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醋酸亮丙瑞林联合地屈孕酮片对子宫内膜异位症的疗效及对血清 HE4、VEGF、TIMP、MCP-1 的影响 *

郑新艳[1] 颜红丽[2△] 李金鸽[2] 邬晋芳[3] 朱 华[4]

（1 西安市第五医院 妇产科 陕西 西安 710082；2 西北妇女儿童医院 妇产科 陕西 西安 710061；
3 西安交通大学第二附属医院 妇产科 陕西 西安 710004；4 陕西省渭南市大荔县医院 妇产科 陕西 渭南 715100）

摘要 目的：探讨醋酸亮丙瑞林联合地屈孕酮片治疗子宫内膜异位症的临床疗效及对患者血清人附睾分泌蛋白 4(HE4)、血管内皮生长因子(VEGF)、基质金属蛋白酶组织抑制因子(TIMP)、单核细胞趋化蛋白 1(MCP-1)水平的影响。**方法：**选择我院 2014 年 1 月~2017 年 1 月收治的 150 例子宫内膜异位症患者，按随机数表法分为对照组和研究组，每组 75 例。对照组予以醋酸亮丙瑞林治疗，研究组在对照组基础上联合地屈孕酮片治疗。比较两组临床疗效，治疗前后血清 HE4、VEGF、TIMP、MCP-1、性激素水平、视觉模拟评分(VAS)及 SF-36 的变化，不良反应的发生情况和随访情况。**结果：**治疗后，研究组显著总有效率高于对照组(96% vs. 85.33%)(P<0.05)；两组血清 HE4、VEGF、TIMP、MCP-1、性激素、VAS 水平均较治疗前显著下降，且研究组以上指标均明显低于对照组(P<0.05)；两组 SF-36 均较治疗前明显上升，且研究组明显高于对照组(P<0.05)。两组不良反应发生率比较差异无统计学意义(P>0.05)。随访结果显示研究组妊娠率及复发率低于对照组(P<0.05)。**结论：**醋酸亮丙瑞林联合地屈孕酮治疗子宫内膜异位症的疗效明显优于单用醋酸亮丙瑞林治疗，其可减轻临床症状，提高妊娠几率，这可能与其有效降低血清 HE4、VEGF、TIMP、MCP-1 水平有关。

关键词：子宫内膜异位症；醋酸亮丙瑞林；地屈孕酮；疗效；人附睾分泌蛋白 4；血管内皮生长因子；基质金属蛋白酶组织抑制因子；单核细胞趋化蛋白 1

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Curative Effect of Leuprolide Acetate Combined with Diprogesterone Tablets in Treatment Endometriosis and its Effect on Serum HE4, VEGF, TIMP and MCP-1*

ZHENG Xin-yan[1], YAN Hong-li[2△], LI Jin-ge[2], WU Jin-fang[3], ZHU Hua[4]

(1 Department of Obstetrics and Gynecology, Xi'an fifth hospital, Xi'an, Shaanxi, 710082, China;
2 Department of Obstetrics and Gynecology, northwest women and children's Hospital, Xi'an, Shaanxi, 710061, China;
3 Department of Obstetrics and Gynecology, Second Affiliated Hospital of Xi'an Jiao Tong University, Xi'an, Shaanxi, 710004, China;
4 Department of Obstetrics and Gynecology, Dali hospital, Weinan, Shaanxi, 715100, China)

ABSTRACT Objective: To research the clinical curative effect of leuprolide acetate combined with diprogesterone tablets in the treatment endometriosis and its effect on the serum levels of human epididymis protein 4 (HE4), vascular endothelial growth factor (VEGF), matrix metalloproteinases tissue inhibitor(TIMP), monocyte chemotactic protein-1(MCP-1). **Methods:** 150 cases of endometriosis patients who were treated from January 2014 to January 2017 were selected and divided into the control group and the research group, according to the random number table method, with 75 cases in each group. The control group was treated with leuprolide acetate, while the research group was treated with the diprogesterone tablets on the basis of control group. Then clinical efficacy, changes of serum HE4, VEGF, TIMP, McP-1, sex hormone level levels, visual analogue score (VAS) and sf-36 before and after treatment, the occurrence and follow-up of adverse reactions were compared between the two groups. **Results:** After treatment, the total effective rate of research group was significant higher than that of the control group(96% vs. 85.33%)(P<0.05). The erum levels of HE4, VEGF, TIMP, McP-1, sex hormone and VAS in both groups were significantly lower than those before treatment,the above indexes in the research group were significantly lower than those in the control group (P<0.05). The SF-36 was significantly higher in the research group than in the control group after treatment (P<0.05). There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). Follow-up results showed that the pregnancy rate and recurrence rate in the study group were lower than those in the control group (P<0.05). **Conclusion:** Liangproterol acetate combined with diprogesterone was more effective than liangproterol acetate alone in the treatment of

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作者简介：郑新艳(1979-)，女，主治医师，本科，研究方向：妇产科临床疾病，电话：15929989225，E-mail：adkod5188@163.com

△ 通讯作者：颜红丽(1977-)，女，硕士研究生，副主任医师，研究方向：优生优育与妇科腹腔镜微创方面

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endometriosis, it could significantly relieve the clinical symptoms and improve the pregnancy rate, which may be related to its effective reduction of serum HE4, VEGF, TIMP and McP-1 levels.

Key words: Endometriosis; Bright propylene acetate; Diprogesterone; Curative effect; Human epididymal protein 4; Vascular endothelial growth factor; Matrix metalloproteinase inhibitors; Monocyte chemotactic protein 1

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前言

子宫内膜异位症是一种生育期妇女的多发性疾病,大部分患者可出现继发性痛经、不育等典型表现[1],虽为良性病变,但仍具有局部浸润生长和转移等恶性肿瘤的能力[2]。子宫内膜异位症的治疗目标在于尽可能的减轻疼痛、缩小病灶、促进生育、减少并预防复发,临床应综合患者生育要求、病变范围、症状等进行个体化治疗[3,4]。

药物是不孕、无卵巢囊肿形成者的重要治疗手段,促性腺激素释放激素激动剂(GnRH-a)能够通过调节垂体功能,降低机体性激素水平,达到药物性卵巢切除,导致病灶萎缩,从而控制疾病进展[5]。醋酸亮丙瑞林为 GnRH-a 的代表药物,有研究显示其在提高临床疗效及妊娠率方面有重要作用[6]。但 GnRH-a 长时间应用能够引起低激素综合征,甚至可出现骨质疏松,从而降低患者治疗依从性[7]。孕激素能够出现无周期性的低激素现象,和内源性雌激素共同作用形成假孕,地屈孕酮为口服孕激素,能够缓解因雌激素所致的子宫内膜增生[8,9]。目前,临床上有关二者联合应用的报道较少,且相关应用机制并不明确。子宫内膜异位症的发病机制较为复杂,相关研究报道,人附睾分泌蛋白 4(HE4)作为一种分泌型糖蛋白,在正常卵巢组织中几乎无表达,卵巢恶性肿瘤中高度表达。血管内皮生长因子(VEGF)可增加子宫内膜异位症的血流供应,促进其增长速度。基质金属蛋白酶组织抑制因子(TIMP)可调控基质金属蛋白酶的代谢,参与多种器官和组织纤维化发病。单核细胞趋化蛋白 1(MCP-1)为趋化性因子,能够激活嗜酸性粒细胞、单核细胞等活性,扩大机体炎症反应,通过测定以上指标浓度改变能够评估疗效[10]。因此,本研究主要分析了醋酸亮丙瑞林联合地屈孕酮片对子宫内膜异位症的疗效及对血清 HE4、VEGF、TIMP 及 MCP-1 水平的影响,并探讨其作用机制。

1 资料与方法

1.1 一般资料

选择 150 例子宫内膜异位症患者,纳入标准:符合子宫内膜异位症诊断标准[11]:伴不孕、持续加重的盆腔疼痛及粘连、痛经等症状,彩超提示无回声区内可见密集光点,腹腔镜可见子宫内膜间质及腺体,并伴纤维化及炎症病变,血清糖类抗原 125 浓度超过 25U/L;均不愿接受手术治疗,且有药物治疗指征;近期未接受激素治疗;既往无其他代谢性、免疫及内分泌疾病;未合并其他妇科疾;有生育要求,且配偶精液无异常;排除标准:心、肝肾等基础疾病;相关药物禁忌症;癫痫、恶性肿瘤等;既往伴子宫手术史。对照组年龄 25~38 岁,平均(29.76± 6.50)岁;病程 1~5 年,平均(2.41± 0.84)年;未育 30 例,经产妇 45 例。研究组年龄 23~39 岁,平均(30.48± 7.11)岁;病程 1~5 年,平均(2.36± 0.79)年;未育 27 例,经产妇 48 例。两组一般资料比较差异无统计学意义(P>0.05),具有可比性。

1.2 治疗方法

对照组予以醋酸亮丙瑞林治疗,于术后月经来潮第 1 天皮下注射 3.75 mg 醋酸亮丙瑞林(天津武田药品有限公司,规格:10 mg,批号:130823),间隔 4 周 1 次,持续治疗 3 个月。研究组基于对照组联合地屈孕酮治疗,于月经来潮第 5 天 ~25 天,口服 10mg 地屈孕酮(AbbottHealthcareProductsB.V,规格:10mg/ 片,批号:130521),每天 2 次,持续治疗 3 个月。两组均定期复查超声情况,并记录 1 年内的妊娠率(排卵后 14 天检测血尿 HCG,阳性即为生化妊娠)、复发率(原有症状再次出现,或者 B 超提示盆腔内伴囊肿)及不良反应情况。

1.3 观察指标

1.3.1 临床疗效评价标准 显效:临床表现全部消失,盆腔未见肿块;有效:临床表现明显缓解,盆腔未见肿块;无效:临床表现无改变或者加重[11]。

1.3.2 指标测定 治疗前及治疗结束时采集患者 2 mL 空腹静脉血,以 GF125 型血液分离机(北京中西泰安技术服务有限公司)按 3000 r/min 分离 10 min,并于低温环境中保留待检。采用酶联免疫法测定 HE4、VEGF、TIMP、MCP-1 水平,试剂盒均由上海科华生物工程股份有限公司提供。采用 DG-300 全自动生化分析仪(厦门科昊自动化有限公司)测定黄体生成素(LH)、卵泡生成激素(FSH)、孕酮(P)、雌二醇(E2)水平。

1.3.3 临床评分 用视觉模拟评分(VAS)评估患者性交痛、痛经及盆腔痛情况,分数为 0~10 分,分数越高提示疼痛程度越明显。简明健康量表 SF-36 评分:包含精神健康、情感职能、社会功能等 8 个维度,总共 36 个项目,分数为 0~100 分,生活质量和分数呈正比[12,13]。

1.4 统计学分析

数据处理选用 SPSS18.0 进行,计量资料以($\bar{x}$± s)表示,组间比较选用独立样本 t 检验进行,计数资料以[(例)%]表示,组间比较用 x^2 检验,以 P<0.05 为差异具有统计学意义。

2 结果

2.1 两组临床疗效比较

治疗后,研究组总有效率为 96%,显著高于对照组(85.33%),差异有统计学意义(P<0.05),见表 1。

2.2 两组治疗前后血清 HE4、VEGF、TIMP、MCP-1 水平的比较

治疗前,两组血清 HE4、VEGF、TIMP、MCP-1 水平比较差异无统计学意义 (P>0.05);治疗后,两组血清 HE4、VEGF、TIMP、MCP-1 水平均较治疗前显著降低,且研究组以上指标均明显低于对照组,组间比较有统计学差异(P<0.05),见表 2。

表 1 两组临床疗效比较[例(%)]

Table 1 Comparison of the clinical efficacy between two groups[n(%)]

Groups	n	Effectiveness	Effective	Ineffective	Total effective rate
Control group	75	31(41.33)	33(44.00)	11(14.67)	64(85.33)
Research group	75	43(57.33)	29(38.67)	3(4.00)	72(96.00)[a]

Note: Compared with the control group [a]$P<0.05$.

表 2 两组治疗前后血清 HE4、VEGF、TIMP、MCP-1 水平的比较($\bar{x}\pm s$)

Table 2 Comparison of the serum HE4, VEGF, TIMP and MCP-1 levels before and after treatment between two group($\bar{x}\pm s$)

Groups	n	Time	HE4(pmol/L)	VEGF(ng/L)	TIMP(pg/mL)	MCP-1(ng/L)
Control group	75	Before treatment	60.81± 9.60	230.12± 39.02	187.49± 21.08	37.49± 4.49
		After treatment	54.31± 6.53[b]	135.28± 16.44[b]	101.33± 13.23[b]	23.11± 4.21[b]
Research group	75	Before treatment	62.02± 7.53	224.32± 42.19	180.62± 23.59	35.86± 5.60
		After treatment	48.70± 6.12[ab]	101.50± 13.28[ab]	85.40± 10.47[ab]	12.50± 1.87[ab]

Note: Compared with control group [a]$P<0.05$; Compared with before treatment [b]$P<0.05$.

2.3 两组治疗前后血清性激素水平的比较

治疗前，两组血清性激素水平比较差异无统计学意义($P>0.05$)；治疗后，两组血清性激素水平均较治疗前显著下降，且研究组以上指标明显低于对照组，组间比较有统计学差异($P<0.05$)，见表 3。

表 3 两组治疗前后血清性激素水平的比较($\bar{x}\pm s$)

Table 3 Comparison of the serum sex hormones levels before and after treatment between two group($\bar{x}\pm s$)

Groups	n	Time	LH(U/L)	FSH(U/L)	P(nmol/L)	E2(pmol/L)
Control group	75	Before treatment	6.30± 0.87	14.73± 2.69	21.40± 2.87	230.19± 34.28
		After treatment	3.17± 0.45[b]	8.11± 1.25[b]	14.08± 1.90[b]	62.05± 9.52[b]
Research group	75	Before treatment	5.98± 0.94	15.20± 2.34	20.95± 2.34	223.80± 37.1
		After treatment	2.06± 0.30[ab]	5.65± 0.78[ab]	12.14± 1.63[ab]	54.32± 7.50[ab]

Note: Compared with control group [a]$P<0.05$; Compared with before treatment [b]$P<0.05$.

2.4 两组治疗前后 VAS 及 SF-36 评分的比较

治疗前，两组 VAS 及 SF-36 评分比较差异无统计学意义($P>0.05$)；治疗后，两组 VAS 均较治疗前显著下降，且研究组明显低于对照组，而两组 SF-36 评分均较治疗前显著上升，且研究组明显高于对照组，组间比较有统计学差异($P<0.05$)，见表4。

表 4 两组治疗前后 VAS 及 SF-36 评分比较($\bar{x}\pm s$，分)

Table 4 Comparison of the VAS and SF-36 score before and after treatment between two group($\bar{x}\pm s$, score)

Groups	n	Time	VAS			SF-36
			Sexual pain	Dysmenorrhea	Pelvic Pain	
Control group	75	Before treatment	1.19± 0.21	4.97± 0.69	2.45± 0.36	70.54± 9.88
		After treatment	0.22± 0.06[b]	0.23± 0.04[b]	0.30± 0.07[b]	80.39± 11.26[b]
Research group	75	Before treatment	1.23± 0.18	4.50± 0.75	2.68± 0.32	71.96± 7.61
		After treatment	0.13± 0.03[ab]	0.11± 0.02[ab]	0.19± 0.03[ab]	87.40± 12.42[ab]

Note: Compared with the control group [a]$P<0.05$; Compared with before treatment [b]$P<0.05$.

2.5 两组不良反应发生情况的比较

两组均有阴道异常出血、乳房胀痛、皮疹、胃肠道不适发生，两组总不良反应发生率比较差异无统计学意义($P>0.05$)，见表 5。

2.6 两组随访结果比较

研究组妊娠率、复发率均显著低于对照组，比较有统计学差异($P<0.05$)，见表 6。

3 讨论

子宫内膜异位症多好发于育龄女性，近年来发病率呈明显上升趋势，具有病情迁延、易复发等特点[14]。药物已成为病情轻微、不愿接受手术治疗者的首选治疗方法，主要有疼痛对症治

表 5 两组不良反应发生情况的比较[例(%)]

Table 5 Comparison of the incidence of adverse reactions between two groups[n(%)]

Groups	n	Abnormal vaginal bleeding	Breast pain	Rash	Gastrointestinal distress	Total adverse reaction rate
Control group	75	2(2.67)	1(1.33)	2(2.67)	1(1.33)	6(8.00)
Research group	75	1(1.33)	2(2.67)	5(6.67)	3(4.00)	11(14. 67)

表 6 两组随访结果比较[例(%)]

Table 6 Comparison of the follow-up results between two groups[n(%)]

Groups	n	Pregnancy rate	Recurrence rate
Control group	75	31(41.33)	8(10.67)
Research group	75	44(5.87)[a]	2(2.67)[a]

Note: Compared with the control group [a]P<0.05.

疗、阻断下丘脑 - 垂体 - 卵巢轴的性激素治疗、异位内萎缩治疗等[15]。GnRH-a 为临床公认治疗子宫内膜异位症的常用药物之一，其对 GnRH 受体的亲和力明显高于天然 GnRH，能够竞争阻断 GnRH 受体，阻断 GnRH 和受体的结合，抑制性激素的分泌，避免卵泡发育，降低雌激素水平，引起病灶萎缩[16,17]。醋酸亮丙瑞林属 GnRH-a 类药物，抗性腺效应较强，作用于机体虎吼能够调节机体雌激素水平，利于子宫内膜的吸收，其药效持久，半衰期长[18]。尽管醋酸亮丙瑞林能够发挥不错的临床效果，但其副反应较明显，容易引起多种不适，影响患者生活质量，限制了其临床应用[19]。

近年来，子宫内膜异位症的反加疗法越发得到临床重视，其无指定用药，但药物应具有给药方便、安全性高等特点[20]。既往研究已证实[21]子宫内膜异位症患者予以孕激素治疗能够明显改善患者临床症状。地屈孕酮经口服后能够快速吸收，结构和孕酮相似，以单纯孕激素活性为主要表现，无肾上腺皮质激素、雄激素及雌激素作用，且不影响脂代谢[22]。动物试验结果显示[23]地屈孕酮能够增强上皮细胞内的自噬活性，从而引起异位内膜的萎缩，以阻止病灶进步扩张，且对正常内膜的生长发育无明显影响。本研究结果显示醋酸亮丙瑞林联合地屈孕酮组总有效率较醋酸亮丙瑞林单用组高，说明二者联合治疗在临床疗效方面有一定优势，可能是治疗子宫内膜异位症患者的良好选择，考虑与二者共同作用可从多个途径产生治疗作用有关，但具体起效机制有待进一步探讨[24]。

相关研究表明[25]多种细胞因子能够在子宫内膜异位症发生、发展的多个环节中起到重要作用。子宫内膜异位症具有和恶性肿瘤类似的特点，HE4 作为一种新型的肿瘤标记物，能够在宫颈腺体、输卵管等组织中表达[26]。脱落的子宫内膜细胞的生长需依赖血供，新生血管可提供丰富的营养，促进病灶组织的生长发育。VEGF 作为一种促血管生成因子，能够刺激内皮细胞出现增生，诱导新生血管形成，且可引起血管通透性增加，为血管形成创造良好条件，进一步促进病灶的进展[27,28]。Szymanowski K 等[29]研究报道子宫内膜异位症能够增加机体巨噬细胞的分泌，从而刺激 MMP 表达，促进新生血管的形成，加强细胞间黏附，从而在细胞增生及肿瘤发病中起到重要作用。TIMP 为内源性低分子量蛋白，能够影响 MMPs 活性，维持细胞基质平衡，TIMP 在机体体液及组织中广泛分布，能够抑制多种胶原酶活性，细胞增生时 MMPs 及 TIMP 表达明显上升，若二者表达失衡，可促进血管形成，增强细胞黏附作用，导致细胞异位黏附及种植，基底膜完整性是反映子宫内膜侵袭、浸润的主要标志[30]。MCP-1 为单核细胞及巨噬细胞特异性激活和趋化因子，能够诱导纤维母细胞浸润至异位病灶，导致盆腔粘连，并可生成多种生长因子[31]。本研究结果显示子宫内膜异位症患者血清 HE4、VEGF、TIMP、MCP-1 水平均较高，提示宫内膜异位症发病和血管形成、细胞基质失衡有良好相关性，而两组治疗后上述指标均降低，但醋酸亮丙瑞林联合地屈孕酮组下降更明显，说明二者联合治疗更能从多个途径干预疾病，发挥治疗作用。同时，醋酸亮丙瑞林联合地屈孕酮组治疗后在性激素调节方面的作用更明显，能够有效抑制垂体释放性激素。进一步研究发现，醋酸亮丙瑞林联合地屈孕酮组治疗后 VAS 下降更明显，SF-36 相应上升，说明二者联合应用更能减轻疼痛，提高患者生活质量。且联合用药的安全性较高，未增加药物不良反应。子宫内膜异位症的病灶组织的长期分泌及吸收，能够引起周围组织出现粘连，改变组织之间的解剖关系，影响受孕的器官功能，导致不孕[32]。随访结果显示醋酸亮丙瑞林联合地屈孕酮组妊娠率相对较高，且复发率低于醋酸亮丙瑞林组，进一步证实了其可行性。

综上所述，醋酸亮丙瑞林联合地屈孕酮治疗子宫内膜异位症的疗效明显优于单用醋酸亮丙瑞林治疗，其可减轻临床症状，提高妊娠几率，这可能与其有效降低血清 HE4、VEGF、TIMP、MCP-1 水平有关。

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