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【临床研究】

子痫前期患者血清妊娠相关血浆蛋白-A 和血管内皮生长因子水平与妊娠结局的关系

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摘要: 目的 探讨子痫前期(PE)患者血清妊娠相关血浆蛋白(PAPP)-A、血管内皮生长因子(VEGF)水平与妊娠结局的关系。**方法** 选择2020年5月至2021年5月信阳市中心医院收治的118例PE患者为研究对象,所有患者于入院当天至分娩后1 d接受临床观察,评估患者妊娠不良事件发生情况,根据评估结果将发生妊娠不良事件的患者纳入妊娠结局不良组,未发生妊娠不良事件患者纳入妊娠结局良好组。于入院次日,收集患者空腹外周静脉血8 mL,采用酶联免疫吸附试验法检测患者血清PAPP-A、VEGF水平;使用全自动血细胞分析仪检测患者全血白细胞(WBC)计数及血小板(PLT)、血红蛋白(Hb)水平。入院次日清晨,收集患者24 h尿液,采用酶联免疫吸附试验法检测患者24 h尿蛋白水平。设计一般资料调查问卷,收集2组患者临床资料,包括:年龄、分娩方式、入院时孕周、分娩时孕周、孕次、孕前体质量指数(BMI)、疾病类型等。采用logistic回归分析PE患者妊娠结局的影响因素。绘制受试者操作特征(ROC)曲线,分析血清PAPP-A、VEGF水平对PE患者妊娠结局不良的预测效能,以曲线下面积(AUC)表示预测价值。**结果** 本研究纳入的118例PE患者中,86例(72.88%)患者妊娠结局良好(妊娠结局良好组);32例(27.12%)患者发生妊娠不良事件(妊娠结局不良组),其中孕妇不良事件22例,胎儿不良事件10例。2组患者的年龄、孕前BMI、分娩方式、分娩时孕周、孕次、疾病类型比较差异无统计学意义($P>0.05$)。妊娠结局不良组患者全血Hb、PLT及血清PAPP-A、VEFG水平显著低于妊娠结局良好组,24 h尿蛋白水平显著高于妊娠结局良好组($P<0.05$);2组患者的全血WBC计数比较差异无统计学意义($P>0.05$)。Logistic回归分析结果显示,血清PAPP-A、VEGF与PE患者妊娠结局不良有关($P<0.05$),全血Hb、PLT、24 h尿蛋白与PE患者妊娠结局无关($P>0.05$)。ROC曲线分析显示,血清PAPP-A、VEGF预测PE患者不良妊娠结局的截断值分别为2 718.780 mU·L^{-1}、29.495 ng·L^{-1};血清PAPP-A联合VEGF预测PE患者不良妊娠结局的敏感度显著高于PAPP-A单独检测($P<0.05$);血清PAPP-A与VEGF预测PE患者不良妊娠结局的敏感度比较差异无统计学意义($P>0.05$);血清PAPP-A、VEGF、PAPP-A联合VEGF预测PE患者不良妊娠结局的AUC、特异度比较差异无统计学意义($P>0.05$)。**结论** 血清PAPP-A、VEGF水平与PE患者妊娠结局不良有关,血清PAPP-A、VEGF水平可作为预测PE患者不良妊娠结局的生物标志物。

关键词: 子痫前期;妊娠相关血浆蛋白-A;血管内皮生长因子;妊娠结局
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Relationship between serum pregnancy associated plasma protein-A, vascular endothelial growth factor levels and pregnancy outcome in patients with preeclampsia

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Abstract: Objective To investigate the relationship between serum pregnancy-associated plasma protein (PAPP)-A, vascular endothelial growth factor (VEGF) and pregnancy outcome in patients with preeclampsia (PE). **Methods** A total of 118 PE patients admitted to Xinyang Central Hospital from May 2020 to May 2021 were selected as the study objects. All patients received clinical observation from the day of admission to the first day after delivery, and the incidence of adverse pregnancy events was evaluated. According to the evaluation results, the patients with adverse pregnancy events were included in the adverse pregnancy outcome group, and the patients without adverse pregnancy events were included in the good pregnancy outcome group. On the next day after admission, 8 mL of fasting peripheral venous blood was collected, and the

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serum PAPP-A and VEGF levels were detected by enzyme linked immunosorbent assay. The white blood cell (WBC) count, platelet(PLT) and hemoglobin(Hb) levels of the patients were detected by automatic blood cell analyzer. In the morning of the next day after admission, 24 h urine was collected and the 24 h urine protein level was detected by enzyme linked immunosorbent assay. A general data questionnaire was designed to collect the clinical data of patients in the two groups, including age, mode of delivery, gestational week at admission, gestational week at delivery, the number of pregnancies, pre-pregnancy body mass index (BMI), disease type, etc. The influencing factor of the pregnancy outcome of PE patients was analyzed by logistic regression analysis. Receiver operating characteristic (ROC) curve was drawn to analyze the predictive efficacy of serum PAPP-A and VEGF levels on adverse pregnancy outcomes in PE patients, and the predictive value was represented by the area under curve (AUC). **Results** Of the 118 PE patients included in this study, 86 patients (72.88%) had a good pregnancy outcome (good pregnancy outcome group); 32 patients (27.12%) had adverse pregnancy events (adverse pregnancy outcome group), including 22 cases of adverse events of pregnancy and 10 cases of fetal adverse events. There was no significant difference in terms of age, BMI before pregnancy, delivery mode, gestational week, number of pregnancies and disease type of patients between the two groups ($P>0.05$). Whole blood Hb, PLT, serum PAPP-A and VEFG levels of patients in the adverse pregnancy outcome group were significantly lower than those in the good pregnancy outcome group, and 24 h urinary protein level was significantly higher than that in the good pregnancy outcome group ($P<0.05$). There was no significant difference in whole blood WBC of patients between the two groups ($P>0.05$). Logistic regression analysis showed that the levels of serum PAPP-A and VEGF were related to the adverse pregnancy outcome of PE patients ($P<0.05$), while the whole blood Hb, PLT and 24 h urine protein were not related to the pregnancy outcome of PE patients ($P>0.05$). The results of ROC curve showed that the cutoff values of serum PAPP-A and VEGF for predicting adverse pregnancy outcomes in PE patients were 2 718.780 $mU \cdot L^{-1}$ and 29.495 $ng \cdot L^{-1}$, respectively. The sensitivity of serum PAPP-A combined with VEGF to predict adverse pregnancy outcome in PE patients was significantly higher than that of PAPP-A alone ($P<0.05$); there was no significant difference in the sensitivity between PAPP-A alone and VEGF alone in predicting adverse pregnancy outcome in PE patients ($P>0.05$); there was no significant difference in AUC and specificity of predicting adverse pregnancy outcome in PE patients among the serum PAPP-A, VEGF alone and PAPP-A combined with VEGF ($P>0.05$). **Conclusion** The levels of serum PAPP-A and VEGF are related to the adverse pregnancy outcome of PE patients. The levels of serum PAPP-A and VEGF can be used as biomarkers to predict the adverse pregnancy outcome of PE patients.

Key words: preeclampsia; pregnancy-associated plasma protein-A; vascular endothelial growth factor; pregnancy outcome

子痫前期(preeclampsia, PE)为妊娠期特发疾病,位居孕产妇及胎儿病死原因第 2 位,已成为不良妊娠结局的主要原因之一[1]。临床治疗 PE 主要是减轻症状、延长孕周,从而尽可能保障孕妇安全分娩,但仍有部分患者病情未能得到有效控制而发展至重度 PE 或子痫,进而导致器官功能障碍,被迫终止妊娠,甚至增加病死率[2]。因此,为改善 PE 患者妊娠结局,探索与 PE 病情进展的有关标志物意义重大。妊娠相关血浆蛋白(pregnancy-associated plasma protein, PAPP)-A 是一种大分子蛋白,参与胚胎早期发育、孕卵着床、胎儿生长等过程[3]。研究显示,PAPP-A 与多种妊娠不良事件有关[4]。罗晓华等[5]研究显示,PE 发病与血管内皮损伤有关,血管内皮损伤导致组织和胎盘缺血缺氧,进而增加器官功能障碍风险,不利于妊娠。血管内皮生长因子(vascular endothelial growth factor, VEGF)是一种促血管生长因子,参与血管重构、新生血管生成,对器官供血具有一定影响[6]。因此,推测血清 PAPP-A、VEGF 可能通过影响胚胎发育和组织供血,参与 PE 病情进展,进而影响妊娠结局。基于此,本研究探讨血清 PAPP-A、VEGF 与 PE 患者妊娠结局的关系,旨在为临床改善 PE 患者妊娠结局提供参考。

1　资料与方法

1.1　一般资料　选择 2020 年 5 月至 2021 年 5 月信阳市中心医院收治的 118 例 PE 患者为研究对象。病例纳入标准:(1)符合 PE 相关诊断标准[7];(2)24 h 尿蛋白≥300 mg;(3)单胎妊娠;(4)入院时病情稳定,均在医院接受相关治疗;(5)入院时产检胎心正常。排除标准:(1)合并原发性高血压、原发性凝血功能障碍、自身免疫性疾病、妊娠期梅毒者;(2)合并其他妊娠期并发症,如妊娠期糖尿病、贫血等;(3)合并子宫疾病,如子宫肌瘤、子宫内膜炎等;(4)有习惯性流产史者;(5)有子宫、卵巢手术史(剖宫产除外)者;(6)长期服用雌激素药物者。本研究获信阳市中心医院医学伦理委员会批准,患者及家

属签署知情同意书。

1.2 PE 患者妊娠结局评估方法 所有患者于入院当天至分娩后 1 d 接受临床观察,并评估患者妊娠不良事件发生情况,包括:(1)孕妇不良事件:早产(胎儿娩出时孕周 <37 周)、胎盘早剥(胎盘在胎儿娩出前从子宫壁剥离)、HELLP 综合征[7]、羊水过少(经超声检查,羊水指数 <5 cm 或最大羊水池深度 <2 cm)等;(2)胎儿不良事件:新生儿窒息[8]、胎儿窘迫[9]等。将发生妊娠不良事件的患者纳入妊娠结局不良组,未发生妊娠不良事件患者纳入妊娠结局良好组。

1.3 实验室指标检测 (1)血清 PAPP-A、VEGF 水平:于入院次日,收集患者空腹外周静脉血 8 mL,分别置于 2 支含抗凝剂试管中保存待检。取其中 1 支试管,以 4 000 r · min^{-1} 离心 5 min(离心半径 10 cm)取上清,使用酶联免疫吸附试验检测试剂盒(武汉赛培生物科技有限公司)检测血清 PAPP-A、VEGF 水平,严格按照试剂盒说明书进行操作。(2)全血白细胞(white blood cell,WBC)计数及血红蛋白(hemoglobin,Hb)、血小板(platelet,PLT)水平:取另 1 支试管,使用全自动血细胞分析仪(济南欧莱博技术有限公司)检测 WBC 计数及 Hb、PLT 水平。(3)24 h 尿蛋白水平:入院次日清晨,收集患者 24 h 尿液,置于干燥、无菌容器中,采用酶联免疫吸附试验检测患者 24 h 尿蛋白水平,人尿蛋白酶联免疫吸附试验检测试剂盒购自武汉赛培生物科技有限公司,严格按照说明书进行操作。

1.4 临床资料收集 设计一般资料调查问卷,收集 2 组患者临床资料,包括:年龄、分娩方式(阴道分娩/剖宫产)、分娩时孕周、孕次(首次/多次)、孕前体质量指数(body mass index,BMI)、疾病类型(晚发型/早发型)等。

1.5 统计学处理 应用 SPSS 25.0 软件进行统计学处理。符合正态分布的计量资料以均数 ± 标准差($\bar{x} \pm s$)表示,2 组间比较采用独立样本 t 检验;计数资料以例数和百分率表示,2 组间比较采用 χ^2 检验;采用 logistic 回归分析 2 组间比较差异有统计学意义的指标与 PE 患者妊娠结局的关系;绘制受试者操作特征(receiver operating characteristic,ROC)曲线,分析血清 PAPP-A、VEGF 水平对 PE 患者妊娠结局不良的预测效能,以曲线下面积(area under curve,AUC)表示预测价值,AUC >0.9 表示预测价值较高,AUC 为 >0.7 ~0.9 表示有一定预测价值,AUC 为 0.5 ~0.7 表示预测价值较低,AUC <0.5 表示无预测价值;P <0.05 为差异有统计学意义。

2 结果

2.1 PE 患者妊娠结局 118 例 PE 患者中,86 例(72.88%)患者妊娠结局良好(妊娠结局良好组);32 例(27.12%)患者发生妊娠不良事件(妊娠结局不良组),其中孕妇不良事件 22 例,胎儿不良事件 10 例。

2.2 2 组患者一般资料比较 结果见表 1。2 组患者的年龄、孕前 BMI、分娩方式、分娩时孕周、孕次、疾病类型比较差异无统计学意义(P >0.05)。

表 1 2 组患者一般资料比较

Tab.1 Comparison of general data of patients between the two groups

一般资料	妊娠结局良好组(n =86)	妊娠结局不良组(n =32)	t/χ^2	P
年龄/岁	29.85 ±1.78	30.14 ±1.86	0.777	0.439
孕前 BMI/(kg · m^{-2})	21.82 ±0.76	21.74 ±0.72	0.516	0.607
分娩方式				
阴道分娩/例(%)	40(46.51)	20(62.50)	2.385	0.123
剖宫产/例(%)	46(53.49)	12(37.50)		
分娩时孕周/周	38.12 ±0.85	37.82 ±0.82	1.721	0.088
孕次				
首次/例(%)	38(44.19)	18(56.25)	1.361	0.243
多次/例(%)	48(55.81)	14(43.75)		
疾病类型				
晚发型/例(%)	70(81.40)	22(68.75)	2.171	0.141
早发型/例(%)	16(18.60)	10(31.25)		

2.3 2 组患者实验室指标比较 结果见表 2。妊娠结局不良组患者全血 Hb、PLT、血清 PAPP-A、VEFG 水平显著低于妊娠结局良好组,24 h 尿蛋白水平显著高于妊娠结局良好组,差异有统计学意义(P <0.05)。2 组患者的全血 WBC 计数比较差异无统计学意义(P >0.05)。

表 2 2 组患者实验室指标比较

Tab.2 Comparison of laboratory indexes of patients between the two groups ($\bar{x} \pm s$)

组别	WBC/($\times 10^9$ L^{-1})	Hb/(g · L^{-1})	PLT/($\times 10^9$ L^{-1})	24 h 尿蛋白定量/mg	PAPP-A/(mU · L^{-1})	VEGF/(ng · L^{-1})
妊娠结局良好组(n =86)	10.74 ±1.64	131.55 ±10.66	111.12 ±9.57	292.25 ±28.46	2 810.02 ±262.36	32.30 ±3.28
妊娠结局不良组(n =32)	11.32 ±1.85	126.19 ±0.11	106.54 ±9.26	308.22 ±32.25	2 511.88 ±254.60	28.72 ±2.91
t	1.649	2.457	2.369	2.612	5.531	5.428
P	0.102	0.015	0.021	0.010	0.000	0.000

2.4 PE 患者妊娠结局影响因素 logistic 回归分析 结果见表 3。以 PE 患者妊娠结局作为因变量,以 Hb、PLT、24 h 尿蛋白定量、PAPP-A、VEGF 水平为自变量进行 logistic 回归分析,结果显示,血清PAPP-A、VEGF 水平与 PE 患者妊娠结局不良呈负相关(P <0.05),全血 Hb、PLT、24 h 尿蛋白定量与 PE 患者妊娠结局无关(P >0.05)。

表 3　PE 患者妊娠结局影响因素 logistic 回归分析

Tab. 3　Logistic regression analysis of the influencing factor of pregnancy outcome of patients with PE

指标	*B*	标准误	*Wald*	*P*	比值比	95% 置信区间	
						下限	上限
Hb	-0.052	0.029	3.379	0.066	0.949	0.897	1.003
PLT	-0.058	0.032	3.299	0.069	0.943	0.886	1.005
24 h 尿蛋白	1.568	0.811	3.735	0.053	4.796	0.978	23.515
PAPP-A	-0.004	0.001	9.726	0.002	0.996	0.994	0.999
VEGF	-0.461	0.130	12.637	0.000	0.630	0.489	0.813
常量	32.886	7.823	17.670	0.000	-	-	-

2.5　血清 PAPP-A、VEGF 水平对 PE 患者妊娠结局不良的预测价值　结果见表 4 和图 1。ROC 曲线分析显示，血清 PAPP-A、VEGF 预测 PE 患者不良妊娠结局的截断值分别为 2 718.780 mU · L^{-1}、29.495 ng · L^{-1}。血清 PAPP-A 联合 VEGF 预测 PE 患者不良妊娠结局的敏感度显著高于 PAPP-A，差异有统计学意义（$P<0.05$）。血清 PAPP-A 与 VEGF 预测 PE 患者不良妊娠结局的敏感度比较差异无统计学意义（$P>0.05$）。血清 PAPP-A、VEGF、PAPP-A 联合 VEGF 预测 PE 患者不良妊娠结局的 AUC、特异度比较差异无统计学意义（$P>0.05$）。

表 4　血清 PAPP-A、VEGF 水平对 PE 患者妊娠结局不良的预测价值

Tab. 4　Predictive value of serum PAPP-A and VEGF levels on adverse pregnancy outcome in patients with PE

指标	AUC	95% 置信区间		特异度	敏感度	约登指数
		下限	上限			
PAPP-A	0.794	0.706	0.882	0.844	0.651	0.495
VEGF	0.785	0.695	0.874	0.656	0.756	0.412
PAPP-A 联合 VEGF	0.877	0.809	0.944	0.719	0.849[a]	0.568

注：与 PAPP-A 比较[a]$P<0.05$。

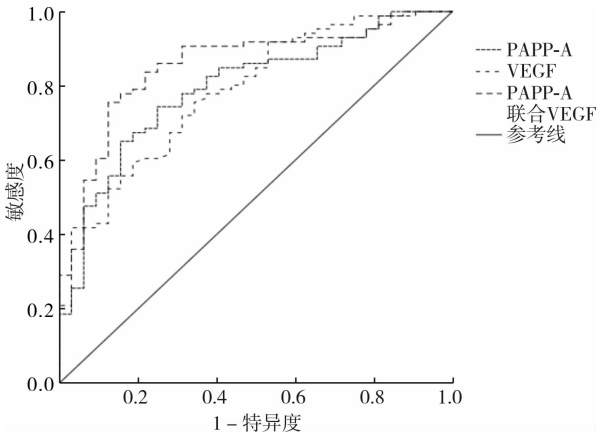

图 1　血清 PAPP-A、VEGF 水平预测 PE 患者不良妊娠结局的 ROC 曲线

Fig. 1　ROC curve of serum PAPP-A and VEGF levels in predicting adverse pregnancy outcomes in patients with PE

3　讨论

PE 患者常因血管内皮损伤、小血管痉挛等因素导致全身器官供血量减少，进而导致器官功能障碍、胎盘供血不足，增加妊娠不良事件发生风险，影响妊娠结局[10]。王莹等[11]在研究 PE 患者妊娠结局中发现，PE 患者妊娠结局不良发生率约为 28.13%。本研究收治的 118 例 PE 患者中，妊娠结局不良发生率为 27.12%，进一步证明了 PE 患者妊娠结局较差。因此，探究 PE 患者妊娠结局有关的指标以改善患者妊娠结局非常重要。

PAPP-A 是存在于孕妇血液中的一种糖蛋白，孕期主要由胎盘合体滋养细胞、蜕膜细胞等分泌，在滋养细胞生长和胎儿生长发育中起重要作用[12]。TALASAZ 等[13]研究显示，PAPP-A 与部分妊娠期并发症有关。VEGF 属于自分泌和旁分泌生长因子，参与血管内皮细胞分裂、增殖，对胎盘血管生长具有一定影响[14]。本研究结果显示，妊娠结局不良组患者的血清 PAPP-A 水平显著低于妊娠结局良好组，且进一步 logistic 回归分析显示，血清 PAPP-A 水平与 PE 患者妊娠结局不良呈负相关。原因可能为：PE 患者发病时常导致胎盘浸润不足，胎盘功能降低，PAPP-A 作为一种大分子蛋白，则难以通过胎盘血流屏障进入胎儿血液，导致胎儿 PAPP-A 水平降低[15]；而 PAPP-A 对胰岛素样生长因子（insulin-like growth factor，IGF）具有调控作用，IGF 可促进血管生长因子合成释放，利于改善组织供血；PAPP-A 水平降低后导致 IGF 释放减少，进一步影响器官及胎盘血流灌注，进而导致器官缺血性损伤、胎盘缺血缺氧，增加妊娠不良事件发生风险[16-17]。此外，严东琴等[18]研究显示，PAPP-A 低表达可导致胎盘血流灌注阻力增加，进而导致子宫及胎盘呈缺血状态，不利于临床妊娠。另有研究报道，PAPP-A 减少可影响胎盘滋养层细胞增殖、分化，导致胎盘功能异常，进一步加重胎盘损伤，进而影响妊娠结局[19]。WRIGHT 等[20]研究显示，PAPP-A 异常与胎儿宫内生长迟缓、胎膜早破、自发性流产等不良事件有关。因此，血清 PAPP-A 低表达可增加 PE 患者不良妊娠结局风险。

本研究结果显示，妊娠结局不良组患者的血清 VEGF 水平显著低于妊娠结局良好组，且进一步 logistic 回归分析显示，血清 VEGF 水平与 PE 患者妊娠结局不良呈负相关。原因可能为：VEGF 具有促进新生血管生成作用，VEGF 过表达可通过促进纤溶酶原激活物及其蛋白质分解酶释放，促使毛细血管基底膜降解，进而诱导新生血管生成，有利于改善器官和胎盘供血；而 VEGF 低表达则导致新生血管合成量减少，胎盘血流灌注进一步降低，进而导致胎盘缺血缺氧，不利于临床妊娠[21-22]。黄淑晖等[23]

研究发现,重度 PE 患者血清 VEGF 水平明显低于轻度 PE 患者,认为血清 VEGF 表达异常可加重 PE 病情,一定程度上影响妊娠结局。此外,VEGF 在血管重构中发挥重要作用,VEGF 可通过促进血管内皮细胞迁徙,诱导胎盘损伤血管重构;而 VEGF 低表达可影响血管内皮细胞和胎盘滋养细胞修复,进一步影响胎盘供血[23-24]。KESHAVARZI 等[25]研究发现,VEGF 与 PE 发病有关,可通过影响胎盘供血而影响 PE 患者妊娠结局。张颖等[26]研究发现,血清 VEGF 水平与 PE 病情进展有关,认为血清VEGF 对预测 PE 患者预后具有积极意义。由此可见,PE 患者血清 VEGF 低表达可导致胎盘供血障碍,增加不良妊娠结局风险。因此,建议 PE 患者入院时检测血清 PAPP-A、VEGF 水平,以预测患者妊娠结局。

本研究 ROC 曲线分析显示,血清 PAPP-A、VEGF 及 PAPP-A 联合 VEGF 预测 PE 患者不良妊娠结局的 AUC 分别为 0.794、0.785、0.877,均有一定的预测价值;血清 PAPP-A 联合 VEGF 检测预测 PE 患者不良妊娠结局的敏感度显著高于 PAPP-A 单独检测;提示可通过检测血清 PAPP-A、VEGF 水平预测 PE 患者不良妊娠结局发生风险。未来可通过监测血清 PAPP-A、VEGF 水平变化,评估 PE 患者病情进展程度,预测患者妊娠结局。

综上所述,血清 PAPP-A、VEGF 水平与 PE 患者妊娠结局不良有关,血清 PAPP-A、VEGF 水平可作为预测 PE 患者不良妊娠结局的生物标志物。临床可将血清 PAPP-A、VEGF 作为 PE 治疗靶点之一,通过改善 PAPP-A、VEGF 水平,改善胎盘血流灌注,减轻胎盘缺血程度,为胚胎着床发育提供良好条件,进而改善妊娠结局。

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