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达英-35 治疗多囊卵巢综合征合并不孕症的疗效及对患者血清 FSH、LH、TOS、TAS 水平的影响 *

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摘要 目的:研究达英-35 治疗多囊卵巢综合征合并不孕症的疗效及对患者血清卵泡刺激素(FSH)、促黄体生成素(LH)、总氧化态(TOS)、抗氧化态(TAS)水平的影响。**方法:**选取 2015 年 8 月至 2016 年 7 月我院收治的 76 例多囊卵巢综合征合并不孕症患者,根据随机数字法分为观察组和对照组,38 例每组。对照组使用克罗米芬,观察组在此基础上加以达英-35。比较两组患者临床疗效,治疗前后血清 FSH、LH、TOS、TAS 水平、卵泡数、卵巢体积、体重指数的变化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[89.47%(34/38) vs. 60.53%(23/38)]($P<0.05$);两组患者的血清 FSH、LH、TOS 水平、卵泡数、卵巢体积、体重指数明显减少较治疗前均显著降低($P<0.05$),而血清 TAS 水平较治疗前显著上升($P<0.05$),且观察组的血清 FSH、LH、TAS 水平明显低于对照组($P<0.05$),而血清 TAS 水平显著高于对照组($P<0.05$)。观察组和对照组的不良反应的发生率比较无明显差异($P>0.05$)。**结论:**达英-35 治疗多囊卵巢综合征合并不孕症患者能有效提高患者的临床疗效和改善其临床症状,且安全性高,这可能与有效改善患者血清 FSH、LH、TOS、TAS 水平有关。

关键词:达英-35; 多囊卵巢综合征; 不孕症

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Clinical Efficacy of Daying-35 in the Treatment of Polycystic Ovary Syndrome Complicated with Infertility and Its Effect on the Serum FSH, LH, TOS and TAS Levels*

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ABSTRACT Objective: To study the application of DaYing-35 in the treatment of polycystic ovary syndrome with infertility and its effects on the serum follicle stimulating hormone (FSH), luteinizing hormone (LH), total oxidative state (TOS), antioxidant State (TAS) levels. **Methods:** 76 patients with polycystic ovary syndrome complicated with infertility were enrolled in our hospital from August 2015 to July 2016. According to the random number method, those patients were divided into the observation group and the control group. The control group was given clomiphene, while the observation group was given DaYing-35 on this basis of control group. The changes of serum levels of FSH, LH, TOS, TAS, follicle count, ovarian volume, body mass index before and after treatment and the incidence of adverse reaction were compared between the two groups. **Results:** After treatment, the total effective rate of observation group was significantly higher than that of the control group [89.47% (34/38) vs. 60.53% (23/38)] ($P<0.05$). After treatment, the levels of FSH, LH, TOS, number of follicles, ovarian volume and body mass index of both groups were significantly decreased ($P<0.05$), and the levels of TAS, of both groups were significantly increased ($P<0.05$). Compared with the control group, the levels of FSH, LH, TOS, follicle count, ovarian volume and body mass index in the observation group were obviously lower ($P<0.05$), and the level of TAS was significantly higher ($P<0.05$). There was no significant difference in the adverse reaction rate between the two groups ($P>0.05$). **Conclusion:** Daying-35 can effectively enhance the clinical efficacy and improve the clinical symptoms in the treatment of polycystic ovary syndrome complicated with infertility, it might be related to the improvement of serum FSH, LH, TOS, TAS levels.

Key words: Da Ying -35; Polycystic ovary syndrome; Infertility

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前言

多囊卵巢综合征属于女性生殖系统较为常见的一种内分泌

紊乱性疾病,主要表现为高雄激素血症、不孕、闭经、月经稀少、肥胖、高胰岛素血症等,常常伴有糖耐量异常、高胰岛素血症、胰岛素抵抗等异常代谢,也是无排卵性不孕症的一大

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重要因素^[1]。关于多囊卵巢综合征的病因目前尚未完全明确,已有研究显示此病的病因和胰岛素抵抗有关^[2]。目前,多囊卵巢综合征合并不孕症以药物治疗为主,其中达英-35是其常用药,主要成分包括炔雌醇 35~50 ug+ 醋酸环丙孕酮 2 mg,能有效改善青春期内分泌-垂体调节中枢渐渐成熟过程中所发生的痤疮、多毛、月经不规律等症状^[3,4]。为给临床治疗多囊卵巢综合征合并不孕症提供更多的参考之处,本研究主要探讨了达英-35治疗多囊卵巢综合征合并不孕症的疗效及对血清卵泡刺激素(FSH)、促黄体生成素(LH)、总氧化态(TOS)、抗氧化态(TAS)水平的影响,结果报道如下。

1 资料与方法

1.1 临床资料

选取 2015 年 8 月至 2016 年 7 月我院收治的 76 例多囊卵巢综合征合并不孕症患者,纳入标准:① 无排卵或排卵稀少;② 雄激素水平较高;③ 通过 B 超检查提示任意探测截面上 >12 个 2~9 mm 的卵泡或单侧卵巢体积超过 10 mL;④ 患者自愿加入本次研究。排除标准:① 全身性疾病者;② 精神异常难以合作者;③ 其他内分泌疾病者。本次研究已获得我院伦理委员会批准实施,同时取得患者及其家属的知情同意。

根据随机数字法将所有患者分为观察组和对照组,每组 38 例。观察组年龄为 22~39 岁,平均(28.28±2.74)岁;病程为 1~5 年,平均(3.03±0.31)年;临床症状:闭经者 7 例,经量稀少者 22 例,多毛者 1 例,痤疮者 8 例。对照组年龄为 23~38 岁,平均(28.31±2.79)岁;病程为 1~6 年,平均(3.06±0.34)年;临床症状:闭经者 6 例,经量稀少者 24 例,多毛者 2 例,痤疮者 6 例。两组患者年龄、病程等方面比较差异无明显统计学意义($P>0.05$)。

1.2 治疗方法

对照组使用克罗米芬(生产厂家:上海衡山药业有限公司,规格:50 mg,生产批号:20150403)完成治疗,在月经周期第 5 天使用克罗米芬,100 mg/d,连续治疗 5d,借助 B 超于月经周期第 10 天起检测内膜厚度及卵泡大小。当卵泡直径 ≥ 18 mm 时则需肌肉注射 1000U 的人绒毛膜促性腺激素(HCG),并指导

同房,在注射 HCG 36h 后通过 B 超监测是否排卵。若存在排卵则需定期予以黄体支持治疗,若无排卵并出现卵泡未破裂综合征,则需放弃本周期。在排卵后 14 天监测尿早早孕确定是否妊娠。观察组在月经周期第 2~4 天测定血清 FSH、LH 水平,抽血后第 5 天在对照组基础上加以达英-35 (生产厂家:Schering GmbH & Co. Produktions KG, 规格:2 mg : 0.035 mg×21 片/盒,生产批号:20150321)完成治疗,1 片/次,工需治疗 21 天,连续治疗 3 个月,在第 4 个月月经第 2~4 天检查血激素水平。肥胖者需适当运动和控制饮食。

1.3 观察指标

临床疗效评价:治疗后,体征及临床症状得到明显改善,血脂、血糖、激素水平显著改善,均接近正常水平或恢复至正常水平则为显效;治疗后,体征及临床症状获得有效改善,激素水平明显改善,然而并未完全恢复则为有效;治疗后,体征及临床症状并未发生变化,血脂、血糖、激素水平等无变化甚至为进行性加重则为无效^[5]。

抽取两组患者治疗前后 5 mL 的静脉血,测量卵泡刺激素(FSH)、促黄体生成素(LH)、总氧化态(TOS)、抗氧化态(TAS),采取双抗体夹心法检测 FSH 水平,使用酶联免疫技术检测 LH 水平,使用日本 HITACHI 全自动生化分析仪、二甲酚橙法检测 TOS 水平,ABTS 法检测 TAS 法。比较两组患者治疗前后卵泡数、卵巢体积、体重指数各项指标变化,通过 B 超来测定患者卵泡数、卵巢体积。分析两组患者不良反应。

1.4 统计学处理

选取 spss11.5 软件包对本次实验数据进行统计学分析,计量资料以($\bar{x}\pm s$)表示,组间比较采用 t 检验,计数资料以[例(%)]表示,组间比较采用 χ^2 检验,以 $P<0.05$ 为差异存在统计学意义。

2 结果

2.1 两组患者临床疗效的比较

治疗后,观察组临床总有效率显著高于对照组[89.47%(34/38) vs. 60.53%(23/38)]($P<0.05$),见表 1。

表 1 两组患者临床疗效的比较[例(%)]

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

Groups	Case	Effective	Valid	Invalid	Total efficacy
Observation group	38	25(65.79)	9(23.68)	4(10.53)	34(89.47)*
Control group	38	6(15.79)	17(44.74)	15(39.47)	23(60.53)

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

2.2 两组患者治疗前后血清 FSH、LH、TOS、TAS 水平的比较

治疗前,两组患者血清 FSH、LH、TOS、TAS 水平比较差异无统计学意义($P>0.05$),治疗后,两组患者的血清 FSH、LH、TOS 水平较治疗前显著降低($P<0.05$),而血清 TAS 水平较治疗前显著上升($P<0.05$),与对照组相比,观察组的血清 FSH、LH、TOS 水平较低($P<0.05$),血清 TAS 水平较高($P<0.05$),见表 2。

2.3 两组患者治疗前后卵泡数、卵巢体积、体重指数的比较

治疗前,两组患者卵泡数、卵巢体积、体重指数比较差异无统计学意义($P>0.05$)。治疗后,两组患者的卵泡数、卵巢体积、体

重指数均较治疗前明显减少($P<0.05$),且观察组的卵泡数、卵巢体积、体重指数均明显少于对照组($P<0.05$),见表 3。

2.4 两组不良反应发生情况的比较

对照组中,有 2 例患者伴有下腹部痛,3 例出现肿胀;观察组中,1 例患者出现头痛,1 例发生乳房痛,2 例出现恶心、呕吐,3 例肿胀。观察组和对照组的不良反应率比较差异无统计学意义($P>0.05$)。

3 讨论

表 2 两组患者治疗前后血清 FSH、LH、TOS、TAS 水平的比较($\bar{x}\pm s$)Table 2 Comparison of the serum FSH, LH, TOS, TAS levels between two groups before and after treatment($\bar{x}\pm s$)

Groups	Case	Time	FSH(IU/L)	LH(IU/L)	TOS(mmol H ₂ O ₂ equiv/L)	TAS(mmol trolox equiv/L)
Observation group	38	Before treatment	5.82±0.56	15.24±1.58	17.94±1.86	1.38±0.12
		After treatment	3.04±0.31**	6.31±0.67**	14.87±1.43**	1.72±0.18**
Control group	38	Before treatment	5.83±0.57	15.31±1.59	18.02±1.84	1.39±0.14
		After treatment	4.28±0.43*	8.75±0.87*	16.58±1.62*	1.53±0.16*

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

表 3 两组患者治疗前后卵泡数、卵巢体积、体重指数的比较($\bar{x}\pm s$)

Table 3 Comparison of the follicle count, ovarian volume, body mass index between two groups of patients before and after treatment

Groups	Case	Time	Follicle count(Piece)	Ovarian volume(mm ³)	BMI(kg/m ²)
Observation	38	Before treatment	26.48±2.73	9.87±0.93	28.43±2.57
		After treatment	7.46±0.73	7.02±0.75	22.26±2.04
Control	38	Before treatment	26.51±2.76	9.91±0.94	28.51±2.54
		After treatment	13.87±1.65	8.51±0.86	25.87±2.73

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

在育龄期妇女中,多囊卵巢综合征属于较为常见的一种内分泌系统疾病,临床主要表现为闭经、月经稀少、排卵异常、高雄激素血症等^[6,7]。伴随着多囊卵巢综合征的发生及发展,再加之糖尿病、冠心病、子宫内膜癌的逐渐形成,极易引发不孕症^[8,9]。多囊卵巢综合征患者不孕症属于较为常见的并发症,给育龄女性的身心健康带来严重影响^[10,11]。可见,为改善多囊卵巢综合征合并不孕症者的生育要求,探讨其治疗措施显得尤为重要。

达英-35 作为口服避孕药,主要包括炔雌醇和醋酸环丙孕酮,于原始卵泡期在促进卵泡生长方面游离雄性激素浓度发挥着极其重要的作用,形成多滤泡卵巢^[12,13]。然而,在窦卵泡及以后的发育阶段中,在血中的高浓度游离雄激素会阻碍卵泡的发育^[14,15]。达英-35 可阻碍 5 α -还原酶活性,能增加清除睾酮的速度,在阻碍下丘脑分泌 GnRH 中,能降低垂体分泌 LH 量,减少卵巢分泌的性激素,有利于月经处于规律状态^[16,17]。此外,达英-35 能阻碍雄激素分泌,在阻碍雄激素受体结合和内源性雄激素过程中,能降低患者体内雄激素水平^[18]。

此病的发病机制在目前尚未得到完全明确,大部分研究者提出此病的发生和下丘脑-垂体-卵巢调节紊乱有关,属于全身性神经-内分泌-代谢反射异常的异质性综合征,下丘脑促性腺激素释放激素分泌的增加,会相应的增加垂体分泌的 LH 量,LH 过多会刺激卵泡膜细胞有过量的雄激素产生,因此,可通过血清学检测患者体内过高浓度水平的雄激素和 LH 浓度水平^[19,21]。多囊卵巢综合征合并不孕症者病情的发生发展和氧化应激状态存在着密切关联性,在指导临床疾病诊治中随时关注机体血清氧化应激状态显得尤为重要,多囊卵巢综合征合并不孕症的发生发展很大程度上和异常的过氧化-抗氧化防御系统有关,主要表现为过氧化物质 TOS 水平显著^[23,24]。相关研究显示多囊卵巢综合征合并不孕症者的血清 LH、TOS 水平相对高于健康人群,血清 TAS 水平相对低于健康人群,提

示二者联合检测能有效评价机体氧化应激状态,对健康和疾病状态做到明确区分,同时能评估多囊卵巢综合征合并不孕症的病情^[25,26]。

本研究结果显示,以达英-35 联合克罗米芬治疗的血清 FSH、LH、TOS 水平明显降低,TAS 水平有所升高,上述指标的改善效果优于单纯克罗米芬治疗者。究其原因可能是因为达英-35 中的醋酸环丙孕酮能在雄性激素靶器官上和雄性激素竞争受体,进而抑制雄激素受体复合物流入靶器官细胞细胞核,此外,此成分能阻碍垂体分泌促性腺激素,特别是 LH 的分泌,从中降低卵巢所分泌的雄激素水平^[27,28]。相关研究显示在多囊卵巢综合征合并不孕症患者中,卵泡数量和卵巢体积会因为抗苗勒管激素在循环血中的上升而显著增加^[29,30]。本研究结果显示通过对多囊卵巢综合征合并不孕症者予以达英-35 联合克罗米芬治疗后,患者的卵泡数、卵巢体积明显减少,临床有效率显著高于单纯克罗米芬治疗者,可能和达英-35 中的炔雌醇能在肝脏中可促使肝脏细胞的产生,同时分泌结合球蛋白,进而减少血中游离睾酮浓度水平,相应的降低雌性激素学效应有关。

总之,达英-35 治疗多囊卵巢综合征合并不孕症患者,能有效改善患者血清 FSH、LH、TOS、TAS 水平和临床症状,临床疗效良好。

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