤60.0 ng/L) | 1 | 1 | 1 | 1 | 1 |
| High expression(>60.0 ng/L) | 0.734(0.652~0.847) | 0.713(0.617~0.811) | 0.743(0.656~0.872) | 0.761(0.568~0.883) | 0.773(0.671~0.885) |
| PLGF quintile array | | | | | |
| Q1(≤20.00 ng/L) | 1 | 1 | 1 | 1 | 1 |
| Q2(20.01~40.00 ng/L) | 0.722(0.643~0.827) | 0.734(0.666~0.878) | 0.743(0.648~0.861) | 0.756(0.651~0.848) | 0.765(0.639~0.837) |
| Q3(40.01~75.00 ng/L) | 0.698(0.620~0.802) | 0.711(0.654~0.839) | 0.726(0.647~0.828) | 0.743(0.642~0.831) | 0.752(0.624~0.818) |
| Q4(75.01~100.00 ng/L) | 0.642(0.612~0.786) | 0.663(0.638~0.838) | 0.674(0.635~0.812) | 0.685(0.632~0.826) | 0.696(0.615~0.813) |
| Q5(≥100.01 ng/L) | 0.593(0.583~0.772) | 0.622(0.613~0.796) | 0.623(0.611~0.788) | 0.635(0.583~0.783) | 0.642(0.591~0.733) |
| $P_{Trend}$ | 0.001 | 0.002 | 0.001 | 0.001 | <0.001 |

PLGF: Placental growth factor. Model 1: Uncorrected confounding factors; Model 2: Adjusting for the influence of age and BMI; Model 3: Based on Model 2, adjust the influences of history of hypertension, history of diabetes, negative emotions, prenatal check-up conditions, abnormal fetal heart rate, history of adverse pregnancy and childbirth, history of cesarean section, and mode of delivery; Model 4: Adjusting the influence of pregnancy number, delivery number, miscarriage and surviving children on the basis of Model 3; Model 5: Adjusting the effects of systolic blood pressure, diastolic blood pressure, sFlt-1, VEGF, NO, TM, TXA2 and VwF on the basis of Model 4




A: ROC curve of non-severe PE; B: ROC curve of severe PE. PE: Preeclampsia; PLGF: Placental growth factor

图2 28~29$^{+6}$孕周血清PLGF水平预测非重度PE和重度PE患者不良妊娠结局的ROC曲线

Figure 2 ROC curves of serum PLGF level at 28~29$^{+6}$ gestational weeks for predicting adverse pregnancy outcomes in patients with non-severe PE and severe PE

## 3 讨论

### 3.1 PLGF水平与PE病情严重程度及妊娠结局的关联

妊娠期高血压综合征中,PE是导致不良妊娠结局的主要风险因素,其核心病理机制在于子宫螺旋动脉滋养细胞重塑障碍引发的胎盘缺血缺氧,进而诱发血管内皮损伤[10-13]。PLGF作为调控胎盘血管生成的关键分子,其水平变化与PE的发生发展密切相关[14-15]。本研究发现,对照组、非重度PE组、重度PE组的PLGF水平依次降低,且不同孕周PLGF水平呈峰形变化,在28~29$^{+6}$周处于较低水平,30~31$^{+6}$周达高峰后逐渐下降,这一动态特征与胎盘功能的生理演变规律一致。本研究进一步聚焦于28~29$^{+6}$孕周这一特定时期,发现该时期血清PLGF水平与PE病情严重程度及不良妊娠结局存在独立相关性,为PE的中期预警与风险分

层提供了新的临床依据。PLGF能有效促进滋养细胞的侵袭潜能,在一定程度上遏制胎儿宫内生长受限的进展与恶化[16]。研究表明[17]PE的发生伴随着一种早期的抗血管生成状态,而这种状态与血清中PLGF水平的显著降低密切相关。相关研究发现[18]孕早期至中期的PE患者其血清PLGF平均值低于正常组,孕早期至中期PLGF水平的异常降低可能与PE的后续发展密切相关。因此,动态监测孕期PLGF的变化对于PE的预防和治疗具有重要意义。有研究[19]对妊娠34~36$^{+6}$周的PE孕妇进行PLGF水平监测发现,在PLGF水平低于60 pg/mL时进行促胎儿肺成熟治疗并分娩,可显著避免母体发生严重的并发症,且可避免新生儿发生不良结局。本研究发现28~29$^{+6}$孕周血清PLGF水平预测非重度PE和重度PE不良妊娠结局的曲线下面积分别为0.830、0.874,敏感度分别为88.37%和88.89%,特异度分别为71.30%和50.00%,充分说明28~29$^{+6}$孕周血清PLGF水平与非重度PE和重度PE不良妊娠结局有关,且预测价值较高。28~29$^{+6}$孕周处于孕中期向孕晚期过渡阶段,此时检测PLGF可有效识别PE高风险孕妇。对于PLGF水平降低者,应加强后续孕期监测(如动态血压、尿蛋白、胎儿生长发育评估),尽早干预以降低子痫、胎儿生长受限等不良结局风险。

### 3.2 PLGF与血管内皮功能指标的关系

胎盘血管内皮细胞的损伤及重铸障碍被视为PE发生的潜在机制。VEGF及其受体家族,尤其是sFlt-1,不仅是VEGF信号传导的关键受体,还参与胎盘血管网络的构建与重塑,同时也在胎盘绒毛的增殖与侵袭活动中发挥作用[20]。sFlt-1表达水平的上升也被视为胎儿不良结局风险增加的一个预警信号,不良风险与sFlt-1表达水平存在显著的正相关关系[21]。本研究观察到28~29$^{+6}$孕周PLGF浓度与sFlt-1、VEGF、NO、TM、TXA2以及VwF均具有一定的非线性关系,这与PE中血管内皮损伤、全身小动脉痉挛的病理特征高度一致[22]。在PE等疾病中,当血管内皮遭受损伤时,原本附着于血管内壁的TM会被蛋白酶水解,随后释放至血液循环中,导致血清中TM浓度显著上升。NO不仅是介导内皮依赖性血管舒张的关键分子,还参与调控内皮细胞的多种保护性反应,包括抗炎、抗血小板聚集、阻止白细胞黏附于血管壁以及抑制平滑肌细胞的异常增殖等。高血压、血脂异常及高血糖等代谢紊乱状态,均能对内皮功能造成不同程度的损害,进而影响NO的生成及其生理效应的发挥[23]。TXA2是重要的收缩血管物质,其表达升高提示PE患者血管舒张状态被抑制,引发不良妊娠结局[24]。血清vWF水平增加是当内皮细胞受损时将vWF释放入血,因此,vWF是反映血管内皮细胞损伤的一种高灵敏指标。当PE患者胎盘缺血、缺氧以及严重的微血管内皮细胞的损伤时,血清vWF水平会明显增加[25]。临床上可以结合本研究中PLGF与血管内皮损伤标志物的关联性,对于PLGF降低的孕妇,临床可考虑针对性评估血=管内皮功能,并探索改善胎盘血流灌注的措施,以延缓疾病进展。

本研究尚存在一定的局限性,样本来源单一中心、未纳入早孕期及分娩时样本等局限,未来需通过多中心、大样本研究验证结论的普适性,并扩大孕周范围以明确PLGF在整个孕期的动态变化规律。本研究未纳入早孕期及分娩发动时样本,未来可扩大孕周范围进一步验证。本研究阐明28~29$^{+6}$孕周PLGF对PE不良结局的预测价值,但需客观认识本研究的局限性:①PLGF水平受孕周、胎盘功能及合并症(如糖尿病)影响,单独检测可能漏诊部分非典型PE病例;②不同人群(如双胎妊娠、高龄孕妇)的PLGF水平存在差异,本研究结果的普适性需进一步验证。未来研究需在扩大人群验证、探索联合干预策略及深化机制研究等方面持续推进,以更好地阐明PLGF在改善母婴预后中的临床价值。

综上所述,28~29$^{+6}$孕周血清PLGF水平与PE病情严重程度及不良妊娠结局密切相关,其变化与血管内皮功能指标存在协同关联,可作为临床评估PE风险的有效指标。及时监测并干预低PLGF水平孕妇,有助于降低母婴并发症发生率,改善妊娠结局。

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