

孕妇血清 CXCL12 和 CXCR4 水平检测联合多普勒超声检查在凶险性前置胎盘诊断中的应用价值研究

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摘要: 目的 探讨孕妇血清 CXC 趋化因子配体 12 (CXC chemokine ligand 12, CXCL12) 和 CXC 趋化因子受体 4 (CXC chemokine receptor 4, CXCR4) 水平检测联合多普勒超声在凶险性前置胎盘诊断中的应用价值。方法 收集 2020 年 6 月~2023 年 1 月河北省沧州中西医结合医院收治的 90 例凶险性前置胎盘患者作为研究对象, 根据产后病理结果分为胎盘植入组 ($n=38$) 和无胎盘植入组 ($n=52$), 另选取同期于河北省沧州中西医结合医院孕检且孕周与患者相匹配的健康孕妇 (胎盘附着于子宫前壁) 90 例为对照组。比较各组血清 CXCL12 和 CXCR4 水平; ROC 曲线分析血清 CXCL12, CXCR4, 多普勒超声对胎盘植入的诊断效能; 以术后病理结果为金标准, 四表格法计算血清 CXCL12, CXCR4 联合多普勒超声对发生胎盘植入的诊断效能。结果 对照组、无胎盘植入组、胎盘植入组血清 CXCL12 (2.75 ± 1.26 ng/ml, 5.82 ± 2.14 ng/ml, 10.24 ± 3.58 ng/ml), CXCR4 (1.84 ± 0.78 ng/ml, 4.47 ± 1.83 ng/ml, 8.32 ± 2.763 ng/ml) 表达水平依次升高, 差异具有统计学意义 ($F=158.998, 199.141$, 均 $P<0.05$)。CXCL12, CXCR4 和多普勒超声联合检测诊断胎盘植入的 AUC 为 0.948, 敏感度和特异度分别为 92.11%, 86.54%, 优于 CXCL12, CXCR4, 多普勒超声各自单独预测 ($Z=2.266, 2.682, 3.472, P=0.023, 0.007, 0.001$)。结论 凶险性前置胎盘患者血清 CXCL12, CXCR4 表达水平显著升高, 血清 CXCL12 和 CXCR4 联合多普勒超声对凶险性前置胎盘患者胎盘植入的发生具有较好的诊断效能。

关键词: CXC 趋化因子配体 12; CXC 趋化因子受体 4; 多普勒超声; 胎盘植入; 凶险性前置胎盘

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Value of Serum CXCL12 and CXCR4 Levels Detection in Pregnant Women Combined with Doppler Ultrasound in the Diagnosis of Dangerous Placenta Previa

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Abstract: Objective To explore the application value of serum CXC chemokine ligand 12 (CXCL12) and CXC chemokine receptor 4 (CXCR4) detection combined with Doppler ultrasound in the diagnosis of dangerous placenta previa. **Methods** A sum of 90 patients with dangerous placenta previa admitted to Cangzhou Hospital of Integrated Traditional Chinese Medicine and Western Medicine in Hebei from June 2020 to January 2023 were collected as research subjects. According to the postpartum pathological results, they were grouped into the placental implantation group ($n=38$) and the non placental implantation group ($n=52$), while another 90 healthy pregnant women (with placenta attached to the anterior wall of the uterus) who underwent pregnancy examination in Cangzhou Hospital of Integrated Traditional Chinese Medicine and Western Medicine in Hebei and matched with the patient's gestational age were regarded as the control group. The serum levels of CXCL12 and CXCR4 in each group were compared. ROC curve was applied to analyze the diagnostic efficacy of serum CXCL12 and CXCR4 levels for placental implantation. Using postoperative pathological results as the gold standard, the fourfold table method was applied to calculate the diagnostic efficacy of serum CXCL12 and CXCR4 combined with Doppler ultrasound in the occurrence of placental implantation. **Results** The serum levels of CXCL12 (2.75 ± 1.26 ng/ml, 5.82 ± 2.14 ng/ml, 10.24 ± 3.58 ng/ml) and CXCR4 (1.84 ± 0.78 ng/ml, 4.47 ± 1.83 ng/ml, 8.32 ± 2.763 ng/ml) in the control group, non placental implantation group and placental implantation group were increased successively, and the differences were significant ($F=158.998, 199.141$, all $P<0.05$). The detection of serum CXCL12 and CXCR4 combined with Doppler ultrasound in the diagnosis of placental implantation had

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an AUC of 0.948, and sensitivity and specificity were 92.11% and 86.54%, respectively, which was better than CXCL12, CXCR4, and Doppler ultrasound alone predicting separately ($Z=2.266, 2.682, 3.472, P=0.023, 0.007, 0.001$). **Conclusion** The expression levels of serum CXCL12 and CXCR4 in patients with dangerous placenta previa are increased. The combination of serum CXCL12 and CXCR4 with Doppler ultrasound may have good diagnostic efficacy for the occurrence of placental implantation in dangerous placenta previa patients.

Keywords: CXC chemokine ligand 12; CXC chemokine receptor 4; doppler ultrasound; placental implantation; dangerous placenta previa

近年来随着我国生育政策不断改革, 剖宫产率逐渐升高, 凶险性前置胎盘的发生有所增加, 严重威胁产妇生命安全^[1]。在正常妊娠期间, 胎盘上的绒毛可以与子宫内膜上的绒毛相互作用, 促进胎盘着床; 但是, 在多种不良因素的诱导下, 胚胎附着在子宫内膜损伤部位, 会导致胎盘绒毛穿过子宫内膜并侵入子宫肌层, 导致胎盘植入, 使患者出现凝血功能障碍^[2]。凶险性前置胎盘并发胎盘植入是妊娠期最严重的并发症, 会导致分娩时大出血、子宫穿孔、感染, 甚至危及母体和胎儿生命^[3-4]。寻找准确有效的生物标志物联合影像学指标对凶险性前置胎盘的发生进行诊断, 并积极采取合适治疗措施, 对提高分娩质量, 改善妊娠结局具有重要意义。多普勒超声是一种无创诊断方法, 无辐射, 对孕妇和胎儿伤害较低, 可以看到清晰图像, 因此常用于危险性前置胎盘诊断^[5]。但患者体质、胎盘位置、外界环境等因素都会严重影响诊断结果^[6]。趋化因子在胚胎发生、先天免疫、适应性免疫中发挥积极作用, CXC趋化因子配体12 (CXC chemokine ligand 12, CXCL12) 是与CXC趋化因子受体4 (CXC chemokine receptor 4, CXCR4) 结合的趋化因子, 在肿瘤中广泛表达, 与细胞增殖、迁移和肿瘤转移有关^[7-8]。CXCL12/CXCR4轴激活各种信号通路, 在各种生理过程、体内平衡和免疫细胞运输中起着重要作用^[9]。然而, 血清CXCL12和CXCR4联合多普勒超声在凶险性前置胎盘诊断中的应用尚未报道。因此, 本研究分析三者联合对胎盘植入的诊断效能, 为凶险性前置胎盘的有效诊治提供参考依据。

1 材料与方 法

1.1 研究对象 收集2020年6月~2023年1月河北省沧州中西医结合医院收治的90例凶险性前置胎盘患者作为研究对象, 根据产后病理^[10]结果分为胎盘植入组 ($n=38$) 和无胎盘植入组 ($n=52$), 其中胎盘植入组年龄 30.58 ± 3.85 岁, 孕周 34.52 ± 3.64 周, 孕次 2.61 ± 1.08 次, 剖宫产次 1.36 ± 0.47 次, 产次 1.54 ± 0.65 次; 无胎盘植入组年龄 30.16 ± 3.47 岁, 孕周 34.48 ± 3.59 周, 孕次 2.59 ± 1.03 次, 剖宫产次 1.18 ± 0.31 次, 产次 1.46 ± 0.54 次。纳入标准: ①符合凶险性前置胎盘相关诊断标准^[11]; ②单胎妊娠; ③研究对象本人详

知此项研究内容, 并自愿签署同意书。排除标准: ①胎盘存在血池、血肿等异常; ②患有妇科恶性肿瘤产妇; ③不耐受手术患者; ④生命体征不稳定产妇。本研究遵循《世界医学协会赫尔辛基宣言》。另选取同期于我院孕检且孕周与患者相匹配的健康孕妇 (胎盘附着于子宫前壁) 90例为对照组, 其中年龄 31.24 ± 3.54 岁, 孕周 34.17 ± 3.53 周, 孕次 2.34 ± 0.98 次, 剖宫产次 1.21 ± 0.43 次, 产次 1.33 ± 0.45 次。三组年龄、孕周、孕次、剖宫产次、产次相比, 差异无统计学意义 ($F=1.575, 0.190, 1.460, 2.417, 2.458$, 均 $P>0.05$)。

1.2 仪器与试剂 PHILIPS EPIQ 7多普勒彩色超声诊断仪 (荷兰飞利浦公司), Varioskan LUX多功能酶标仪 (美国赛默飞公司), CXCL12酶联免疫试剂盒 (货号: ml058438, 上海酶联生物科技有限公司), CXCR4酶联免疫试剂盒 (货号: ml057567, 上海酶联生物科技有限公司)。

1.3 方 法

1.3.1 多普勒超声检查: 采用PHILIPS EPIQ 7多普勒彩色超声诊断仪进行检查, 探头频率为3.5~5.0 MHz。检查前适度充盈膀胱, 受检者取平卧体位, 探头置于孕妇腹壁, 重点观察孕子宫形态、内部回声、肌层、胎盘厚度、位置与血管情况, 探寻疑似的胎盘植入区域, 观察感兴趣区周围血管的分布情况, 显示胎盘基底部和胎盘实质内血流信号丰富且杂乱, 有侵及膀胱壁, 彩色血流信号红蓝相间, 可判定为发生胎盘植入。

1.3.2 样本收集: 所有孕妇均于入院24 h内, 采集空腹静脉血3~5 ml, 离心半径为12 cm, 时间为10 min, 分离血清后, 放入-20℃冰箱中保存, 待检。

1.3.3 血清CXCL12, CXCR4水平检测: 采用酶联免疫吸附法检测血清CXCL12, CXCR4水平, 具体操作严格按照试剂说明书进行。

1.3.4 病理诊断及阳性判定标准: 以分娩情况及产后病理结果为金标准: 分娩时胎盘无法完全娩出且徒手剥离困难, 取病灶送病理检查后, 显示子宫肌层内有绒毛组织。血清CXCL12和CXCR4联合多普勒超声对凶险性前置胎盘发生胎盘植入进行诊断时, 其中一项诊断结果为阳性, 即联合诊断为阳性。

1.4 统计学分析 数据以SPSS 25.0软件进行统计学

分析,经正态性检验符合正态分布,以均数 ± 标准差 ($\bar{x} \pm s$) 描述,多组间计量资料的比较采用单因素方差分析,进一步两两比较行 Snk-*q* 检验;ROC 曲线分析血清 CXCL12, CXCR4 和多普勒超声对胎盘植入的诊断效能。 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 多普勒超声诊断结果分析 多普勒超声诊断结果显示发生胎盘植入的有 33 例,无胎盘植入的有

57 例,以分娩情况及产后病理结果为金标准,金标准与多普勒超声共同阳性者 28 例,共同阴性者 47 例,多普勒超声诊断凶险性前置胎盘敏感度和特异度分别为 73.68% (28/38), 90.38% (47/52)。

2.2 三组血清 CXCL12, CXCR4 水平比较 见表 1。对照组、无胎盘植入组、胎盘植入组血清 CXCL12, CXCR4 表达水平依次升高,差异具有统计学意义 (均 $P < 0.05$)。

表 1 三组血清 CXCL12, CXCR4 水平比较 ($\bar{x} \pm s$)

| 项目 | 对照组 (n=90) | 无胎盘植入组 (n=52) | 胎盘植入组 (n=38) | F 值 | P 值 |
|--------|-------------|--------------------------|----------------------------|---------|-------|
| CXCL12 | 2.75 ± 1.26 | 5.82 ± 2.14 ^a | 10.24 ± 3.58 ^{ab} | 158.998 | 0.000 |
| CXCR4 | 1.84 ± 0.78 | 4.47 ± 1.83 ^a | 8.32 ± 2.76 ^{ab} | 199.141 | 0.000 |

注: ^a 与对照组比较, $q=13.380, 24.999, 12.619, 27.994$, 均 $P < 0.05$; ^b 与无胎盘植入组比较, $q=13.373, 15.077$, 均 $P < 0.05$ 。

2.3 血清 CXCL12, CXCR4 和多普勒超声对胎盘植入的诊断效能 见表 2, 图 1。CXCL12 诊断胎盘植入的曲线下面积 (area under curve, AUC) 为 0.862, 血清 CXCR4 诊断胎盘植入的 AUC 为

0.825, 多普勒超声诊断胎盘植入的 AUC 为 0.820。三者联合检测诊断胎盘植入的 AUC 为 0.948, 优于 CXCL12, CXCR4 和多普勒超声各自单独预测 ($Z=2.266, 2.682, 3.472, P=0.023, 0.007, 0.001$)。

表 2 血清 CXCL12, CXCR4, 多普勒超声对胎盘植入的诊断效能

| 项目 | AUC | 截断值 | 95%CI | 敏感度 (%) | 特异度 (%) | Youden 指数 |
|--------|-------|------------|---------------|---------|---------|-----------|
| CXCL12 | 0.862 | 8.11 ng/ml | 0.773 ~ 0.926 | 71.05 | 88.46 | 0.595 |
| CXCR4 | 0.825 | 7.10 ng/ml | 0.731 ~ 0.897 | 65.79 | 86.54 | 0.523 |
| 多普勒超声 | 0.820 | 阳性 | 0.725 ~ 0.893 | 73.68 | 90.38 | 0.641 |
| 联合检测 | 0.948 | - | 0.880 ~ 0.984 | 92.11 | 86.54 | 0.787 |

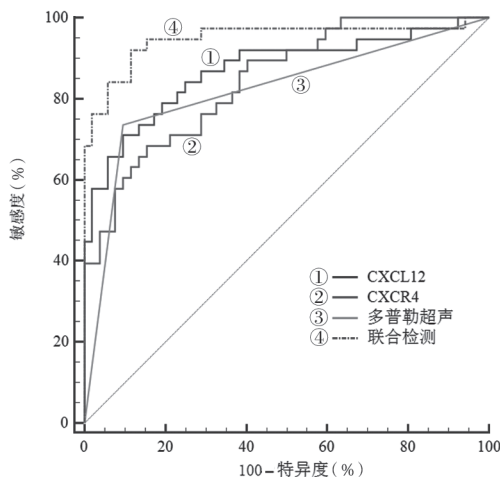


图 1 血清 CXCL12, CXCR4 和多普勒超声预测凶险性前置胎盘发生胎盘植入的 ROC 曲线

3 讨论

凶险性前置胎盘是由于滋养层细胞的侵袭和子宫脱落组织的异型增生所引起,胎盘植入多发生于子宫前壁下段,凶险性前置胎盘为胎盘植入最常见的高危因素^[12]。凶险性前置胎盘并发胎盘植入患者的术中出血量、术后感染率远高于凶险性前置胎盘孕妇,对母体和胎儿的生命造成巨大威胁^[13]。因此,产前明确诊断,并积极采取治疗措施,对于凶险性

前置胎盘患者的母婴安全具有重要意义。

目前临床高危因素结合辅助检查是凶险性前置胎盘常用的产前诊断方法,多普勒超声具有操作简单、无创、安全、无辐射、可反复开展等优势,兼具二维超声结果图像的优点和血流动力学的信息,应用广泛^[13-14]。但多普勒超声检查容易受到操作者的经验影响,准确度存在一定的主观性^[15]。本研究发现,多普勒超声对凶险性前置胎盘发生胎盘植入具有较好的诊断效能。研究表明,应用影像学结合血清学检测有利于提高凶险性前置胎盘的产前诊断率^[16]。

CXCL12 在肝、肺、骨髓、淋巴结、间质细胞、内皮细胞等多种人体组织中表达, CXCR4 也在中枢神经系统、神经干细胞、肝卵圆/干细胞、CD34⁺ 造血祖细胞、白细胞、原始生殖细胞、骨髓肌卫星祖细胞等多种细胞和组织中表达, CXCR4 是 CXCL12 的受体,两者相互作用,可广泛参与人体多种生理、病理活动^[17]。SHI 等^[18]发现 CXCL12/CXCR4 诱导下游信号通路,对趋化性、细胞增殖、迁移和基因表达产生广泛影响,在膀胱癌、胃癌、肝细胞癌、前列腺癌等多种肿瘤中高表达, CXCL12/CXCR4 在肿瘤的发展、存活、血管生成、转移和肿瘤微环境中起着关键作用。LIU 等^[19]

发现 CXCL12 和 CXCR4 在脊髓背角组织中增加, CXCL12/CXCR4 信号通过中枢敏化机制调节神经性疼痛的发展。GARCÍA-CUESTA 等^[20]发现 CXCL12/CXCR4 不仅可以干扰细胞迁移, 还可以调节免疫反应, 是多种炎症性疾病的潜在治疗靶点。本研究发现胎盘植入组血清 CXCL12 和 CXCR4 水平显著高于无胎盘植入组和对照组, 无胎盘植入组血清 CXCL12, CXCR4 水平显著高于对照组, 提示 CXCL12 可能通过与 CXCR4 互作, 介导细胞的恶性生物学行为、炎症反应等过程, 促进凶险性前置胎盘的发生发展, CXCL12, CXCR4 水平对初步判断凶险性前置胎盘的发生和发生胎盘植入具有一定意义。GOKCE 等^[21]发现, 流产孕妇 CXCR4, CXCL12 蛋白水平显著升高, 在孕妇免疫耐受中发挥调节作用, 与流产密切相关, 并可作为妊娠结局的重要生物标志物。ZHANG 等^[22]发现 CXCL12/CXCR4 通过调节巨噬细胞募集、极化和细胞因子分泌, 进而影响滋养细胞侵袭、增殖和存活、胎盘血管生成、免疫耐受等多个过程, 与复发性自然流产、先兆子痫和早产等多种妊娠期疾病的发生、发展密切相关。本研究进一步绘制 ROC 曲线显示, CXCL12, CXCR4 和多普勒超声联合检测诊断胎盘植入效能优于三者各自单独预测, 提示 CXCL12/CXCR4 可能介导巨噬细胞、滋养细胞等细胞的生物学行为, 影响孕妇的免疫耐受、血管生成, 而血清学指标 CXCL12, CXCR4 联合多普勒超声对胎盘植入的发生具有较好的诊断效能。

综上所述, 凶险性前置胎盘患者血清 CXCL12, CXCR4 表达水平显著升高, 血清 CXCL12, CXCR4 联合多普勒超声对凶险性前置胎盘并发胎盘植入具有较好的诊断效能。然而, 本研究纳入样本例数有限, 研究结果可能存在一定偏倚, 且 CXCL12, CXCR4 参与凶险性前置胎盘并发胎盘植入的具体机制仍需进一步研究。

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