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百令胶囊对多囊卵巢综合征患者卵泡液骨形态蛋白、生长分化因子-9及胰岛素样生长因子的影响*

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摘要 目的:探讨百令胶囊对多囊卵巢综合征患者卵泡液骨形态蛋白(BMP)、生长分化因子(GDF)-9及胰岛素样生长因子(IGF)的影响。**方法:**选择2013年7月至2016年7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=45)和对照组(n=45),对照组使用达英-35治疗,观察组在此基础上使用百令胶囊。比较两组糖代谢指标、内分泌指标、卵泡液BMP-15、GDF-9、IGF-1水平的变化以及临床疗效。**结果:**治疗后,观察组空腹血糖(FBG)、空腹胰岛素(FINS)、胰岛素抵抗(HOMA-IR)、血清卵泡刺激素(FSH)、黄体生成素(LH)、睾酮(T)水平均显著低于对照组($P<0.05$),卵泡液BMP-15、GDF-9水平显著高于对照组,IGF-1水平明显低于对照组($P<0.05$),总有效率显著高于对照组($P<0.05$)。**结论:**百令胶囊质量多囊卵巢综合征效果显著,可有效调节内分泌,并改善卵泡液BMP-15、GDF-9、IGF-1的水平。

关键词:多囊卵巢综合征;百令胶囊;骨形态蛋白;生长分化因子;胰岛素样生长因子

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Effects of Bailing Capsule on the Follicular Fluid Bone Morphogenetic Protein, Growth Differentiation Factor -9 and Insulin Like Growth Factor of Patients with Polycystic Ovary Syndrome*

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ABSTRACT Objective: To study the effects of bailing capsules on levels of follicular fluid bone morphogenetic protein (BMP), growth differentiation factor -9 (GDF) and insulin like growth factor (IGF) of patients with polycystic ovary syndrome. **Methods:** 90 patients with polycystic ovary syndrome who had received therapy from July 2013 to July 2016 in our hospital were selected and randomly divided into the observation group (n=45) and the control group (n=45). The patients in the control group were treated with Diane -35, while the patients in the observation group were treated with bailing capsules on the basis of the control group. Then the levels of glucose metabolism index, endocrine index, BMP-15, GDF-9 and IGF-1 and clinical curative effect between the two groups were observed and compared before and after the treatment. **Results:** After treatment, the levels of fasting blood glucose (FBG), fasting insulin (FINS) and insulin resistance (HOMA-IR) in the observation group were lower than those of the control group ($P<0.05$); the levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone (T) in the observation group were lower than those of the control group ($P<0.05$); the levels of BMP-15 and GDF-9 in the observation group were higher than those of the control group, and the levels of IGF-1 was lower than that of the control group ($P<0.05$); the total effective rate of the observation group was higher than that of the control group ($P<0.05$). **Conclusion:** Bailing capsules was effective for polycystic ovary syndrome, which could effectively regulate the endocrine and improve the expression of BMP-15, GDF-9 and IGF-1 in the follicular fluid.

Key words: Polycystic ovary syndrome; Bailing capsules; Bone morphogenetic protein; Growth differentiation factor; Insulin like growth factor

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前言

多囊卵巢综合征是种伴随生殖功能紊乱的内分泌疾病,发病机制尚未完全阐明,研究显示与胰岛素抵抗、高雄激素血症、

高胰岛素血症密切相关^[1,2],临床症状多表现为月经稀发、无排卵、痤疮、多毛,远期合并症多包括2型糖尿病、肥胖、心血管疾病、代谢综合征等,严重影响患者生活质量。对于该病的治疗临床上多使用达英-35治疗,但疗效仍存在着争议^[3]。随着祖国医

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学对该病的不断深入研究,提出多囊卵巢综合征属于"不孕"、"闭经"、"月经后期"等范畴。百令胶囊在临床上具有显著的调脂、调糖作用,可有效改善代谢紊乱状态^[4]。因此,本研究主要探讨了百令胶囊治疗多囊卵巢综合征患者的疗效及对患者卵泡液骨形态蛋白(BMP)、生长分化因子(GDF)-9及胰岛素样生长因子(IGF)的影响,现报道如下。

1 资料与方法

1.1 一般资料

选择2013年7月至2016年7月我院接诊的90例多囊卵巢综合征患者。纳入标准^[5]:①符合多囊卵巢综合征诊断标准;②年龄≤35岁;③同意参与此次研究。排除标准^[6]:①近3月内有降糖药、降压药、口服避孕药等激素类药物的服用,以及减肥药等影响脂代谢的药物;②肝功能异常;③伴有乳腺癌、血栓病史。通过随机数表法分为观察组和对照组,各45例。观察组年龄22~34岁,平均(28.45±1.13)岁;已婚30例,未婚15例;病程3~9年,平均(5.67±0.45)年。对照组年龄21~35岁,平均(28.71±1.05)岁;已婚32例,未婚13例;病程2~10年,平均(5.84±0.42)年。本次研究已获得我院伦理委员会批准下实施,两组患者一般资料无显著差异($P>0.05$),具有可比性。

1.2 治疗方法

对照组在药物撤退性出血后或者月经来潮第5d使用达英-35(规格2mg:0.035mg,厂家:Schering GmbH & Co. Produktions KG,国药准字J2010003),1片/d,连续21d,停药后,在撤退性出现后第5d,开始下一周期服药。连续治疗3个周期。观察组在此基础上,使用百令胶囊(规格0.5g,厂家:杭州中美华东制药有限公司,国药准字Z10910036),2g/次,3次/d,与达英-35服用周期相同。

1.3 观察指标

①在治疗前后抽取5mL空腹静脉血,使用日立7600全自动生化分析仪测定空腹血糖(FBG)、空腹胰岛素(FINS)、胰岛素抵抗(HOMA-IR)的评价使用胰岛素抵抗指数稳态模型评估法;②使用电化学发光法测定卵泡刺激素(FSH)、黄体生成素(LH)、睾酮(T),使用罗氏E170型电化学发光全自动免疫分析仪检测;③治疗前后在阴道B超下行穿刺取卵术,选取直径18~20mm的优势卵泡的卵泡液,使用PowerVision免疫组织化学二步法检测卵泡液骨形态蛋白(BMP)-15、生长分化因子-9(GDF-9)的表达,试剂盒购于北京中杉金桥生物有限公司,使用Trizol一步法测定胰岛素样生长因子(IGF-1)的表达,试剂盒购于美国Invotrigen公司。

1.4 疗效评定标准

显效:卵巢体积、形态恢复正常,连续2个月以上正常周期排卵,月经规律≥3个月;有效:卵巢体积、形态得到缩小,月经规律≥3个月,偶有排卵;无效:月经周期仍不正常,排卵功能没有恢复。

1.5 统计学分析

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

2 结果

2.1 两组糖代谢指标比较

治疗前,两组FBG、FINS、HOMA-IR水平比较差异无统计学意义($P>0.05$);治疗后,两组FBG、FINS、HOMA-IR水平均较治疗前有所下降($P<0.05$),且观察组结果均比对照组低($P<0.05$),见表1。

表1 两组糖代谢指标比较($\bar{x} \pm s$)

Table 1 Comparison of the glucose metabolism index between the two groups ($\bar{x} \pm s$)

Groups		FBG(mmol/L)	FINS(pmol/L)	HOMA-IR
Observation group(n=45)	Before treatment	5.39±0.53	123.18±13.45	4.01±0.62
	After treatment	4.42±0.33	80.42±11.25	1.61±0.24
Control group(n=45)	Before treatment	5.41±0.47	122.93±13.51	3.98±0.63
	After treatment	5.21±0.43	107.21±12.74	2.94±0.35

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

2.2 两组内分泌指标比较

治疗前,两组FSH、LH、T水平无显著差异($P>0.05$);治疗

后,两组FSH、LH、T水平均降低($P<0.05$),观察组结果均低于对照组($P<0.05$),见表2。

表2 两组内分泌指标比较($\bar{x} \pm s$)

Table 2 Comparison of the endocrine index between the two groups ($\bar{x} \pm s$)

Groups		FSH(IU/L)	LH(IU/L)	T(mmol/L)
Observation group(n=45)	Before treatment	15.54±3.17	16.30±3.29	6.20±1.37
	After treatment	5.82±0.91**	7.97±1.03**	1.65±0.42**
Control group(n=45)	Before treatment	15.60±2.15	16.21±3.23	6.22±1.33
	After treatment	9.54±1.23*	11.29±2.30*	3.16±0.56*

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

2.3 两组卵泡液BMP-15、GDF-9、IGF-1水平比较

治疗前,两组卵泡液BMP-15、GDF-9、IGF-1水平无显著差

异($P>0.05$);治疗后,两组卵泡液BMP-15、GDF-9升高,IGF-1降低($P<0.05$),观察组卵泡液BMP-15、GDF-9高于对照组,

IGF-1 比对照组低($P<0.05$),见表 3。

2.4 两组临床疗效比较

观察组总有效率(95.56%)比对照组显著升高(71.11%)($P<0.05$),见表 4。

表 3 两组卵泡液 BMP-15、GDF-9、IGF-1 水平比较($\bar{x} \pm s$)

Table 3 Comparison of the levels of BMP-15, GDF-9 and IGF-1 in the follicular fluid between the two groups ($\bar{x} \pm s$)

Groups		BMP-15	GDF-9	IGF-1(ng/mL)
Observation group(n=45)	Before treatment	0.82± 0.25	1.24± 0.24	94.53± 13.40
	After treatment	2.49± 0.36* [#]	1.69± 0.36* [#]	63.83± 9.56* [#]
Control group(n=45)	Before treatment	0.85± 0.22	1.21± 0.25	94.61± 13.23
	After treatment	1.29± 0.28*	1.40± 0.29*	79.42± 10.56*

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

表 4 两组临床疗效比较(例,%)

Table 4 Comparison of the clinical efficacy between the two groups(n, %)

Groups	Effective	Valid	Invalid	Total effective rate
Observation group(n=45)	25(55.56)	18(40.00)	2(4.44)	43(95.56)*
Control group(n=45)	16(35.56)	17(37.78)	13(28.89)	32(71.11)

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

3 讨论

多囊卵巢综合征基本生理病理改变主要是由于雄激素、LH 过多、发育停滞、卵泡募集亢进、卵泡闭锁退化失调、优势卵泡选择受阻等,各期的卵泡包括窦前卵泡均多于正常卵巢,大量小卵泡积聚,致使卵巢呈多囊样,临床症状多表现为月经紊乱、雄激素水平过高、不孕、肥胖、胰岛素抵抗、LH 水平过高等^[8,9]。多囊卵巢综合征的基本特征主要为糖、脂代谢异常,中医认为肝瘀、脾虚、痰湿、血瘀等和多囊卵巢综合征之间存在着密切的关系^[10,11]。该病的治疗应以健脾补肾、化痰祛瘀为主。百令胶囊经过低温发酵的冬虫夏草菌种所制作而成。冬虫夏草是中名贵的传统药用真菌,已有两千多年的历史,和人参、鹿茸并作中国的三大补益要吃。《本草纲目拾遗》等较多文献中提出冬虫夏草可阴阳并补,功效和人参、鹿茸相似,且药性温和,老少皆宜。由于冬虫夏草可达到“益肾、保肺、化痰、止血”等功效,在糖尿病肾病、哮喘中应用较多,现代药理学指出其具有抗肿瘤、免疫调节、抗病毒、抗炎性反应、护肝等功效。Song J 等^[12]在早期糖尿病肾病患者中应用百令胶囊后,可有效改善患者糖脂代谢紊乱,且对肾功能具有保护作用。Wang W 等^[13]的研究也证实百令胶囊可达到有效的免疫调节效果。本次研究显示使用百令胶囊的患者糖代谢指标、内分泌指标的改善效果更明显,证实了百令胶囊在调节代谢紊乱上的有效性,并且治疗后患者总有效率达 95.56%,明显比单独应用达英-35 的患者更高,也显示出百令胶囊在改善临床症状体征、促排卵效果更加显著。

BMP-15 是转化生长因子超家族成员。有研究指出 BMP-15 的异常表达和多囊卵巢综合征患者卵泡发育障碍之间存在着密切的关系,在卵泡发育过程中。BMP-15 的减少,会对靶细胞的生长分化造成影响,减弱卵巢组织 BMP-15mRNA 的表达和蛋白生物活性,致使早期卵泡发育异常,卵巢呈多囊样改变^[14]。Persani L 等^[15]的研究证实多囊卵巢综合征患者中 BMP-15 的表达明显较低,和卵泡发育障碍之间存在着密切的关系。GDF-9 是卵母细胞来源的生长因子,其在卵泡生长发育

中产生着十分重要的作用,主要通过自分泌的形式,使卵母细胞的有丝分裂得到促进,通过旁分泌的形式,达到调节颗粒细胞、卵泡膜细胞的增值分化的作用。Berberoglu Z 等^[16]研究证实多囊卵巢综合征患者中,GDF-9 的表达比正常人明显较低。Wei LN 等^[17]的研究提出在妊娠人群中,GDF-9 的表达明显较高,提示 GDF-9 的高表达可预示良好的妊娠结局。IFG 是种单链多肽生长因子,和胰岛素结构相似,而卵泡液中 IGF-1 的表达在多囊卵巢综合征患者中也产生着重要的作用,其具有促进有丝分裂、参与新陈代谢等胰岛素样生物学效应^[18]。有研究提出如果 IGF-1 发生过度表达,则会下调 IGF-1 受体,使卵巢对 LH 的敏感性以及卵泡募集数增加,并扩大 LH 作用,难以形成优势卵泡,致使持续性的无排卵症状,形成多囊卵巢^[19]。Shah-nazi V 等^[20]研究中也证实卵泡液中过高的 IGF-1 会直接或间接的影响到卵母细胞的成熟、受精、卵裂,导致不良妊娠结局。为进一步评价临床疗效,本次研究也对 BMP-15、GDF-9、IGF-1 水平的变化进行了观察,结果显示,使用百令胶囊的患者 BMP-15、GDF-9 水平明显增加,IGF-1 水平降低,分析是由于百令胶囊在有效调节糖、脂代谢后,优势卵泡增多的原因,但具体作用机制还有待进一步深入研究,这可能应用百令胶囊的患者疗效更显著的原因之一。

综上所述,百令胶囊治疗多囊卵巢综合征患者的临床效果显著,可有效调节患者内分泌,并改善卵泡液 BMP-15、GDF-9、IGF-1 的表达。

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