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妊娠高血压视网膜病变影响因素分析及血管内皮功能检测的临床意义*

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摘要 目的:探讨妊娠高血压视网膜病变的影响因素及血管内皮功能检测的临床意义。**方法:**前瞻性选取 2017 年 1 月~2018 年 12 月期间湖北省妇幼保健院收治的 150 例妊娠高血压视网膜病变患者作为观察组, 根据国际通用的 Duker-Elder 眼底分期标准分为 I 期组 69 例, II 期组 57 例, III 期组 24 例。选取同时期该院收治的妊娠高血压无视网膜病变患者 40 例为对照组。采用酶联免疫吸附法检测血清胰岛素样生长因子(IGF-1)、内皮素-1(ET-1)水平, 采用 Pearson 相关性分析 IGF-1 和 ET-1 水平与病变程度的相关性, 采用多因素 Logistic 回归分析妊娠高血压视网膜病变的影响因素。**结果:**随着 Duker-Elder 眼底分期的增加, 血清 ET-1 水平呈不断升高趋势, IGF-1 水平呈不断下降趋势($P<0.05$)。Pearson 相关性分析显示, 病变程度与血清 IGF-1 水平呈负相关, 而与 ET-1 水平呈正相关($P<0.05$)。单因素分析结果显示, 妊娠高血压视网膜病变的发生与病程、孕周、血压、体重、蛋白尿、红细胞压积有关($P<0.05$), 而与年龄无关($P>0.05$)。Logistic 回归分析结果显示, 病程 $>3W$ 、血压 $\geq 160/110$ mmHg、体重 >85 kg、蛋白尿为+++、红细胞压积 >0.35 均是妊娠高血压视网膜病变发生的独立危险因素($P<0.05$), 而孕周 $>28W$ 则是其保护因素($P<0.05$)。**结论:**妊娠高血压视网膜病变患者存在 IGF-1、ET-1 的异常表达, 且其表达水平与病变程度息息相关。血压、病程、蛋白尿、体重、红细胞压积均是妊娠高血压视网膜病变发生的独立危险因素, 孕周则是其保护因素。

关键词:妊娠; 高血压; 视网膜病变; 影响因素; 胰岛素样生长因子; 内皮素-1

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Analysis of Influencing Factors of Retinopathy in Pregnancy-induced Hypertension and Clinical Significance of Detection of Vascular Endothelial Function*

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ABSTRACT Objective: To investigate the influencing factors of retinopathy in pregnancy-induced hypertension and the clinical significance of the detection of vascular endothelial function. **Methods:** 150 patients with hypertensive retinopathy of pregnancy who were admitted to Maternal and Child Health Hospital of Hubei Province from January 2017 to December 2018 were prospectively selected as observation group. According to the international standard of Duker-Elder fundus staging, they were divided into phase I group (69 cases), phase II group (57 cases) and phase III group (24 cases). 40 patients with pregnancy-induced hypertension without retinopathy who were admitted to the hospital during the same period were selected as the control group. The serum levels of insulin-like growth factor-1 (IGF-1) and endothelin-1 (ET-1) were detected by enzyme-linked immunosorbent assay. The correlation between the levels of IGF-1 and ET-1 and the severity of retinopathy were analyzed by Pearson correlation analysis, and the influencing factors of retinopathy in pregnancy-induced hypertension were analyzed by multivariate logistic regression. **Results:** With the increase of Duker-Elder's fundus staging, the level of serum ET-1 increased, and the level of serum IGF-1 decreased ($P<0.05$). Pearson correlation analysis showed that the severity of lesion was negatively correlated with level of serum IGF-1, but it was positively correlated with level of serum ET-1 ($P<0.05$). Univariate analysis showed that the incidence of retinopathy in pregnancy-induced hypertension were related to course of disease, gestational age, blood pressure, body mass, proteinuria and hematocrit ($P<0.05$), and it was not related with age ($P>0.05$). Logistic regression analysis showed that Course of disease $>3W$, blood pressure $>160/110$ mmHg, body weight >85 kg, proteinuria $+++$, hematocrit >0.35 were all independent risk factors for retinopathy of pregnancy-induced hypertension ($P<0.05$), while gestational age $>28W$ was the protective factor ($P<0.05$). **Conclusion:** There are abnormal expressions of IGF-1 and ET-1 in patients with pregnancy-induced hypertensive retinopathy, and the expression level is closely related to the degree of retinopathy. The blood pressure, course of disease, proteinuria, body weight and hematocrit are the main risk factors for the occurrence of pregnancy-induced hypertension

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retinopathy, and the gestational age is the protective factor.

Key words: Pregnancy; Hypertension; Retinopathy; Influencing factors; IGF-1; ET-1

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前言

妊娠高血压是妊娠期孕妇特有的疾病之一,多发于妊娠20周以后,是孕产妇和围生儿死亡的重要原因^[1]。该病的早期病理改变为全身小动脉痉挛,以视网膜血管功能性收缩为主,随即引发周围组织缺血缺氧,致使毛细血管内皮受损,引发视网膜病变^[2,3]。网膜病变若未能及时予以治疗,可引视力障碍、眼出血等情况,严重者甚至需要终止妊娠以维持生命^[4,5]。因此,有效防治妊娠高血压视网膜病变对改善母婴预后具有重要的临床意义。胰岛素样生长因子(Insulin-like growth factor-1, IGF-1)是重要的血管新生相关因子,在正常生理状态下具有促进细胞分裂、分化和抑制凋亡等功能^[6]。内皮素-1(Endothelin-1, ET-1)是已知缩血管作用最强的标志物,具有维持血管张力的作用^[7]。现临床有关 IGF-1、ET-1 水平与妊娠高血压视网膜病变的具体关系尚不十分明确,且目前针对妊娠高血压视网膜病变的影响因素也报道不一。鉴于此,本研究通过探讨妊娠高血压视网膜病变的影响因素及血管内皮功能检测的临床意义,旨在进一步了解、认识妊娠高血压视网膜病变,以期减少和避免该病的发生。

1 资料与方法

1.1 一般资料

前瞻性选取2017年1月~2018年12月期间湖北省妇幼保健院收治的150例妊娠高血压视网膜病变患者作为观察组,纳入标准:(1)均符合《妊娠期高血压疾病诊治指南(2015)》^[8]中有关妊娠高血压的相关诊断标准;(2)均符合《实用眼科学》^[9]中的相关视网膜病变诊断及分级标准;(3)均为单胎;(4)患者及其家属知情本次研究且已签署了同意书。排除标准:(1)既往存在高血压者;(2)既往存在眼部疾病者;(3)既往存在糖尿病及肾病者;(4)临床资料缺失者。本次研究已获取湖北省妇幼保健院伦理学委员会批准进行。将观察组依据国际通用的Duker-Elder眼底分期标准^[10]分为I期组69例,II期组57例,III期组24例。I期组年龄22~36岁,平均(29.34±2.67)岁;孕周23~39周,平均(30.46±3.49)周;初产妇39例,经产妇30例;妊娠高血压患者42例,轻度子痫前期患者27例。II期组年龄22~35岁,平均(29.63±3.45)岁;孕周24~38周,平均(30.58±4.03)周;初产妇31例,经产妇26例;妊娠高血压患者38例,轻度子痫前期患者19例。III期组年龄22~37岁,平均(29.94±4.21)岁;孕周24~40周,平均(30.46±3.97)周;初产妇15例,经产妇9例;妊娠高血压患者18例,轻度子痫前期患者6例。选取同时期我院收治的妊娠高血压无视网膜病变患者40例为对照组,年龄23~38岁,平均(30.06±2.49)岁;孕周24~38周,平均(29.92±4.06)周;初产妇23例,经产妇17例;妊娠高血压患者26例,轻度子痫前期患者14例。四组患者一般资料对比无差异($P>0.05$),组间可比。

1.2 Duker-Elder 眼底分期标准^[10]

I期:处于动脉痉挛期,眼底表现为视网膜动脉变细,管径粗细不均匀;II期:处于动脉硬化期,眼底表现为视网膜动脉狭窄,反光能力增强,并伴有动脉交叉压迫现象;III期:处于视网膜病变期,眼底表现为视网膜水肿、出血及渗出,严重者形成渗出性视网膜脱离。

1.3 方法

1.3.1 血清学指标 采集所有研究对象的清晨空腹静脉血6mL,室温下静置30min,3600 r/min离心15min,离心半径10cm,分离上清液,置于-50℃冰箱内保存待测。采用酶联免疫吸附法检测血清 IGF-1、ET-1 水平,严格遵守试剂盒(上海恒远生化试剂有限公司)说明书进行操作。

1.3.2 临床资料 所有患者入院后由临床经验丰富的医师进行眼底镜检查,针对瞳孔过小不便检查者,经5g/L复方托吡卡胺滴眼液滴眼处理后再行检查。具体操作如下:患者取卧位或者坐位,记录视网膜动脉血管管径,观察反光情况、有无动脉交叉压迫、视网膜水肿、出血及渗出现象,根据眼底镜检查结果确认其有无视网膜病变,有视网膜病变者则确认其分期情况。观察并记录所有患者孕周、病程、体质量、血压、蛋白尿、红细胞压积等数据。

1.4 统计学方法

使用Epidata3.3软件对数据进行双录入,交叉核对无误后导入SPSS25.0统计软件。计量资料采用($\bar{x}\pm s$)描述,组间比较行LSD-t检验,多组比较行F检验。计数资料采用率(%)描述,行 χ^2 检验。采用Pearson相关性分析 IGF-1 和 ET-1 与病变程度的相关性,采用多因素 Logistic 回归分析妊娠高血压视网膜病变的影响因素。检验标准设置为 $\alpha=0.05$ 。

2 结果

2.1 各组研究对象血清 IGF-1、ET-1 水平比较

I期组、II期组、III期组的血清 ET-1 水平均高于对照组, IGF-1 水平则低于对照组($P<0.05$);随着 Duker-Elder 眼底分期的增加,血清 ET-1 水平呈不断升高趋势, IGF-1 水平呈不断下降趋势($P<0.05$);详见表1。

2.2 血清 IGF-1 和 ET-1 水平与病变程度的相关性

Pearson 相关性分析显示,病变程度与血清 IGF-1 水平呈负相关($r=-0.591, P=0.0000$),而与 ET-1 水平呈正相关($r=0.529, P=0.000$)。

2.3 妊娠高血压视网膜病变的影响因素的单因素分析

单因素分析结果显示,妊娠高血压视网膜病变的发生与病程、孕周、血压、体质量、蛋白尿、红细胞压积有关($P<0.05$),而与年龄无关($P>0.05$);详见表2。

2.4 妊娠高血压视网膜病变影响因素的多因素 Logistic 回归分析

以是否发生妊娠高血压视网膜病变为因变量,表2中 $P<0.05$ 的指标为自变量,行多因素 Logistic 回归分析。回归结果显

示,病程>3W、血压 $\geq 160/110$ mmHg、体质量>85 kg、蛋白尿为+++、红细胞压积>0.35均是妊娠高血压视网膜病变发生的独立危险因素($P<0.05$),而孕周>28W则是其保护因素($P<0.05$),详见表3。

表1 各组研究对象血清 IGF-1、ET-1 水平比较($\bar{x}\pm s$)
Table 1 Comparison of levels of serum IGF-1 and ET-1 in each group($\bar{x}\pm s$)

Groups	n	IGF-1($\mu\text{g/L}$)	ET-1(pg/mL)
Control group	40	182.38 $\pm$ 20.54	55.37 $\pm$ 12.75
Phase I group	69	163.59 $\pm$ 21.62 ^a	72.57 $\pm$ 13.63 ^a
Phase II group	57	139.55 $\pm$ 18.37 ^{ab}	91.15 $\pm$ 14.27 ^{ab}
Phase III group	24	107.34 $\pm$ 19.53 ^{abc}	112.84 $\pm$ 15.93 ^{abc}
F	-	94.068	63.482
P	-	0.000	0.000

Note: Compared with the control group, ^a $P<0.05$; compared with the phase I group, ^b $P<0.05$; compared with the phase II group, ^c $P<0.05$.

表2 妊娠高血压视网膜病变的影响因素的单因素分析[n(%)]
Table 2 Univariate analysis of influencing factors of retinopathy in pregnancy-induced hypertension [n(%)]

Factors		Control group (n=40)	Observation group (n=150)	χ^2	P
Age (years)	≤ 30	35(87.50)	137(91.33)	0.548	0.462
	>30	5(12.50)	13(8.67)		
Course of disease(W)	≤ 3	34(85.00)	32(21.33)	56.463	0.000
	>3	6(15.00)	118(78.67)		
Blood pressure (mmHg)	$<160/110$	36(90.00)	93(62.00)	11.362	0.000
	$\geq 160/110$	4(10.00)	57(38.00)		
Body mass(kg)	<75	27(67.50)	32(21.33)	32.932	0.000
	75~85	9(22.50)	53(35.33)		
	>85	4(10.00)	65(43.33)		
Proteinuria	-	35(87.50)	22(14.67)	81.693	0.000
	+	4(10.00)	29(19.33)		
	++	1(2.50)	43(28.67)		
	+++	0(0.00)	56(37.33)		
Hematocrit	≤ 0.35	32(80.00)	39(26.00)	37.356	0.000
	>0.35	8(20.00)	111(74.00)		
Gestational age(W)	≤ 28	11(27.50)	103(68.67)	22.308	0.000
	>28	29(72.50)	47(31.33)		

3 讨论

在我国,妊娠高血压的发病率高达9.4%,位居孕产妇死亡原因的第二位^[11]。而视网膜病变作为妊娠高血压综合征的合并症之一,可在一定程度上反映全身小血管痉挛状态^[12]。据统计^[13],约有50%~80%的妊娠高血压患者存在不同程度的视网膜病变。妊娠高血压视网膜病变可分级为I期、II期及III期,当患者处于I期、II期时给予适当药物治疗后患者可继续妊娠,而当患者处于III期时,此时或已发生器质性损伤,可能会引发视力障碍,而眼底出血也可能诱发脑出血,此时患者除了需要给予降压、解痉治疗外,还需立刻终止妊娠^[14-16]。鉴于妊娠高血

压视网膜病变所带来的严重后果,探明其作用机制及影响因素,对评估妊娠高血压病情、终止妊娠及治疗指导均具有重要价值。

由于视网膜病变是机体微血管受损的表现,微血管的形成、血管内皮功能受损是视网膜病变的中心环节^[17,18]。IGF-1是重要的血管新生相关因子,具有促进细胞分裂、分化及抑制凋亡等功能,既往研究显示^[19],IGF-1与糖尿病视网膜病变发生发展关系密切。ET-1存在于内皮细胞,是最强的缩血管物质之一,是临床最常见的反映血管内皮功能指标之一。本研究中随着病情的加重,血清ET-1水平呈不断升高趋势,IGF-1呈不断下降趋势,可见IGF-1、ET-1在妊娠高血压视网膜病变的进展中发挥重要作用。由于母血IGF-1水平受生长激素调节,而妊

表 3 妊娠高血压视网膜病变影响因素的多因素 Logistic 回归分析

Table 3 Multivariate Logistic regression analysis of influencing factors of retinopathy in pregnancy-induced hypertension

Variable	β	SE(β)	Wald χ^2	P	OR	95%CI
Gestational age > 28W	-1.746	0.437	12.397	0.015	0.217	0.078~0.529
Course of disease > 3W	2.268	0.521	14.739	0.011	5.607	3.728~11.489
Blood pressure $\geq 160/110$ mmHg	1.634	0.639	6.538	0.021	4.428	3.657~5.794
Proteinuria +++	2.293	0.379	7.493	0.019	2.726	2.489~6.731
Hematocrit > 0.35	2.942	0.431	9.312	0.017	3.492	2.945~6.918
Body mass > 85 kg	0.925	0.273	8.637	0.019	3.428	2.561~6.914

娠时母体生长激素合成受到限制,致使胎盘生长激素成为母体生长激素的主要来源。妊娠高血压时,患者胎盘绒毛浅着床及血管痉挛,致使胎盘血流下降,胎盘生长激素进入母体减少,加之胎盘血管螺旋动脉痉挛,内皮损伤,使胎盘发生缺氧、缺血及功能障碍,最终引起 IGF-1 水平的分泌减少^[20-22]。此外,随着妊娠高血压视网膜病变的病情进展,全身小动脉痉挛加剧,导致肾脏血管阻力增加,促进血管紧张素-醛固酮的大量分泌,致使血压明显升高,进一步加重血管内皮细胞损伤,出现 ET-1 水平的升高^[23-25]。Pearson 相关性分析结果显示,血清 IGF-1 和 ET-1 水平与病变程度相关,提示临床上可通过检测上述两指标的水平变化,尽早判定病变程度并进行相应的干预治疗。

本文中单因素分析结果表明妊娠高血压视网膜病变的发生与多种因素有关,经多因素 Logistic 回归分析,结果显示,病程 > 3W、血压 $\geq 160/110$ mmHg、体质量 > 85 kg、蛋白尿为 +++、红细胞压积 > 0.35 均是妊娠高血压视网膜病变发生的独立危险因素,而孕周 > 28W 则是其保护因素。分析其原因,随着病程的增加,血压的升高现象持续不受控制,毛细血管内皮受损加剧,血管壁通透性增加,致使出现蛋白尿,这是全身器官小动脉出现病变及器官损害的标志。而红细胞压积可反映机体代谢情况,可评估患者是否存在扩容状态^[26,27],红细胞压积增加,扩容状态加重,从而增加视网膜病变发生的风险。黄初梅等人^[28]研究亦表明,病程、血压、蛋白尿、红细胞压积是妊娠高血压视网膜病变发生的影响因素。与本研究中的结果基本一致。而孕期体质量超多会加重水钠潴留,进一步增加血液循环量,加重高血压^[29,30]。临床可考虑通过对上述影响因素进行针对性的干预,以减少妊娠高血压视网膜病变患者的发生风险。

综上所述,妊娠高血压视网膜病变患者存在 IGF-1、ET-1 的异常表达,可能参与着疾病进展。病程 > 3W、血压 $\geq 160/110$ mmHg、体质量 > 85 kg、蛋白尿为 +++、红细胞压积 > 0.35 均是妊娠高血压视网膜病变发生的独立危险因素,孕周 > 28W 则是其保护因素,应在临床上引起足够重视。

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