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来曲唑联合妈富隆治疗多囊卵巢综合征患者的疗效探讨 *

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摘要 目的:探讨来曲唑联合妈富隆治疗多囊卵巢综合征患者的临床疗效。**方法:**选择 2015 年 12 月至 2017 年 12 月我院接诊的 90 例多囊卵巢综合征患者,通过随机数表法分为观察组(n=46)和对照组(n=44)。对照组给予妈富隆治疗,观察组联合来曲唑治疗。比较两组治疗前后血清卵泡刺激素(FSH)、黄体生成素(LH)、睾酮(T)、血清血管内皮生长因子(VEGF)、内皮抑素(ES)、肝细胞生长因子(HGF)、单核细胞趋化蛋白 -1(MCP-1)水平的变化和治疗后的临床疗效,并随访半年,记录排卵率和妊娠率。**结果:**治疗后,两组血清 FSH、LH、T、VEGF、ES、HGF、MCP-1 水平均较治疗前明显降低(P＜0.05),且观察组以上指标均明显低于对照组(P＜0.05);观察组临床总有效率[91.30% vs. 75.00%]、排卵率[78.26% vs. 36.96%]、妊娠率[59.09% vs. 5.91%]均明显高于对照组(P＜0.05)。**结论:**来曲唑联合妈富隆治疗多囊卵巢综合征的临床效果显著优于妈富隆单药治疗,其可有效改善患者内分泌,提高妊娠率,可能与降低血清 VEGF、ES、HGF、MCP-1 的表达相关。

关键词:多囊卵巢综合征;来曲唑;妈富隆;性激素

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Curative Efficacy of Letrozole Combined with Marvelon in the Treatment of Polycystic Ovary Syndrome*

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ABSTRACT Objective: To study the curative efficacy of letrozole combined with marvelon in treatment of polycystic ovary syndrome. **Methods:** 90 cases of patients with polycystic ovary syndrome who were treated from December 2015 to December 2017 in our hospital were selected. According to random number table, those patients were divided into the observation group (n=46) and the control group (n=44). The control group was treated with marvelon, while the observation group was combined with letrozole. The changes of serum follicle stimulating hormone(FSH), luteinizing hormone(LH), testosterone(T) and serum ascular endothelial growth factor(VEGF), endostatin(ES), hepatocyte growth factor(HGF) and monocyte chemoattractant protein 1(MCP-1) levels before and after treatment, clinical efficacy, ovulation rate and pregnancy rate after six months follow-up were compared between two groups. **Results:** After treatment, the serum FSH, LH, T, VEGF, ES, HGF and MCP-1 of both groups were significantly lower than those before treatment(P＜0.05), which were significantly lower in the observation group than those of the control group (P＜0.05); the total effective rate [91.30% vs. 75.00%], ovulation rate[78.26% vs. 36.96%] and pregnancy rate[59.09% vs. 5.91%]in the observation group were significantly higher than those of the control group(P＜0.05). **Conclusion:** Letrozole combined with marvelon was more effective for polycystic ovary syndrome than marvelon alone, which was helpful to improve the endocrine and increase the pregnancy rate, it's intrinsic mechanism may be related to the decrease of serum VEGF, ES, HGF and MCP-1 levels.

Key words: Polycystic ovary syndrome; Letrozole; Marvelon; Sex hormone

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前言

多囊卵巢综合征是育龄期女性中较为常见的一种内分泌疾病,该病的病因尚未明确阐明,主要症状以高雄激素、排卵障碍、卵巢多囊样改变等为主,且患者可伴有胰岛素抵抗、高胰岛素血症、多毛、肥胖、不孕等特征,83%左右的患者合并不孕[1]。该病的治疗目前多采用促排卵、降低雄激素及黄体生成素(LH)、并对胰岛素抵抗症状改善等方式。妈富隆是临床上常用促排卵药物,但若用药不当引发多胎、卵巢过度刺激综合征等并发症,可影响预后,且排卵率、妊娠率欠佳[2]。

芳香化酶抑制剂来曲唑是新一代促排卵药物，自从其2000年在氯米芬促排卵失败的多囊卵巢综合征患者中应用来曲唑

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并获得成功以来,临床学者们逐渐开始重视其促排卵效果[3]。近年来,国内外均有学者提出卵巢血管生成异常、内分泌紊乱、趋化因子表达异常等在多囊卵巢综合症的发生、发展中起着重要作用,而对血清血管内皮生长因子(VEGF)、内皮抑素(ES)、肝细胞生长因子(HGF)、单核细胞趋化蛋白 - 1(MCP-1)的检测有助于进一步评价临床疗效[4,5]。本研究主要探讨了来曲唑联合妈富隆的治疗多囊卵巢综合症患者的临床疗效。

1 资料与方法

1.1 一般资料

选择 2015 年 12 月至 2017 年 12 月我院接诊的 90 例多囊卵巢综合征患者作为本研究对象。纳入标准[6]:① 符合多囊卵巢综合征诊断标准;② 年龄≤ 40 岁,有生育要求;③ 男方生育功能正常;④ 知情同意此次研究,完成随访。排除标准[7]:① 近期服用过降压、降糖药、避孕药等激素类药物;② 由于其余原因所致的不孕;③ 合并心脑血管疾病、严重糖尿病、肝肾功能异常的患者;④ 对研究药物具有禁忌症。通过随机数表法将所有患者分为 2 组,观察组 46 例,年龄 23~38 岁,平均(31.42± 1.74)岁;不孕年限 1~7 年,平均(4.15± 0.83)年。对照组 44 例,年龄 24~37 岁,平均(31.56± 1.65)岁;不孕年限 1~8 年,平均(4.06± 0.89)年。两组一般资料比较差异均无统计学意义(P＞0.05),具有可比性。

1.2 治疗方法

对照组给予妈富隆 (规格:0.15 mg/30 μg/ 片, 厂家:N.V. Organon,国药准字 H20130491)治疗,于月经来潮第 3 d 口服,1 片 /d,连续用药 3 周。观察组联合来曲唑(规格:2.5 mg/ 片,厂家:Novartis Pharma Stein AG,国药准字)治疗,于月经来潮第 5 d 口服,1 片 /d,连续服用 5 d。

1.3 观察指标

1.3.1 血清性激素 于治疗前、后检测血清卵泡刺激素(FSH)、LH、睾酮(T)水平的变化,以电化学发光法,使用罗氏 E170 型电化学发光全自动免疫分析仪。

1.3.2 血清 VEGF、ES、HGF、MCP-1 于治疗前、后检测,检测方式均使用酶联免疫吸附法检测,试剂盒均购于美国 R&D 公司。

1.3.3 出院后随访 随访半年,记录排卵率、妊娠率。

1.4 疗效评价标准

显效:临床症状、体征完全消失,卵巢体积及形态得到正常恢复, 连续 2 个月以上有正常周期性排卵, 月经周期规律≥ 3 个月;有效:临床症状、体征有所改善,卵巢体积、形态缩小,月经周期规律≥ 3 个月,偶尔有排卵;无效:未达到上述标准,甚至恶化。以显效 + 有效为总有效率。

1.5 统计学分析

以 SPSS18.0 软件包处理,计量资料用均数± 标准差($\bar{x}$± s)表示,组间比较采用 t 检验,计数资料比较以 x^2 检验,以 P<0.05 表示差异具有统计学意义。

2 结果

2.1 两组治疗前后血清 FSH、LH、T 水平的比较

治疗后,观察组血清 FSH、LH、T 水平明显低于对照组(P＜0.05),见表 1。

表 1 两组治疗前后血清 FSH、LH、T 水平比较($\bar{x}$± s)

Table 1 Comparison of the serum FSH, LH, T levels before and after treatment between two groups($\bar{x}$± s)

Groups		FSH(IU/L)	LH(IU/L)	T(mmol/L)
Observation group(n=46)	Before treatment	7.86± 1.26	13.74± 2.03	1.74± 0.23
	After treatment	3.27± 0.52*#	6.85± 1.14*#	0.89± 0.10*#
Control group(n=44)	Before treatment	7.94± 1.22	13.81± 1.96	1.69± 0.26
	After treatment	5.15± 0.73*	9.34± 1.48*	1.25± 0.17*

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

2.2 两组治疗前后血清 VEGF、ES、HGF、MCP-1 水平的比较

治疗后, 观察组血清 VEGF、ES、HGF、MCP-1 水平均明显比对照组低(P＜0.05),见表 2。

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

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

Groups		VEGF(ng/L)	ES(μg/L)	HGF(ng/L)	MCP-1(μg/L)
Observation group (n=46)	Before treatment	112.73± 25.84	178.56± 24.23	574.34± 62.30	124.73± 24.50
	After treatment	56.34± 12.15*#	92.12± 17.30*#	217.23± 30.21*#	67.81± 15.24*#
Control group(n=44)	Before treatment	113.01± 25.34	179.32± 24.04	578.31± 61.72	125.01± 24.27
	After treatment	78.52± 17.32*	124.59± 19.45*	342.78± 35.67*	95.62± 17.50*

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

2.3 两组临床疗效的比较

治疗后,观察组临床疗效总有效率明显比对照组高(91.3% vs. 75%,P＜0.05),见表 3。

表 3 两组临床疗效比较[例(%)]

Table 3 Comparison of the clinical efficacy between two groups [n(%)]

Groups	Effective	Valid	Invalid	Total effective rate
Observation group(n=46)	26(56.52)	16(34.78)	4(8.70)	42(91.30)
Control group(n=44)	19(43.18)	14(31.82)	11(25.00)	33(75.00)

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

2.4 两组排卵率、妊娠率比较

观察组排卵率、妊娠率分别为 78.26%、36.96%，明显高于对照组(59.09%、15.91%，P＜0.05)，见表 4。

表 4 两组排卵率、妊娠率比较[例(%)]

Table 4 Comparison of the ovulation rate and pregnancy rate between two groups[n(%)]

Groups	Ovulation rate	Pregnancy rate
Observation group(n=46)	36(78.26)*	17(36.96)*
Control group(n=44)	26(59.09)	7(15.91)

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

3 讨论

育龄期女性多囊卵巢综合征的发病率大约在 5%~10%，且近年来呈逐渐升高的趋势，其所造成的不孕、闭经、月经稀少等，对患者及其家庭均造成较大痛苦[8]。该病的发病机制目前仍不明确，较多研究指出和和肾上腺功能异常、下丘脑 - 垂体 - 卵巢轴功能异常，致使内分泌功能紊乱等相关[9,10]。妈富隆是第三代甾体类短效口服避孕药，其具有较强的孕激素受体亲和力，目前临床上多用于调整月经周期、预防子宫内膜癌等疾病中。Leelaphiwat S 等[11]研究表明妈富隆可通过抑制 LH，降低 LH/FSH，减少卵巢激素的分泌。但也有较多研究显示仅口服妈富隆在排卵率、妊娠率上效果欠佳，且会增加多胎、卵巢过度刺激综合征等并发症的发生率[12,13]。

来曲唑是第三代非甾体类芳香化酶抑制剂，通过解除雌激素对下丘脑 / 垂体的反馈抑制作用，继而诱导卵泡生长发育，令保持宫颈粘液良好，利于精子通过。国外 Hassan A 等[14]研究显示来曲唑可同步内膜和胚胎之间的发育，令子宫内内膜充分生长，保持较好的厚度和形态，更有助于胚胎着床，且具有令人满意的排卵率、妊娠率，流产率更低。Chen Y 等[15]研究显示来曲唑无明显的抗雌激素样效果，且可促进单个优势卵泡成熟排卵，有助于避免卵巢过度刺激，预后更佳。本研究结果也显示联用来曲唑的患者在 FSH、LH、T 降低程度更加明显，临床疗效、排卵率、妊娠率相比于单独使用妈富隆患者的更具有优势，可能是由于联合用药可更明显改善患者性激素表达，进而获得更令人满意的临床疗效。Ma QW 等[16]研究也证实联合来曲唑治疗可提高促排卵药物的敏感性，进而改善预后。

VEGF 是一种高效的促血管生成因子，在多囊卵巢综合征患者中，高水平的 LH 可促进卵巢大量分泌 VEGF，且呈激素依赖性[17]。Cheng F 等[18]研究显示 VEGF 也是导致多囊卵巢综合征患者无优质卵泡发育的重要原因之一。ES 作为特异性的抑血管生长因子，可通过促进内皮细胞凋亡、抑制血管内皮迁移等途径，对新生血管的形成产生抑制作用。Kun A 等[19]研究显示多囊卵巢综合患者 ES 表达明显升高，且患者存在血管生成增多表现。Kollmann M 等[20]研究显示 ES 的升高是引发多囊卵巢综合症患者卵巢间质血流的异常化重要因素，也是致使患者出现代谢紊乱、排卵障碍的重要原因。HGF 主要是由氨基酸所形成的一种糖蛋白，多表达于卵巢组织中，国内外均有学者指出其可对癌细胞、上皮细胞的生长产生促进作用，卵巢中 HGF 表达增加时可发挥其至分泌效果，对正常的激素分泌产生扰乱作用，增加雄激素的水平[21,22]。Şahin N 等[23]实验也证实多囊卵巢综合征患者血清 HGF 表达明显升高，而抑制 HGF 的表达可通过对其内分泌产生影响，改善内分泌紊乱，有助于患者排卵。MCP-1 属 CC 类趋化因子，可在炎症因子的作用下对巨噬细胞 / 单核细胞产生趋化作用，参与心血管疾病、动脉粥样疾病。近年来研究表明多囊卵巢综合征患者去 MCP-1 表达明显比正常人群高，且随着疾病的好转，其表达可逐渐降低，证实其在多囊卵巢综合征的病理生理过程中发挥着重要作用[24]。本研究结果显示联合应用来曲唑的患者血清 VEGF、ES、HGF、MCP-1 的降低程度比单独使用妈富隆的患者更具有优势，通过分析是由于联合来曲唑可更有效改善血管化、调节卵巢内分泌等，进而更有助于降低血清 VEGF、ES、HGF、MCP-1 的表达，但具体作用机制仍需进一步深入研究，这也可能是联合来曲唑的患者临床疗效更显著的内在机制之一。

综上所述，来曲唑联合妈富隆治疗多囊卵巢综合征的临床效果显著优于妈富隆单药治疗，其可有效改善患者内分泌，提高妊娠率，可能与降低血清 VEGF、ES、HGF、MCP-1 的表达相关。

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