

doi: 10.13241/j.cnki.pmb.2020.16.027

醋酸戈舍瑞林缓释植入剂联合地屈孕酮对子宫内膜异位症患者血清 VEGF、E2、CA125 水平的影响*

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摘要 目的: 研究醋酸戈舍瑞林缓释植入剂联合地屈孕酮对子宫内膜异位症患者血清血管内皮生长因子 (vascular endothelial growth factor, VEGF)、雌二醇(Estradiol, E2)和肿瘤标志物糖类抗原 125 (Carbohydrate antigen 125, CA125)水平的影响。**方法:** 选择我院 2013 年 1 月~2017 年 12 月收治的 71 例子宫内膜异位症患者, 将其随机分为两组。对照组每次月经后第 2 d 服用地屈孕酮, 每次 1 片, 每天两次; 观察组联合皮下注射醋酸戈舍瑞林缓释植入剂, 每次 3.6 mg, 每月给药 1 次, 共给药 4 次。比较两组治疗前后的血清 VEGF、E2、CA125 水平和子宫内膜厚度的变化。**结果:** 治疗后, 观察组的有效率为 94.59%, 明显高于对照组(71.43%, $P<0.05$)。两组治疗后的血清 VEGF、E2 和 CA125 水平均较治疗前明显降低($P<0.05$), 且观察组的血清 VEGF、E2 和 CA125 水平明显低于对照组($P<0.05$); 两组治疗后的血清基质金属蛋白酶-9(Matrix metalloproteinases -9, MMP-9)和肿瘤坏死因子(Tumor necrosis factor, TNF- α)水平均较治疗前明显降低($P<0.05$), 且观察组的血清 MMP-9 和 TNF- α 水平明显低于对照组($P<0.05$); 两组治疗后的子宫内膜厚度均较治疗前明显降低($P<0.05$), 且观察组的子宫内膜厚度明显低于对照组($P<0.05$)。两组子宫内膜异位症患者于治疗的过程中均未出现任何与药物相关的不良反应。**结论:** 醋酸戈舍瑞林缓释植入剂联合地屈孕酮可以有效缓解子宫内膜异位症患者的病情, 可能与其改善血清 VEGF、E2、CA125、MMP-9 和 TNF- α 水平有关。

关键词: 醋酸戈舍瑞林缓释植入剂; 地屈孕酮; 子宫内膜异位症

中图分类号: R711.71 文献标识码: A 文章编号: 1673-6273(2020)16-3125-04

Effect of Goserelin Acetate Sustained-Release Depot Combined with Dydrogesterone on the Serum VEGF, E2 and CA125 Levels of Patients with Endometriosis*

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ABSTRACT Objective: To investigate the effect of Goserelin Acetate Sustained-Release Depot combined with dydrogesterone on the serum VEGF, E2 and CA125 levels of patients with endometriosis. **Methods:** 71 cases of endometriosis admitted to our hospital from January 2013 to December 2017 were selected and randomly divided into two groups. In the control group, 1 tablet of dydrogesterone was taken twice a day on the second day after menstruation; in the observation group, 3.6 mg of goserelin acetate sustained-release implant was injected subcutaneously once a month for a total of 4 times. The levels of VEGF, E2 and CA125 and endometrial thickness before and after treatment were compared between the two groups. **Results:** After treatment, the effective rate of the observation group was 94.59%, significantly higher than that of the control group(71.43%, $P<0.05$). After treatment, the serum VEGF, E2 and CA125 levels in the two groups were significantly lower than those before treatment ($P<0.05$), and serum VEGF, E2 and CA125 levels in the observation group were significantly lower than those in the control group ($P<0.05$). After treatment, the levels of MMP-9 and TNF- α in serum of the two groups were significantly lower than those before treatment ($P<0.05$), and the levels of MMP-9 and TNF- α in the observation group were significantly lower than control group ($P<0.05$). The endometrial thickness of the two groups after treatment was significantly lower than that before treatment ($P<0.05$), and the observation group was significantly lower than control group ($P<0.05$). Patients in both groups of endometriosis did not experience any drug-related adverse reactions during treatment. **Conclusion:** Goserelin Acetate Sustained-Release Depot combined with dydrogesterone can effectively alleviate the patients with endometriosis, which may be related to the improvement of serum VEGF, E2, CA125, MMP-9 and TNF- α levels.

Key words: Goserelin Acetate Sustained-Release Depot; Dydrogesterone; Endometriosis disease

Chinese Library Classification(CLC): R711.71 **Document code:** A

Article ID: 1673-6273(2020)16-3125-04

* 基金项目: 黑龙江省教育厅科学技术研究项目(12531719)

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(收稿日期: 2020-02-17 接受日期: 2020-03-13)

前言

子宫内膜异位症是一种育龄期女性常见疾病,患者主要表现为性生活不和谐、痛经、不孕等症状^[1-3],其发病机制至今仍未明确,可能与免疫因素、遗传因素和炎症因素相关。手术是治疗子宫内膜异位症的首选方法,可以迅速明确疾病的详细情况,有效地清除病灶,保留患者的生育能力,且创伤程度轻微,术后恢复较快。但手术只能切除表面的病灶,可能会遗留病灶,造成病情反复发作,具有一定的局限性,因此在手术后必须使用药物辅助治疗^[4,5]。

地屈孕酮能促进子宫内膜转变为完全的分泌相,预防子宫内膜增生以及癌变,并不会产生雄激素、雌激素和肾上腺皮质激素作用,对脂代谢无明显影响,且不产热^[6,7]。醋酸戈舍瑞林缓释植入剂能显著改善子宫内膜异位症患者的症状,降低疼痛程度,减少对子宫内膜损伤^[8]。但临床上尚未见关于醋酸戈舍瑞林缓释植入剂以及地屈孕酮联合使用的研究报道。因此,本研究主要探讨了联用醋酸戈舍瑞林缓释植入剂以及地屈孕酮对子宫内膜异位症患者的效果及其对血清 VEGF、E2、CA125 水平的影响。

1 资料与方法

1.1 一般资料

选择 2013 年 1 月~2017 年 12 月我院收治的 71 例子宫内膜异位症患者,纳入标准:符合相关的诊断标准^[9],无严重的重要器官疾病,无过敏体质,知情同意。排除标准:对于醋酸戈舍瑞林缓释植入剂以及地屈孕酮过敏患者;患有严重肝肾功能不全患者;有恶性肿瘤、结缔组织病等病史的患者;伴有自身免疫系统疾病患者。将患者随机分为两组。观察组 36 例,年龄 26~45 岁,平均 (37.14 ± 3.26) 岁;病程 1~12 个月,平均 (4.39 ± 1.13) 个月;经期 2~9 d,平均 (5.14 ± 0.36) d;月经周期 23~42 d,

平均 (32.25 ± 1.29) d;体重 39~70 kg,平均 (56.28 ± 4.53) kg。对照组 35 例,年龄 26~44 岁,平均 (36.95 ± 3.37) 岁;病程 1~12 个月,平均 (4.26 ± 1.05) 个月;经期 2~8 d,平均 (5.64 ± 0.38) d;月经周期 24~42 d,平均 (32.14 ± 1.17) d;体重 39~70 kg,体重 (56.34 ± 3.67) kg。两组的基线资料对比无差异($P>0.05$),具有可比性。

1.2 治疗方法

对照组采用地屈孕酮(荷兰 Abbott Healthcare Products B. V, 进口药批准号 H20110208,)进行治疗,每月经后第 2 d 服用,每次 1 片,每天两次。观察组联合皮下注射醋酸戈舍瑞林缓释植入剂(批号:国药准字 J20120015,生产厂家:阿斯利康制药有限公司)治疗,每次 3.6 mg,每月给药 1 次,共治疗 4 次。

1.3 观察指标

疗效标准^[9]:① 显效:患者的症状基本消失,B 超检查结果显示包块已消失;② 有效:患者的症状有所缓解,B 超检查结果显示包块发生缩小;③ 无效:患者的症状和,B 超检查结果均无明显的变化。于治疗前后抽取 3 mL 静脉血,使用放射免疫法检测两组子宫内膜异位症患者的血清 VEGF、E2 和 CA125 水平,用 ELISA 法检测血清 MMP-9 和 TNF- α 水平,试剂盒购买与南京金益柏生物公司,严格按照说明书操作。比较两组治疗前、治疗 3 个月以及治疗 6 个月的子宫内膜厚度。

1.4 统计学分析

应用 SPSS 19.0 软件对实验数据进行统计学分析,计量资料以 $\bar{x} \pm s$ 表示,组间比较行 t 检验,计数资料用 % 表示,组间比较行 χ^2 检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组疗效的比较

治疗后,观察组的有效率为 94.59%,明显高于对照组(71.43%, $P<0.05$),见表 1。

表 1 两组疗效的比较[例(%)]

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

Groups	n	Effective	Valid	Invalid	The total effect rate
Control group	35	14(40.00)	11(31.43)	10(28.57)	71.43
Observation group	36	20(55.55)	15(41.67)	1(2.78)	94.59*

Note: Compared with the control group, * $P<0.05$.

2.2 两组治疗前后血清 VEGF、E2 和 CA125 水平的比较

两组治疗前血清 VEGF、E2 和 CA125 水平比较差异无

统计学意义($P>0.05$),治疗后上述指标均较治疗前明显降低($P<0.05$),且观察组以上指标明显低于对照组($P<0.05$),见表 2。

表 2 两组治疗前后血清 VEGF、E2 和 CA125 水平的比较($\bar{x} \pm s$)

Table 2 Comparison of the serum VEGF, E2 and CA125 levels between the two groups before and after treatment($\bar{x} \pm s$)

Groups	n		VEGF(pmmol/L)	E2(pmmol/L)	CA125(U/mL)
Control group	35	Before treatment	141.35 $\pm$ 12.98	157.43 $\pm$ 16.21	26.39 $\pm$ 5.42
		After treatment	125.63 $\pm$ 10.24 [#]	150.42 $\pm$ 13.78 [#]	20.38 $\pm$ 4.29 [#]
Observation group	36	Before treatment	142.64 $\pm$ 13.57	156.29 $\pm$ 15.38	25.73 $\pm$ 6.13
		After treatment	98.32 $\pm$ 7.65* [#]	132.74 $\pm$ 11.25* [#]	13.26 $\pm$ 3.45* [#]

Note: Compared with the control group, * $P<0.05$; compared with before treatment, [#] $P<0.05$.

2.3 血清治疗前后血清 MMP-9 和 TNF- α 水平的比较

两组治疗前血清 MMP-9 和 TNF- α 水平比较差异无统计

学意义 ($P>0.05$), 两组治疗后上述指标均较治疗前明显降低 ($P<0.05$), 且观察组以上指标明显低于对照组 ($P<0.05$), 见表 3。

表 3 两组治疗前后血清 MMP-9 和 TNF- α 水平的比较($\bar{x} \pm s$)

Table 3 Comparison of the serum MMP-9 and TNF - α levels between the two groups before and after treatment($\bar{x} \pm s$)

Group	n		MMP-9(ng/mL)	TNF- α (ng/L)
Control group	35	Before treatment	131.72 $\pm$ 12.45	65.43 $\pm$ 5.29
		After treatment	72.48 $\pm$ 7.36 [#]	47.32 $\pm$ 4.51 [#]
Observation group	36	Before treatment	132.64 $\pm$ 11.78	66.38 $\pm$ 4.72
		After treatment	65.31 $\pm$ 4.92 ^{*#}	36.29 $\pm$ 3.74 ^{*#}

2.4 两组治疗前后子宫内膜厚度的比较

两组治疗后 3 个月和 6 个月的子宫内膜厚度均较治疗前

明显降低 ($P<0.05$), 且观察组以上指标明显低于对照组 ($P<0.05$), 见表 4。

表 4 两组治疗前后子宫内膜厚度的比较($\bar{x} \pm s$, mm)

Table 4 Comparison of the endometrial thickness between the two groups before and after treatment($\bar{x} \pm s$, mm)

Groups	n	Before treatment	3 months after treatment	6 months after treatment
Control group	35	7.13 $\pm$ 1.12	4.52 $\pm$ 0.75 [#]	4.28 $\pm$ 0.54 [#]
Observation group	36	7.12 $\pm$ 1.04 [*]	3.67 $\pm$ 0.42 ^{*#}	3.15 $\pm$ 0.47 ^{*#}

2.5 两组不良反应的发生情况

两组治疗的过程中均未出现任何与药物相关的不良反应。

3 讨论

子宫内膜异位症患者病情严重者可见崩漏、肿物增生等^[10-14], 会引发痛经、结节形成、不孕、月经紊乱甚至恶性肿瘤^[15-18]。该病的发病机制与血管转移及雌激素水平过高有关。手术是首选治疗方法, 但无法完全清除微小的病灶, 术后通过服用性激素类药物如高效孕激素、短效避孕药、雄激素衍生物以及促性腺激素释放激素激动药等可以提高手术治疗有效率, 降低复发率^[19,20]。

子宫内膜异位症患者极易反复发生周期性出血, 促进病灶周围组织发生纤维化, 长时间会导致包块形成, 因而清除病灶、改善症状、预防病灶恶变是临床上治疗子宫内膜异位症的关键。临床治疗子宫内膜异位症的原则为消除及降低疼痛, 消除和减灭病灶, 促进及改善生育, 预防及减少复发^[21]。地屈孕酮为口服孕激素药物, 与孕酮具有相近的结构, 能够对机体上皮细胞内自噬活性起到明显的增强作用, 从而对异位内膜生长产生抑制作用, 并促进异位内膜萎缩, 并且对正常内膜无损害, 对排卵也无抑制作用^[22]。戈舍瑞林能对脑垂体促性腺激素的分泌进行有效的抑制, 控制盆腔疼痛, 使子宫内膜异位症患者的血清雌二醇以及卵巢激素水平显著降低, 进而明显抑制体内病灶的生长, 减小子宫内膜的损伤大小和数量, 并使残留的内膜异位病灶萎缩退化, 修复内膜组织^[23,24]。将地屈孕酮与戈舍瑞林两种药物联合, 能够发挥各自优势, 进而发挥降低复发及治疗疾病的效果。本研究中, 观察组的有效率明显更高, 表明醋酸戈舍瑞林缓释植入剂联合地屈孕酮可以有效缓解子宫内膜异位症患者的病情, 其效果明显优于单独服用地屈孕酮。

子宫内膜异位症具有较强的侵袭性。VEGF 作为机体内一种极为重要的促血管生长因子, 有助于形成与女性子宫内膜增殖有关的血管^[25,26]。CA125 作为临床上诊断卵巢癌的一种重要

肿瘤标志物, 主要分布于女性胚胎体腔的上皮细胞内^[27,28]。本研究中, 观察组治疗后血清 VEGF、E2 和 CA125 水平明显低于对照组, 表明醋酸戈舍瑞林缓释植入剂联合地屈孕酮可以有效改善子宫内膜异位症患者的血清性激素水平。胡艳荣^[29]联合给予来曲唑以及地屈孕酮治疗 30 例子宫内膜异位症患者, 发现患者的血清 VEGF、E2 和 CA125 水平均显著降低, 与本研究结果相一致。子宫内膜异位会对机体的细胞外基质造成破坏, 引起炎症反应, 而炎症反应发生时最早出现的细胞因子即为 TNF- α ^[30]。子宫内膜细胞会穿破基底膜, 将细胞外基质降解, 主要依靠半胱氨酸蛋白酶、天冬氨酸蛋白酶、基质金属蛋白酶和丝氨酸蛋白酶, 其中最为重要的是 MMP-9, 能有效降解纤维黏连蛋白以及 IV 型胶原等基质^[31]。治疗后, 两组的血清 MMP-9 和 TNF- α 水平均明显降低, 观察组的血清 MMP-9 和 TNF- α 水平明显更低; 表明醋酸戈舍瑞林缓释植入剂联合地屈孕酮能明显改善子宫内膜异位症患者的细胞因子水平。而两组治疗后的子宫内膜厚度均明显降低, 且观察组明显低于对照组, 表明醋酸戈舍瑞林缓释植入剂联合地屈孕酮可以通过不同机制抑制卵巢功能, 从而降低雌激素水平以及子宫内膜厚度。

综上所述, 醋酸戈舍瑞林缓释植入剂联合地屈孕酮可以有效缓解子宫内膜异位症患者的病情, 可能与其改善血清 VEGF、E2、CA125、MMP-9 和 TNF- α 水平有关。

参考文献(References)

- [1] Fauconnier A, Borghese B, Huchon C, et al. Epidemiology and diagnosis strategy: CNGOF-HAS Endometriosis Guidelines [J]. Gynecol Obstet Fertil Senol, 2018, 46(3): 223-230
- [2] Oranous Bashti, Mehrdad Noruzinia, Masoud Garshasbi, et al. miR-31 and miR-145 as Potential Non-Invasive Regulatory Biomarkers in Patients with Endometriosis[J]. Cell Journal, 2018, 20(1): 84-89
- [3] Samadieh Y, Favaedi R, Ramezanali F, et al. Epigenetic Dynamics of HOXA10 Gene in Infertile Women With Endometriosis [J]. Reprod

- Sci, 2019, 26(1): 88-96
- [4] Nahid Nasiri, Ashraf Moini, Poopak Eftekhari-Yazdi, et al. Oxidative Stress Statues in Serum and Follicular Fluid of Women with Endometriosis[J]. Cell Journal, 2017, 18(4): 582-587
- [5] Insa Winzenborg, Ahmed Nader, Akshanth R. Polepally, et al. Population Pharmacokinetics of Elagolix in Healthy Women and Women with Endometriosis[J]. Clinical Pharmacokinetics, 2018, 57(10): 1-12
- [6] Jui-Tung Chen, Kazuhiko Kotani. Different Effects of Oral Contraceptive and Dydrogesterone Treatment on Oxidative Stress Levels in Premenopausal Women[J]. J Clin Medi Res, 2018, 10(2): 146-153
- [7] Shan Wang, Xie-Tong Wang, Rui-Hua Liu, et al. Dydrogesterone has no effect on uterine fibroids when used to prevent miscarriage in pregnant women with uterine fibroids [J]. Ginekologia Polska, 2017, 88(12): 679-685
- [8] Heo JY, Yi H, Fava M, et al. Agoraphobia and Follicle-Stimulating Hormone Levels between Tamoxifen and Goserelin versus Tamoxifen Alone in Premenopausal Hormone Receptor-Positive Breast Cancer: A 12-Month Prospective Randomized Study [J]. Psychiatry Investig, 2017, 14(4): 491-498
- [9] 谢幸, 苟文丽. 妇产科学 [M]. 第 8 版. 北京: 人民卫生出版社, 2013: 345-347
- [10] Dominic Byrne, Tamara Curnow, Paul Smith, et al. Laparoscopic excision of deep rectovaginal endometriosis in BSGE endometriosis centres: A multicentre prospective cohort study[J]. Bmj Open, 2018, 8(4): e018924
- [11] Victor Desplats, René-Louis Vitte, Joseph du Cheyron, et al. Preoperative rectosigmoid endoscopic ultrasonography predicts the need for bowel resection in endometriosis[J]. World J Gastroenterol, 2019, 25(6): 696-706
- [12] Surrey E, Taylor HS, Giudice L, et al. Long-Term Outcomes of Elagolix in Women With Endometriosis: Results From Two Extension Studies[J]. Obstet Gynecol, 2018, 132(1): 147-160
- [13] Maignien C, Santulli P, Gayet V, et al. Prognostic factors for assisted reproductive technology in women with endometriosis-related infertility[J]. Am J Obstet Gynecol, 2017, 216(3): 280.e1-280.e9
- [14] Gemmell LC, Webster KE, Kirtley S, et al. The management of menopause in women with a history of endometriosis: A systematic review[J]. Human Reproduction Update, 2017, 23(4): 1-20
- [15] Mina Jafarabadi, Mojdeh Salehnia, Rana Sadafi. Evaluation of two endometriosis models by transplantation of human endometrial tissue fragments and human endometrial mesenchymal cells [J]. Intern J Reprod Biomed, 2017, 15(1): 21-32
- [16] Philip C Logan, Pamela Yango, Nam D Tran. Endometrial Stromal and Epithelial Cells Exhibit Unique Aberrant Molecular Defects in Patients With Endometriosis[J]. Reprod Sci, 25(1): 140-159
- [17] Xu X, Li Z, Liu J, et al. MicroRNA expression profiling in endometriosis-associated infertility and its relationship with endometrial receptivity evaluated by ultrasound [J]. J Xray Sci Technol, 2017, 25(3): 523-532
- [18] Carneiro MM, Costa LMP, Ávila ID. To operate or not to operate on women with deep infiltrating endometriosis (DIE) before in vitro fertilization (IVF)[J]. JBRA Assist Reprod, 2017, 21(2): 120-125
- [19] Fuminori Taniguchi. New knowledge and insights about the malignant transformation of endometriosis: Malignant change of endometriosis[J]. J Obstet Gynaecol Res, 2017, 43(7): 1093-1100
- [20] Yasaman Samadieh, Raha Favaedi, Fariba Ramezani, et al. Epigenetic Dynamics of HOXA10 Gene in Infertile Women With Endometriosis[J]. Reprod Sci, 2019, 26(1): 88-96
- [21] Reka Brubel, Attila Bokor, Akos Pohl, et al. Serum galectin-9 as a noninvasive biomarker for the detection of endometriosis and pelvic pain or infertility-related gynecologic disorders [J]. Fertility Sterility, 2017, 108(6): 1016-1025
- [22] 任红娟, 王学博, 孙丽. 地屈孕酮联合芳香化酶抑制剂治疗子宫内膜异位症的临床效果及对血清 CA125、MMP-3、VEGF 的影响 [J]. 中国计划生育学杂志, 2018, 26(11): 1044-1047
- [23] Howell A, Ashcroft L, Fallowfield L, et al. RAZOR: a phase II open randomized trial of screening plus goserelin and raloxifene versus screening alone in premenopausal women at increased risk of breast cancer[J]. Cancer Epidemiol Biomarkers Prev, 2017, 27(1): 58-66
- [24] Metrics. Bicalutamide/goserelin [J]. Reactions Weekly, 2017, 1646(1): 69-69
- [25] Mingde Zang, Lei Hu, Baogui Zhang, et al. Luteolin suppresses angiogenesis and vasculogenic mimicry formation through inhibiting Notch1-VEGF signaling in gastric cancer [J]. Biochem Biophys Res Commun, 2017, 490(3): 913-919
- [26] Beata Kotowicz, Malgorzata Fuksiewicz, Joanna Jonska-Gmyrek, et al. Clinical significance of pretreatment serum levels of VEGF and its receptors, IL- 8, and their prognostic value in type I and II endometrial cancer patients[J]. Plos One, 2017, 12(10): e0184576
- [27] Etsuko Miyagi, Yasuyo Maruyama, Tae Mogami, et al. Comparison of plasma amino acid profile-based index and CA125 in the diagnosis of epithelial ovarian cancers and borderline malignant tumors[J]. Inter J Clin Oncol, 2017, 22(1): 118-125
- [28] Suher O Abu Hassan, Dorte L Nielsen, Malgorzata K Tuxen, et al. Performance of seven criteria to assess CA125 increments among ovarian cancer patients monitored during first-line chemotherapy and the post-therapy follow-up period [J]. Future Science Oa, 2017, 3(3): FSO216
- [29] 胡艳荣. 地屈孕酮联合来曲唑对子宫内膜异位症患者 E2、VEGF 及 CA125 水平的影响[J]. 西藏医药, 2017, 38(5): 39-41
- [30] 梁小玲, 林文英, 刘琼珊, 等. 子宫内膜异位症患者腹腔液中血管内皮生长因子测定及其相关性研究[J]. 白求恩医学杂志, 2017, 15(6): 712-713
- [31] 高永彬, 张凌云, 刘颖. 消癥丸联合米非司酮改善子宫内膜异位症痛经的临床效果及对血清 ICAM-1、MMP-9、LXA4 水平的影响[J]. 国际医药卫生导报, 2019, 25(5): 754-758