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醋酸亮丙瑞林对子宫内膜异位症患者血清雌二醇、孕酮及黄体生成素水平的影响*

王 磊[1] 孙海茹[1△] 孙丽妍[1] 冀雪霞[1] 杨 静[2]

（1 衡水市人民医院生殖医学科 河北 衡水 053000；2 河北医科大学第二医院内科 河北 石家庄 050005）

摘要 目的：研究醋酸亮丙瑞林对子宫内膜异位症患者血清雌二醇、孕酮及黄体生成素水平的影响。**方法：**选取2016年10月至2017年9月我院收治的84例子宫内膜异位症患者，根据患者入院顺序分为观察组和对照组，每组42例。观察组使用醋酸亮丙瑞林治疗，对照组使用炔雌醇环丙孕酮片。比较两组患者的临床疗效，治疗前后痛经评分、血清雌二醇、孕酮、黄体生成素、TGF-β、IL-4、IL-10、IL-17水平的班花及不良反应的发生情况。**结果：**治疗后，观察组临床总有效率显著高于对照组 [90.48%(38/42) vs. 64.29%(27/42)](P<0.05)。两组患者治疗后痛经评分、雌二醇、孕酮、黄体生成素、TGF-β、IL-4及IL-10水平均较治疗前显著降低(P<0.05)，且观察组以上指标均明显低于对照组(P<0.05)。两组患者治疗后血清IL-17水平及不良反应发生率与治疗前相比均无明显差异(P>0.05)。**结论：**与炔雌醇环丙孕酮片相比，醋酸亮丙瑞林能有效提高子宫内膜异位症患者的临床疗效，降低其血清雌二醇、孕酮及黄体生成素水平，改善患者的痛经情况，且安全性较高。

关键词：醋酸亮丙瑞林；子宫内膜异位症；血清雌二醇；孕酮；黄体生成素

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Efficacy of Leuprolide Acetate in the Treatment of Patients with Endometriosis and Its Effects on the Serum Estradiol, Progesterone and Luteinizing Hormone Levels*

WANG Lei[1], SUN Hai-ru[1△], SUN Li-yan[1], JI Xue-xia[1], YANG Jing[2]

(1 Department of Reproductive Medicine,Hengshui People's Hospital, Hengshui, Hebei, 053000, China;

2 Department of Medicine, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, 050005, China)

ABSTRACT Objective: To study the effects of leuprolide acetate on the serum estradiol, progesterone and luteinizing hormone levels in patients with endometriosis. **Methods:** Eighty-four patients with endometriosis admitted in our hospital from August 2015 to July 2016 were enrolled. The patients were divided into the observation group and the control group according to the patient admission order, with 42 cases in each group. The observation group was treated with leuprolide acetate, and the control group was treated with ethinyl estradiol cyproterone tablets. The clinical efficacy, incidence of dysmenorrhea, changes of serum estradiol, progesterone, luteinizing hormone, TGF-b, IL-4, IL-10, IL-17 levels before and after treatment and incidnece of adverse reactionswere compared Between two groups. **Results:** After treatment, the total clinical effective rate of observation group was significantly higher than that of the control group [90.48% (38/42) vs. 64.29% (27/42)] (P<0.05). The dysmenorrhea scores, estradiol, progesterone, luteinizing hormone, TGF-β, IL-4 and IL-10 levels of both groups were significantly lower than those before treatment (P<0.05), and the above indicators were obviously lower in the observation group lower than those of the control group (P<0.05). There was no significant difference in the serum IL-17 levels and incidence of adverse reactions between the two groups after treatment (P>0.05). **Conclusion:** Compared with ethinyl estradiol cyproterone tablets, leuprolide acetate can effectively improve the clinical efficacy of patients with endometriosis, reduce the serum estradiol, progesterone and luteinizing hormone levels, improve patients' condition of dysmenorrhea with high safety.

Key words: Leuprolide acetate; Endometriosis; Serum estradiol; Progesterone; Luteinizing hormone

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前言

子宫内膜异位症是临床上较为常见的妇科疾病，主要表现为患者子宫腔之外的部位如横膈、腹股沟等出现子宫内膜组织，大部分发生在盆腔中生殖器内及有关器官腹膜面上，伴有包块和结节形成，是导致患者不孕和疼痛的重要因素[1]。子宫内

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作者简介：王磊(1987-)，女，本科，主治医师，研究方向：主要从事妇科内分泌、促排卵治疗、输卵管造影、复发性流产、辅助生殖技术方向研究

△ 通讯作者：孙海茹，女，医学硕士，副主任医师，主要从事生殖医学临床研究，电话：18732852345，E-mail：wangleileiyx2017@qq.com

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膜异位症在育龄女性中的发病率达 15%,在盆腔疼痛的育龄女性和青春期女性中,大约有 55%的患者合并子宫内膜异位症[2]。子宫内膜异位症的治疗一直存在难度,目前手术治疗仍为首选,但有研究表明保守性手术治疗难以彻底清除病灶,子宫内膜异位症的复发率极高,增加了患者痛苦和后续治疗的难度。

为降低复发率,临床一般在保守性手术治疗后再予以药物治疗[3]。近年来,促性腺激素释放激素激动药治疗子宫内膜异位症获得了良好的临床疗效[4]。醋酸亮丙瑞林也被称之为促性腺激素释放激素,生物活性较高,在刺激垂体分泌促性腺激素后,可促使生殖器增加类固醇的合成[5]。为给临床治疗子宫内膜异位症提供可借鉴之处,本研究主要探讨了醋酸亮丙瑞林治疗子宫内膜异位症患者的临床疗效及其对患者血清雌二醇、孕酮及黄体生成素水平的影响。

1 资料与方法

1.1 临床资料

选取 2016 年 10 月 ~2017 年 9 月我院收治的子宫内膜异位症患者 84 例。纳入标准:① 通过传统开腹手术或腹腔镜病理被诊断为子宫内膜异位症;② 通过妇科及 B 超检查发现盆腔包块;③ 存在腹泻、腹痛、便秘、直肠痛、周期性直肠出血、性交痛、腰骶疼痛、痛经症状中的 1 项或超过 1 项;④ 对本次研究中的药物无过敏史。排除标准:① 孕妇、哺乳期妇女;② 近 3 个月内经孕三烯酮、促性腺激素释放激素激动药、孕激素等激素类药物治疗;③ 肾、肝、心等疾病者;④ 存在异常性器官出血但并没有通过确诊者。本研究已得到患者及家属同意,同时经我院伦理委员会批准。根据入院顺序分为观察组(42 例)和对照组(42 例)。观察组患者年龄为 23~35 岁,平均(27.87± 1.04)岁;病程为 8~89 个月,平均(45.24± 7.05)个月;孕产次为 1.3~3.2 次,平均(2.43± 0.21)次;月经周期为 26.3~29.1d,平均(27.83± 0.32)d;病理类型:13 例为子宫直肠窝包块、8 例为双侧卵巢巧克力囊肿、21 例属于单侧卵巢巧克力囊肿。对照组患者年龄为 24~36 岁,平均(27.92± 1.08)岁;病程为 9~91 个月,平均(46.01± 7.11)个月;孕产次为 1.4~3.3 次,平均(2.45± 0.24)次;月经周期为 26.5~29.8d,平均(27.87± 0.35)d;病理类型:12 例为子宫直肠窝包块、10 例为双侧卵巢巧克力囊肿、20 例属于单侧卵巢巧克力囊肿。两组患者的一般临床资料比较差异无明显统计学意义(P>0.05),具有可比性。

1.2 治疗方法

观察组采取醋酸亮丙瑞林(生产厂家:北京博恩特药业有限公司,规格:3.75 mg,生产批号:20160214)完成治疗,在患者月经周期开始的第 1~5 天开展第 1 次给药,3.75 mg/ 次,在臀部、腹部或臂部处注射,随之为每 4 周注射 1 次,每次注射为 1 个疗程,连续治疗 4 个疗程。对照组采取炔雌醇环丙孕酮片(生产厂家:德国 Schering GmbH & Co. Produktions KG,规格:2mg:0.035 mg× 21 片 / 盒,生产批号:20160402)完成治疗,给药方式为口服,1 片 / 天,在连续治疗 3 周后停药 1 周作为 1 个治疗疗程,均需治疗 4 个疗程。

1.3 观察指标

临床疗效评价:治疗后,盆腔包块等体征得以改善,临床症状均消失则为痊愈;治疗后,盆腔包块缩小范围 >50%,但仍然存在局部体征,临床症状基本消失为显效;治疗后,盆腔包块缩小范围为 30%~50%,停药 3 个月内症状未得到加重,症状得以缓解为有效;临床症状未改善乃至加重为无效[7]。总有效 = 痊愈 + 显效 + 有效。

痛经评分:按照疼痛给患者学习、工作所带来的影响及镇痛药物的使用算出痛经评分,标准如下:工作学习效率低下,疼痛为轻度则计为 1 分;疼痛为中度,需静卧,难以工作则计为 2 分;卧床休息的时间≥ 1 天,疼痛为重度则计为 3 分。服用镇痛药 1 d 则计为 1 分,2 d 计为 2 分,3 d 计为 3 分。疼痛评分和用药评分总和则为痛经评分。

抽取患者 5 mL 的静脉血,转速 4000 r/min,离心 5 min,置于罗氏电化学发光检测仪,采取电化学发光法检测血清雌二醇、孕酮、黄体生成素水平。使用酶联免疫吸附法检测转化生子因子 -β(TGF-β)、白介素 -4(IL-4)、白介素 -10(IL-10)、白介素 -17(IL-17)水平,按照说明书开展本次操作。通过用药半个月阴道出血、多汗、潮热分析不良反应。

1.4 统计学处理

采用 SPSS11.5 软件包处理本次实验数据,计量资料以($\bar{x}$± s)表示,组间比较采用 t 检验,计数资料以[例(%)]表示,组间比较行 x^2 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组临床疗效的比较

治疗后,观察组总有效率显著高于对照组[90.48%(38/42) vs. 64.29%(27/42)](P<0.05),见表 1。

表 1 两组临床疗效比较[例(%)]

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

Group	Case	Cure	Effective	Valid	Invalid	Total effective
Observation group	42	18(42.86)	12(28.57)	8(19.05)	4(9.52)	38(90.48)*
Control group	42	4(9.52)	6(14.29)	17(40.48)	15(35.71)	27(64.29)

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

2.2 两组治疗前后痛经评分比较

治疗前,两组痛经评分比较无明显差异(P>0.05)。治疗后,两组患者痛经评分均明显低于治疗前(P<0.05),且观察组的痛经评分明显低于对照组(P<0.05),见表 2。

2.3 两组治疗前后血清雌二醇、孕酮及黄体生成素水平比较

两组患者治疗前的血清雌二醇、孕酮及黄体生成素水平比较无显著差异(P>0.05),两组患者治疗后的血清雌二醇、孕酮及黄体生成素水平均显著低于治疗前(P<0.05),且观察组血清雌二醇、孕酮及黄体生成素显著低于对照组(P<0.05),见表 3。

表 2 两组治疗前后痛经评分比较($\bar{x}\pm s$)

Table 2 Comparison of the dysmenorrhea score before and after treatment between two groups($\bar{x}\pm s$)

Item	Observation group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
Dysmenorrhea score	4.72± 0.41	1.63± 0.14*#	4.69± 0.39	3.26± 0.34*

Note: Compared with before treatment,*P<0.05; Compared with control group after treatment, #P<0.05.

表 3 两组患者治疗前后血清雌二醇、孕酮及黄体生成素水平比较($\bar{x}\pm s$)

Table 3 Comparison of the serum estradiol, progesterone and luteinizing hormone levels before and after treatment between two group($\bar{x}\pm s$)

Item	Observation group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
Serum estradiol(pmol/L)	191.45± 18.35	73.24± 7.15*#	191.48± 18.39	115.43± 13.76*
Progesteroe(nmol/L)	6.92± 0.68	3.02± 0.28*#	6.91± 0.65	4.87± 0.49*
Luteinizing hormone (U/L)	7.82± 0.73	4.04± 0.41*#	7.81± 0.74	5.19± 0.53*

Note: Compared with before treatment,*P<0.05; Compared with control group after treatment, #P<0.05.

2.4 两组患者治疗前后血清细胞因子水平比较

治疗前,两组患者血清 TGF-β、IL-4、IL-10、IL-17 水平比较无显著差异(P>0.05),治疗后,两组患者血清 IL-17 水平和治疗前相比均无明显差异(P>0.05),血清 TGF-β、IL-4、IL-10 水平均显著低于治疗前(P<0.05),且观察组血清 TGF-β、IL-4、IL-10 水平均明显低于对照组(P<0.05),见表 4。

表 4 两组患者治疗前后血清细胞因子水平比较($\bar{x}\pm s$)

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

	Observation group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
TGF-β(μg/L)	25.78± 2.51	10.34± 1.25*#	26.03± 2.45	15.98± 1.57*
Il-4(ng/L)	113.24± 1.32	41.56± 4.24*#	113.62± 1.36	93.76± 9.25*
IL-10(ng/L)	323.87± 31.56	163.56± 14.58*#	324.06± 31.62	251.34± 22.64*
IL-17(ng/L)	92.34± 9.46	91.59± 9.48	92.38± 9.51	91.28± 9.43

Note: Compared with before treatment,*P<0.05; Compared with control group after treatment, #P<0.05.

2.5 两组不良反应发生情况的比较

观察组和对照组的不良反应率比较差异无统计学意义(P>0.05),见表 5。

表 5 两组患者不良反应发生情况比较[例(%)]

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

Groups	Case	Medication half a month vaginal bleeding	Sweating	Hot flashes	Total
Observation group	42	2(4.76)	4(9.52)	1(2.38)	7(16.67)
Control group	42	1(2.38)	3(7.14)	2(4.76)	6(14.29)

3 讨论

子宫内膜异位症在育龄女性中属于一种较为常见的疾病,发病人群以 30~40 岁为主,临床症状主要表现为性交痛、痛经、月经失调、不孕。近年来,此病的发病率呈现出逐年增加的趋势[8]。关于子宫内膜异位症的发生机制目前尚未完全明确,有研究者提出此病为性激素依赖性疾病,和卵巢分泌激素有着密切的关联性,在临床治疗中主要以降低患者雌激素水平的激素类药物为主[10]。虽然经避孕药治疗可通过负反馈作用阻碍患者排卵,进而降低经血倒流及月经量,但相关研究者提出避孕药的使用尽可短时间内使异位的内膜出现萎缩,难以彻底清除异位内膜,在盆腔粘连中难以发挥临床疗效[11,12],不适宜于有生育要求的患者。且在子宫内膜异位症患者中,经保守手术治疗依然存在较高的复发率。一般情况而言,手术治疗后未加以任何后续药物治疗,在术后 1 年此病的复发率高达 40%[9]。

醋酸亮丙瑞林也被称之为促性腺激素释放激素,在视丘下部所出现的黄体生成激素释放激素类似物,生物活性较高,在刺激垂体分泌促性腺激素后,能促使生殖器增加类固醇的合成[13-15]。长时间大量使用此类药物能阻碍垂体分泌促性腺激素,阻碍睾丸或卵巢生成甾类物质,因此在早熟、前列腺癌、子宫内膜异位症、子宫肌瘤等性激素依赖性疾病治疗中此类药物已得到广泛应用[16]。值得注意的是,醋酸亮丙瑞林有着生物不稳定性,限制了其用药途径,主要是因为进入人体内受到消化酶降解,在穿透小肠上皮方面的能量较差,较为常见的给药方式是经皮下注

射[17,18]。在血浆中,醋酸亮丙瑞林的半衰期相对较短,因此在持续、长期给药的患者中应通过可降解的聚合物作为基质,把半衰期较短的药物制作为能储存的缓释微球制剂, 延长起效时间,同时增强药物的安全性、稳定性[19-21]。

相关研究显示醋酸亮丙瑞林通过调节垂体分泌功能后发挥治疗作用,大量降低卵巢分泌甾类物质的产生,进而缩小患者子宫内膜病灶,从而使临床症状得到缓解[22,23]。本研究结果表明子宫内膜异位症患者经醋酸亮丙瑞林治疗后,其临床有效率显著高于炔雌醇环丙孕酮片治疗者,提示醋酸亮丙瑞林能有效缓解患者临床症状。此外,醋酸亮丙瑞林治疗的患者血清雌二醇、孕酮、黄体生成素水平显著降低,且效果优于炔雌醇环丙孕酮片治疗者,同时患者血清 TGF-β、IL-4、IL-10 水平明显降低,效果也优于炔雌醇环丙孕酮片治疗者。究其原因主要是因为醋酸亮丙瑞林能显著降低雌激素水平,进而有效缓解患者的疼痛感,减轻炎症反应[24,25]。此外,醋酸亮丙瑞林可有效缓解患者的痛经症状,其安全性和炔雌醇环丙孕酮片相当,仅有少数患者发生用药半个月阴道出血、多汗、潮热症状,不良反应均属于轻微型,并不影响患者的月经复潮时间。

总之,与炔雌醇环丙孕酮片相比,醋酸亮丙瑞林能有效提高子宫内膜异位症患者的临床疗效,降低其血清雌二醇、孕酮及黄体生成素水平,改善患者的痛经情况,且安全性较高。

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