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补肾温阳化瘀法对子宫内膜异位症患者子宫内膜腺上皮细胞 OPN 与 MMP-9 的影响 *

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摘要 目的：探讨补肾温阳化瘀法对子宫内膜异位症患者子宫内膜腺上皮细胞骨桥蛋白（OPN）与基质金属蛋白酶 -9（MMP-9）的影响。**方法**：选择我院 2013 年 4 月 ~2016 年 4 月收治的 92 例子宫内膜异位症患者，分为对照组与观察组，各 46 例，对照组行常规西医治疗，观察组行补肾温阳化瘀法治疗，比较两组 OPN 及 MMP-9，雌二醇（E2）、促黄体生成素（LH）、卵泡刺激素（FSH），肿瘤坏死因子 -α（TNF-α）、白细胞介素 -6（IL-6）、白细胞介素 -8（IL-8），$CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$，临床疗效及安全性。**结果**：治疗后，观察组 OPN、MMP-9，TNF-α、IL-6、IL-8，$CD8^+$ 低于对照组，观察组 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 高于对照组，差异有统计学意义（P<0.05）。观察组总有效率高于对照组，不良反应率低于对照组（P<0.05）。**结论**：补肾温阳化瘀法可下调子宫内膜异位症患者子宫内膜腺上皮细胞 OPN 及 MPP-9 表达。

关键词：子宫内膜异位症；补肾温阳化淤法；骨桥蛋白；基质金属蛋白酶 -9

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Effects of Bushen Wenyang Huayu Treatment on Serum Levels of Endometrial Glandular Epithelial Cells OPN and MMP-9 in Patients with Endometriosis*

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ABSTRACT Objective: To investigate the effects of bushen wenyang huayu treatment on serum levels of endometrial glandular epithelial cells osteopontin (OPN) and matrix metalloproteinases-9 (MMP-9) in patients with endometriosis. **Methods:** 92 cases with endometriosis who were treated in our hospital from April 2013 to April 2016 were selected and randomly divided into the control group and the observation group with 46 cases in each group. The patients in the control group were treated with western medicine, while the patients in the observation group were treated with bushen wenyang huayu method. Then the serum levels of OPN, MMP-9, estradiol (E2), luteinizing hormone (LH), follicle-stimulating hormone (FSH), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8), $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$, the clinical efficacy and safety in the two groups were observed and compared before and after the treatment. **Results:** After treatment, the serum levels of OPN, MMP-9, TNF-α, IL-6, IL-8 and $CD8^+$ in the observation group were lower than those of the control group, while the levels of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ were higher, and the differences were statistically significant (P<0.05). The total effective rate of the observation group was higher than that of the control group, while the incidence of adverse reactions was lower (P<0.05). **Conclusion:** Bushen wenyang huayu method can reduce the serum levels of OPN endometrial glandular epithelial cells and MPP-9 of patients with endometriosis.

Key words: Endometriosis; Bushen wenyang huayu method; Osteopontin; Matrix metalloproteinases-9

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前言

子宫内膜异位症是育龄女性的常见疾病，指具有生长能力的子宫内膜组织于子宫腔以外生长，多由免疫紊乱、子宫内膜损伤等多种因素所致，和内膜细胞增强的侵袭性及异位黏附有关，存在局部浸润生长和转移等恶性肿瘤的能力[1,2]。有关研究发现子宫内膜异位症发病期间骨桥蛋白（OPN）及基质金属蛋白酶 9（MMP-9）可发挥关键作用[3,4]。既往多采用孕三烯酮、达那唑等西医治疗，虽可起到一定疗效，但效果并不理想。中医学认为阳虚寒凝及冲任胞宫是子宫内膜异位症的主要发病机制，治疗应以补肾温阳、活血化淤为主[5]。本研究就补肾温阳化瘀法对子宫内膜异位症患者子宫内膜腺上皮细胞 OPN 与 MMP-9 的影响展开探讨。

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1 资料与方法

1.1 一般资料

选择我院 2013 年 4 月 ~2016 年 4 月收治的 92 例子宫内膜异位症患者，纳入标准：(1)同时满足西医、中医诊断标准；(2)经手术诊治后复发者，尚无手术指征；(3)月经比较规律；(4)既往未见其他代谢性、免疫及内分泌疾病；(5)近 3 个月内无激素治疗史。排除标准：(1)伴盆腔感染、子宫肌瘤等妇科疾病；(2)恶性肿瘤；(3)主要器官功能不全。本研究已得到医院伦理委员会许可，家属及患者均签署知情同意书，按抽签法予以分组。对照组年龄 23~40 岁，平均(31.48± 4.13)岁；病变部位：27 例盆腔内异位，19 例卵巢异位；病情程度：轻度 9 例，中度 37 例。观察组年龄 23~42 岁，平均(32.33± 4.54)岁；病变部位：30 例盆腔内异位，16 例卵巢异位；病情程度：轻度 11 例，中度 35 例。比较两组一般资料无统计学意义(P>0.05)，存在比较性。

西医诊断标准[6](同时满足① ~④ 及⑤ ~⑧ 中任 1 项即可确诊)：① 经期伴腰骶部及少腹部不适，出现渐进性加重；② 痛经呈渐进性；③ 直肠刺激症状呈周期性，且渐进性加重；④ 附件粘连包块可见包膜结节感，输卵管畅通；⑤ 后穹窿、子宫峡部及子宫骶骨韧带可见触痛性结节；⑥ 月经前后期间附件肿块大小可见明显改变。中医诊断标准[7](同时满足① ~④ 及⑤ ~⑧ 中任 1 项即可确诊)：① 盆腔可见病理性结节、包块，子宫呈均匀性变大或者可见隆起的局限性结节；② 月经前后可见腰骶部、少腹、肛门疼痛，并呈渐进性加重，或者以上症状于非经期出现，经期可见加重，或者伴性交痛；③ 脉象涩或者代、结；④ 舌质呈紫色或者舌体呈瘀点、瘀斑；⑤ 可见固定性刺痛或者拒按；⑥ 皮下可见瘀斑。

1.2 方法

对照组行常规西药治疗，于月经第 1 天及第 3 天口服 2.5 mg 孕三烯酮(山西桂龙医药有限公司，2.5 mg/ 片，20130312)，每周 2 次，连续使用 3 个月。观察组行补肾温阳化瘀法治疗，将延胡索 15 g、肉桂 10 g、小茴香 10 g、制没药 10 g、制附子 6 g 等加清水浸泡半小时，予以武火快速煮沸(制附子需先煎、肉桂需后下)，后改文火煎煮 20 min 后将药液倒出，并留取药渣按上述方式再次煎煮，每日 1 剂，单剂需进行 2 次煎煮，共留取 200 mL 药汁，于每日早晚分次温服，连续用药 3 个月。记录两组患者用药期间的不良反应。

1.3 观察指标及检测方法

1.3.1 子宫内膜上皮细胞指标测定 于用药前及用药后次采集患者子宫异位内膜组织，取 10%甲醛溶液进行固定，并予以石蜡包埋后行常规切片，取二甲苯进行脱蜡。加入 1:100 稀释的小鼠抗人 OPN 与 MMP-9 单克隆抗体，于 4℃环境中孵育过夜。取二氨基联苯胺进行显色，于显微镜下进行观察、拍照。采用图像分析系统(Image-Pro 6.0)予以图像分析，选择 5 个× 400 高倍镜单个视野，统计其 OPN 及 MMP-9IDO 值。

1.3.2 血清指标测定 于用药前及用药后采集患者空腹外周静脉血 2 mL，常规抗凝后、分离血清，保存待检。雌二醇(E_2)、促黄体生成素(LH)、卵泡刺激素(FSH)予以酶联免疫法测定，试剂盒均由重庆赛维药业有限公司提供；肿瘤坏死因子 -α(TNF-α)、白细胞介素 -6(IL-6)、白细胞介素 -8(IL-8)予以放射比浊法测定，试剂盒均由武汉普生制药有限公司提供；$CD3^+$、$CD4^+$、$CD8^+$ 予以流式细胞术测定，试剂盒均由河北东风药业有限公司提供。以上操作均经同组经验丰富的工作人员严格参照说明书进行。

1.4 临床疗效评估

症候完全消失，局部体征大致消失即痊愈；症候大致消失，盆腔包块有一定缩小即显效；症候缓解，盆腔包块变化不明显，停止用药 3 个月内症状未见加重级好转；症候及体征未见明显改变或者加重即无效。痊愈、显效及好转均视为总有效。

1.5 统计学分析

选择 SPSS18.0 行数据统计，用均数± 标准差($\bar{x}\pm s$)表示计量资料，组间比较用 t 检验，用[(例)%]表示计算资料，用 x^2 检验比较，等级资料用秩和检验，P<0.05 则有统计学意义。

2 结果

2.1 两组患者治疗前后子宫内膜腺上皮细胞 OPN 与 MMP-9 比较

治疗前，比较两组子宫内膜腺上皮细胞 OPN 与 MMP-9 无统计学意义(P>0.05)；治疗后，两组子宫内膜腺上皮细胞 OPN 与 MMP-9 均降低，观察组降低更明显，差异有统计学意义(P<0.05)，见表 1。

表 1 两组患者治疗前后子宫内膜腺上皮细胞 OPN 与 MMP-9 比较($\bar{x}\pm s$)

Table 1 Comparison of endometrial glandular epithelial cells of OPN and MMP - 9 between two groups before and after the treatment ($\bar{x}\pm s$)

Groups	Time	OPN(mmol/L)	MMP-9(mmol/L)
Control group(n=46)	Before treatment	5.23± 0.74	5.62± 0.80
	After treatment	2.98± 0.42 [b]	3.45± 0.49 [b]
Observation group(n=46)	Before treatment	5.45± 0.78	5.56± 0.79
	After treatment	2.71± 0.38 [ab]	3.11± 0.44 [ab]

Note: compared with control group after treatment, [a]P<0.05; compared with before treatment, [b]P<0.05.

2.2 两组患者治疗前后血清性激素水平比较

治疗前，比较两组 E2、LH、FSH 无统计学意义(P>0.05)；治疗后，两组 E2、LH、FSH 均降低，观察组低于对照组，差异有统计学意义(P<0.05)，见表 2。

2.3 两组患者治疗前后血清炎性因子比较

治疗前，比较两组 TNF-α、IL-6、IL-8 无统计学意义(P>0.05)；治疗后，两组 TNF-α、IL-6、IL-8 均降低，观察组低于对照组，差异有统计学意义(P<0.05)，见表 3。

表 2 两组患者治疗前后血清性激素水平比较($\bar{x}\pm s$)

Table 2 Comparison of serum levels of sex hormones between the two groups before and after the treatment ($\bar{x}\pm s$)

Groups	Time	E_2(pmol/L)	LH(U/L)	FSH(U/L)
Control group(n=46)	Before treatment	115.48± 16.43	8.44± 1.20	8.14± 1.13
	After treatment	104.38± 14.92 [b]	7.42± 1.05b	7.20± 1.09[b]
Observation group(n=46)	Before treatment	117.72± 16.70	8.53± 1.26	8.22± 1.24
	After treatment	92.70± 13.21 [ab]	6.89± 0.97[ab]	6.53± 0.93[ab]

Note: compared with control group after treatment, [a]P<0.05; compared with before treatment, [b]P<0.05.

表 3 两组患者治疗前后血清炎性因子水平比较($\bar{x}\pm s$)

Table 3 Comparison of serum levels of inflammatory factors between two groups before and after the treatment ($\bar{x}\pm s$)

Groups	Time	TNF-α(μg/L)	IL-6(ng/L)	IL-8(ng/L)
Control group(n=46)	Before treatment	2.87± 0.41	33.27± 4.73	43.67± 6.23
	After treatment	1.31± 0.18 b	21.30± 3.04 [b]	25.49± 3.66 [b]
Observation group(n=46)	Before treatment	2.83± 0.40	34.68± 4.95	44.80± 6.42
	After treatment	1.10± 0.15 ab	17.42± 2.48 [ab]	

Note: compared with control group after treatment, [a]P<0.05; compared with before treatment, [b]P<0.05.

2.4 两组患者治疗前后免疫功能比较

治疗前,比较两组 $CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 无统计学意义(P>0.05);治疗后,两组 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 均上升,观察组高于对照组,两组 $CD8^+$ 均降低,观察组低于对照组,差异有统计学意义(P<0.05),见表 4。

表 4 两组患者治疗前后免疫功能比较($\bar{x}\pm s$)

Table 4 Comparison of the immune function between two groups before and after the treatment ($\bar{x}\pm s$)

Groups	Time	$CD3^+$	$CD4^+$	$CD8^+$	$CD4^+/CD8^+$
Control group(n=46)	Before treatment	63.80± 9.11	41.87± 5.97	37.80± 5.40	1.10± 0.15
	After treatment	66.40± 9.48 [b]	44.20± 6.31 [b]	34.65± 4.93 [b]	1.32± 0.19 [b]
Observation group (n=46)	Before treatment	62.74± 8.94	42.65± 6.09	38.92± 5.56	1.13± 0.16
	After treatment	68.95± 9.90 [ab]	47.73± 6.81 [ab]	31.23± 4.46 [ab]	1.56± 0.22 [ab]

Note: compared with control group after treatment, [a]P<0.05; compared with before treatment, [b]P<0.05.

2.5 两组患者临床疗效比较

观察组总有效率高于对照组,差异有统计学意义(P<0.05),见表 5。

表 5 两组患者临床疗效比较[(例)%]

Table 5 Comparison of the clinical curative effect between two groups[(n)%]

Groups	Cure	Markedly	Better	Invalid	Total effective rate
Control group(n=46)	7(15.21)	12(26.08)	11(23.92)	16(34.79)	30(65.21)
Observation group (n=46)	13(28.26)	17(36.95)	10(21.71)	6(14.28)	42(91.30)[a]

Note: compared with control group after treatment, [a]P<0.05.

2.6 两组患者安全性比较

对照组不良反应为 28.26%,其中重度痤疮有 2 例,潮红有 5 例,性欲降低有 6 例,观察组不良反应为 4.34%,其中 2 例恶心,差异有统计学意义(P<0.05)。

3 讨论

子宫内膜异位症是妇科的良性疾病,临床多以盆腔痛、痛经、不孕等为主要表现[9]。孕三烯酮是其治疗的的传统药物,存在激素与抗激素作用,可作用于子宫内膜,导致子宫内膜和异位病灶的细胞出现失活及退化,引起病灶萎缩[10]。但可出现多毛、痤疮、乏力、头晕、潮红等不良反应,增加患者痛苦。

中医学认为子宫内膜异位症痛有定处，盆腔内可扪及结节、包块且多固定，属中医血淤证[11]。淤血阻滞冲任胞脉，致血气不通，引发痛经；内结淤血，日久积聚，而生瘕积；经脉闭涩，冲任瘀滞致不孕；又因该病时长，久病必伤肾，且腹部多畏寒喜暖必结寒气[12]。故恶血聚集，血运失常，肾虚阳衰，寒集胞宫为发病之关键，依中医学＂审因论治及治病求本＂之法，选以补肾温阳，散寒化淤治疗[13]。方中延胡索味苦、辛，性温，入肝、脾、心经，可调和气血，除风邪，行活气，暖腰膝，祛除淤血[14]。肉桂味甘、辛，性热，入心、肝肾经，可破血通行，除腹中之寒气，是补肾温阳，散寒止痛的要药。小茴香可散寒去痛，温肾肝阳，可解痛经及少腹冷痛。制附子主辛热，可畅通经脉，温机体之阳气，祛寒解痛。没药味微酸而辛，气淡薄，可行气活血，化淤散血。川芎性温，味辛，入心报、肝胆经，可行气活血；桑寄生可强筋骨，补肝肾；党参可补中益气。全方标本同治，补先天肾气之时又增后天脾气，达旺盛正气，活血祛淤，调经去痛之功，复正气，散瘀滞，养胞宫，调畅冲任[15]。

国外研究发现子宫内膜异位症患者子宫内膜腺上皮细胞中 OPN 及 MMP-9 明显呈过表达，OPN 是一种骨基质非胶原性蛋白，能够于多种细胞组织中广泛分布，可起到细胞粘附，细胞因子表达、信号转导等生物学作用[16]。同时 OPN 能够经细胞外基质及基底膜降解后促进肿瘤的进展、转移，MMP-9 能够使蛋白水解活性激活，并产生纤维酶原的激活剂，从而激活纤维酶系统，诱导血管新生，促进癌细胞浸润[17]。本结果显示，中医治疗后 OPN 及 MMP-9 表达水平显著降低，表明补肾温阳化淤法可有效抑制 OPN 及 MMP-9 过表达，控制疾病的进展。有研究报道，子宫内膜作为卵巢甾体激素的重要靶器官，其生长发育能够影响外周血中性激素水平，与孕激素及雌激素受体浓度有着紧密联系[18]。本结果显示，中医治疗后血清性激素水平显著低于接受西医治疗者，表明补肾温阳化淤法能够减轻性激素水平对疾病的刺激，缓解病情。现代医学发现，异位内膜细胞能够使前列腺素过度释放，诱导局部的炎症反应，从而利于细胞的增殖[19]。本结果显示，中医治疗后 TNF-α、IL-6、IL-8 水平明显降低，表明补肾温阳化淤法可降低机体炎性因子水平，减轻局部炎症反应。有研究指出，子宫内膜异位症患者多伴免疫功能减弱，导致淋巴细胞无法对逆流经血进行有效清除，导致异位病灶[20]。本结果显示，中医治疗后 $CD3^+$、$CD4^+$、$CD4^+$、$CD8^+$ 明显上升，表明补肾温阳化淤法可纠正机体免疫功能紊乱，增强免疫能力，从而利于对循环系统中的有害物质的清除。同时中医治疗的总有效率显著高于接受西医治疗者，且不良反应较少，表明此方疗效肯定，安全性比较高，可长期应用。

综上所述，补肾温阳化瘀法可下调子宫内膜异位症患者子宫内膜腺上皮细胞 OPN 及 MPP-9 表达。但本研究补肾温阳化瘀法为汤剂治疗，可降低患者耐受性，需进一步改善本方的药物剂型，增强其药用价值。

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