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加减黄芪丹参饮联合优思悦治疗多囊卵巢综合征的效果 及对外周血 Th17/Treg 免疫失衡的影响研究 *

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摘要 目的:探讨与研究加减黄芪丹参饮联合优思悦治疗多囊卵巢综合征的效果及对外周血 Th17/Treg 免疫失衡的影响。**方法:**选择 2018 年 7 月到 2022 年 1 月在本医院诊治的多囊卵巢综合征患者 66 例作为研究对象,根据 1:1 简单分配原则把患者分为中药组与对照组各 33 例。对照组给予优思悦治疗,中药组在对照组治疗的基础上给予加减黄芪丹参饮治疗,所有患者都治疗观察 3 个月经周期,测定与计算外周血 Th17/Treg 免疫失衡情况。**结果:**治疗后中药组的总有效率为 100.0%,与对照组的 81.8%相比明显增高($P<0.05$)。两组治疗后的 Th17/Treg 值都明显低于治疗前($P<0.05$),中药组与对照组相比也明显降低($P<0.05$)。两组治疗后的子宫内膜厚度与最大卵泡直径都明显高于治疗前($P<0.05$),治疗后中药组与对照组相比也明显提高($P<0.05$)。两组治疗后的血清雌二醇(E_2)含量明显高于治疗前($P<0.05$),血清催乳素(PRL)含量明显低于治疗前($P<0.05$),治疗后中药组与对照组都有明显差异差异($P<0.05$)。**结论:**加减黄芪丹参饮联合优思悦治疗多囊卵巢综合征能有效调节外周血 Th17/Treg 免疫失衡,促进性激素分泌正常,提高患者的子宫内膜厚度与最大卵泡直径,提高患者的总体治疗效果。

关键词:加减黄芪丹参饮;优思悦;多囊卵巢综合征;子宫内膜厚度;最大卵泡直径;Th17/Treg 免疫失衡

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Study on the Effect of Modified Huangqi Danshen Yin Combined with Yousiyue in the Treatment of Polycystic Ovary Syndrome and its Impact on Peripheral Blood Th17/Treg Immune Imbalance*

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ABSTRACT Objective: To explore and study the efficacy of modified Huangqi Danshen Yin combined with Yousiyue in the treatment of polycystic ovary syndrome and its impact on peripheral blood Th17/Treg immune imbalance. **Methods:** 66 cases of patients with polycystic ovary syndrome who were diagnosed and treated in our hospital from July 2018 to January 2022 were selected as the research subjects. Accorded to the 1:1 simple allocation principle, the patients were divided into the traditional Chinese medicine group and the control group with 33 cases each. The control group were treated with Yousiyue, and the Chinese medicine group were treated with modified Huangqi Danshen Decoction on the basis of the control group. All patients were treated and observed for three Menstrual cycle, and the peripheral blood Th17/Treg immune imbalance were measured and calculated. **Result:** After treatment, the total effective rate of the traditional Chinese medicine group were 100.0%, which were higher than the control group's 81.8%($P<0.05$). The Th17/Treg values after treatment in both groups were lower than before treatment ($P<0.05$), and the traditional Chinese medicine group also showed a decrease compared to the control group($P<0.05$). The endometrial thickness and maximum follicle diameter of the two groups after treatment were higher than before treatment ($P<0.05$), and the traditional Chinese medicine group also showed a increase compared to the control group after treatment ($P<0.05$). The content of serum estradiol (E_2) after treatment were higher than that before treatment($P<0.05$), and the content of serum Prolactin (PRL) were significantly lower than that before treatment ($P<0.05$). There were difference between the Chinese medicine group and the control group after treatment ($P<0.05$). **Conclusion:** The combination of modified Huangqi Danshen Yin and Yousiyue in the treatment of polycystic ovary syndrome can effectively regulate the immune imbalance of peripheral blood Th17/Treg, promote normal secretion of sex hormones, increase the thickness of the patient's endometrium and the maximum follicle diameter, and

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improve the overall treatment effect of the patient.

Key words: Addition and subtraction of Huangqi Danshen Yin; Yousiyue; Polycystic ovary syndrome; Endometrial thickness; Maximum follicle diameter; Th17/Treg immune imbalance

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前言

多囊卵巢综合征是由于代谢功能紊乱、生殖内分泌紊乱引起的排卵障碍性疾病,在生育年龄妇女中的发病率为 5.0%左右^[1,2]。多囊卵巢综合征在的病理机制主要为高胰岛素血症、胰岛素抵抗、内分泌紊乱、雄激素增多、糖耐量异常等,在临床上主要表现为肥胖、闭经、月经稀发、多毛、痤疮、排卵异常、不孕不育等临床症状^[3,4]。多囊卵巢综合征在病程比较长,可长期与反复发病,对于治疗的要求比较高^[5]。西医主要采用降低雄激素、促进排卵等药物进行治疗,多囊卵巢综合征,其中常用的药物为优思悦。优思悦每片含有 35 mg 乙炔雌二醇和 2 mg 醋酸环丙孕酮,可通过多种途径发挥强抗雄作用^[6,7]。但是优思悦在长期的使用过程中可存在停药反应,易发生卵巢过度刺激综合征,还可能对卵巢远期功能有一定的负面影响^[8]。多囊卵巢综合征在祖国医学上可归为“癥瘕”范畴,肾虚为发病之本,血瘀为发病之标,中药在多囊卵巢综合征的诊治中注重辨证施治与整体论治,在逆转病情与改善临床症状等方面具有重要的优

势^[9]。加减黄芪丹参饮为治疗多囊卵巢综合征的经验方,在临床上游比较好的治疗效果^[10,11],但是具体的作用机制还不明确。现代研究表明多囊卵巢综合征可能是一种自身免疫性疾病,而 Th17/Treg 是反映体内免疫稳态的指标,Th17/Treg 免疫失衡与多种免疫性疾病存在相关性,包括免疫性血小板减少性紫癜、多发性硬化、先天性扩张型心肌病、微小病变型肾小球肾炎等^[12,13]。本文探讨与研究了加减黄芪丹参饮联合优思悦治疗多囊卵巢综合征的效果及对外周血 Th17/Treg 免疫失衡的影响,以明确加减黄芪丹参饮的作用机制与效果。现报道如下。

1 临床资料

1.1 一般资料

选择 2018 年 7 月到 2022 年 1 月在本医院诊治的多囊卵巢综合征患者 66 例作为研究对象。根据随机数字表法把患者分为中药组与对照组各 33 例,两组患者的病程、体重指数、年龄、孕次、产次等对比无显著差异($P>0.05$)。见表 1。

表 1 两组一般资料对比

Table 1 Comparison of the two groups of general data

Groups	n	Disease course (month)	Body mass index (kg/m ²)	Age (year)	Pregnant times (times)	Production times (times)
Chinese medicine group	33	5.20± 0.34	26.78± 1.48	40.29± 2.49	2.47± 0.48	1.37± 0.32
Control group	33	5.44± 0.41	26.26± 1.33	40.10± 3.19	2.49± 0.33	1.38± 0.28
t		0.231	0.513	0.198	0.034	0.045
P		0.782	0.515	0.811	0.876	0.856

1.2 诊断标准

(1)西医诊断标准^[7] ① 稀发排卵或无排卵;② 高雄激素临床表现和(或)高雄激素血症;③ 卵巢多囊样改变,即超声提示一侧或双侧卵巢内直径为 2~9 mm 的卵泡≥12 个,卵巢体积≥10 mL;④ 以上 3 项中符合 2 项,并排除其他高雄激素的病因和先天性肾上腺皮质增生、库欣综合征、分泌雄激素的肿瘤,即可诊断为多囊卵巢综合征。

(2)中医诊断标准^[8] ① 经色淡暗,经质稀薄;② 面色淡暗或有暗斑;③ 腰背部酸痛;④ 胫膝酸软或足跟痛;⑤ 耳鸣或耳聋;⑥ 性欲减退;⑦ 舌淡暗,苔薄;⑧ 两尺脉沉弱。以上各证具备其中 3 项,即确诊。

1.3 纳排标准

纳入标准:符合多囊卵巢综合征诊断标准;临床上主要表现为月经异常、排卵障碍等症状;入院前 3 个月未接受过其它任何多囊卵巢综合征相关治疗;患者依从性好;临床资料完整;无药物过敏史,非过敏体质患者;本次研究《赫尔辛基宣言》^[9]要求;所有患者都是自愿参加研究,并签订知情同意书。

排除标准:合并高危传染性疾病者;先天性卵巢发育异常者;合并严重心肝肾功能不全者;小学及其以下文化程度者;有精神障碍或是认知障碍者;存在输卵管、子宫等妇科器质性疾病者;中途退出者;依从性不佳者;心理状态不佳者;过敏体质;入院前 3 个月服用影响免疫细胞药物者。

1.4 治疗方法

对照组 给予优思悦治疗,在月经来潮第 5 天开始给予优思悦 (Bayer Weimar GmbH und Co. KG, 国药准字 H20140972),每天同一时间口服一片,治疗观察 3 个月。

中药组 在对照组治疗的基础上给予加减黄芪丹参饮治疗,组方:丹参 15 克、黄芪 12 克、胆南星 12 克、神曲 12 克、枳壳 10 克、香附 10 克、陈皮 8 克、桃仁 8 克、生姜 5 克、甘草 8 克。随经期进行药材加减,经前期加用川牛膝 10 克、益母草 10 克、桃仁 10 克,经期加用川牛膝 12 克、五灵脂 10 克、蒲黄、10 克,经后期加服枸杞子 10 克、菟丝子 10 克、桑葚 8 克。水煎 200 mL,分早晚 2 次口服,1 次/d,治疗观察 3 个月。

1.5 疗效观察

1.5.1 观察指标 ① 血清 E2、PRL 含量及在治疗前后抽取患者空腹静脉血 5 mL,分为两份。第一份放入促凝管中,静置 30 min 后,2000 rpm 离心 10 min,离心半径为 8 cm,取上层血清保存于 -20.0℃ 冰箱,采用化学发光法检测血清雌二醇(Estradiol 2, E2)、催乳素(Prolactin, PRL)含量。

② Th17/Treg 检测 第二份放入抗凝管中,静置 30 min 后,2000 rpm 离心 10 min,离心半径为 8 cm,取单个核细胞层,采用流式细胞仪检测 Th17 细胞比例与 Treg 细胞比例,计算 Th17/Treg 值。

③ 子宫内膜厚度、最大卵泡直径测量 在治疗前后的月经周期第 6 天左右使用彩色超声诊断仪层与记录患者的子宫内膜厚度、最大卵泡直径,每次测定三次取平均值。

1.5.2 疗效标准 显效:性激素分泌正常,临床症状显著改善;

有效:性激素分泌有所改善,临床症状部分缓解;无效:临床症状无改善或呈加重趋势,性激素分泌无变化甚或更加异常。(显效+有效)/组内例数×100.0%=总有效率。

1.6 统计方法

使用 SPSS22.00 统计学软件对计量数据与计数数据进行统计学处理, $P<0.05$ 为对比差异明显。采用(均数±标准差)、百分比、率等表示计量数据与计数数据,计量数据与计数数据的对比方法为 t 检验与 χ^2 检验,检验水准 $\alpha=0.05$ 。

2 结果

2.1 总有效率对比

治疗后中药组的总有效率为 100.0%,与对照组的 81.8%相比明显增高($P<0.05$)。见表 2。

表 2 两组治疗后总有效率对比(n)

Table 2 Total response rates between the two groups (n)

Groups	n	Excellence	Valid	Invalid	Total effective rate
Chinese medicine group	33	30	3	0	33(100.0%) [▲]
Control group	33	13	14	6	27(81.8%)

Note: compared with the Control group, [▲] $P<0.05$, the same below.

2.2 Th17/Treg 值变化对比

对照组相比也明显降低($P<0.05$)。见表 3。

两组治疗后的 Th17/Treg 值都明显低于治疗前,中药组与

表 3 两组治疗前后 Th17/Treg 值变化对比(均数±标准差)

Table 3 Comparison of Th 17 / Treg values before and after the two treatment groups (mean ± standard deviation)

Groups	n	Pretherapy	Post-treatment
Chinese medicine group	33	1.56± 0.24	0.45± 0.03 [▲]
Control group	33	1.57± 0.31	0.87± 0.09 [▲]

Note: compared with Pretherapy, [▲] $P<0.05$, the same below.

2.3 子宫内膜厚度与最大卵泡直径变化对比

治疗前 ($P<0.05$), 治疗后中药组与对照组相比也明显提高 ($P<0.05$)。见表 4。

两组治疗后的子宫内膜厚度与最大卵泡直径都明显高于

表 4 两组治疗前后子宫内膜厚度与最大卵泡直径变化对比(均数±标准差)

Table 4 Comparison of endometrial thickness and maximum follicle diameter between the two treatment groups (mean ± standard deviation)

Groups	n	Endometrial thickness (mm)		Maximum follicle diameter (cm)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Chinese medicine group	33	6.00± 0.24	8.98± 0.35 [▲]	0.74± 0.07	0.91± 0.06 [▲]
Control group	33	6.09± 0.32	7.26± 0.36 [▲]	0.75± 0.04	0.80± 0.05 [▲]

2.4 血清性激素变化对比

量明显低于治疗前,治疗后中药组与对照组都有明显差异差异 ($P<0.05$)。见表 5。

两组治疗后的血清 E2 含量明显高于治疗前,血清 PRL 含

表 5 两组治疗前后血清性激素变化对比(均数±标准差)

Table 5 Comparison of serum sex steroid changes before and after treatment (mean ± standard deviation)

Groups	n	E2(pmol/L)		PRL(ng/ml)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Chinese medicine group	33	52.44± 3.23	61.48± 3.19 [▲]	19.14± 1.11	15.20± 0.56 [▲]
Control group	33	52.59± 2.58	55.49± 2.58 [▲]	19.28± 0.82	17.38± 0.58 [▲]

3 讨论

由于各种因素的影响,国内外的多囊卵巢综合征发病人数不断增加。多囊卵巢综合征是一种多发于青春期和育龄期女性的最常见的妇科疾病,也是一种糖代谢异常、生殖功能障碍高度关联的一种特殊性综合性疾病^[14,15]。西医认为多囊卵巢综合征主要是由于患者下丘脑促性腺激素的分泌异常,使得大量分泌雄激素,从而诱发出高雄激素血症。同时促黄体生成素分泌过高,可导致促使卵泡膜细胞、卵巢间质细胞增生加快,而卵泡刺激素正常分泌,使得腺激素增强刺激卵泡的形成,使得卵泡形成出现障碍,本病发病多与环境因素、遗传因素、精神心理因素等相关^[16,17]。多囊卵巢综合征主要病理变化是下丘脑-垂体-卵巢轴功能紊乱,而中医学认为正常月经的来潮有赖于"肾气-天癸-冲任-胞宫"。肝、脾、肾功能失调,形成气滞、血瘀、痰湿等病理因素,导致肾-天癸-冲任-胞宫系统紊乱,或肝肾亏虚化血无源,致月经后期、闭经,或卵泡不能发育、排出;或痰湿、血瘀阻滞冲任,胞脉不畅,血不得下而致闭经、卵泡不能顺利排出而致不孕^[18]。基于此,本研究采用中西医治疗多囊卵巢综合征,旨在为临床治疗提供一定的思路。

本研究统计分析总有效率发现:治疗后中药组的总有效率为100.0%,与对照组的81.8%相比明显增高;两组治疗后的子宫内膜厚度与最大卵泡直径都明显高于治疗前,治疗后中药组与对照组相比也明显提高,表明加减黄芪丹参饮联合优思悦治疗多囊卵巢综合征能有效提高子宫内膜厚度与最大卵泡直径,提高患者的总体治疗效果。分析可知,优思悦由醋酸环丙孕酮、决雌醇等主要成分组成,可控制丘脑分泌及肾上腺素分泌,还可抑制性腺激素以及雄激素分泌,减少外周组织的脂肪堆积,改善子宫内膜的形态与功能,抑制排卵并提高排卵效果,调整患者月经周期^[19,20]。加减黄芪丹参饮中黄芪、丹参均具有较强的抗血小板聚集及抗凝血作用,可降低血液黏度,可促雌激素样作用,丹参还可抗雄激素活性;胆南星、神曲、枳壳具有兴奋卵巢作用,有明显的免疫调节作用,经前期及经期加川牛膝可活血,引血下行,经后期加枸杞子、菟丝子、桑葚等,可提高下丘脑、垂体及卵巢促黄体功能,诸药合用,可调节卵泡发育、促进促性腺激素分泌,从而提高患者的总体治疗效果^[21,22]。

分析两组免疫功能相关指标发现,两组治疗后的Th17/Treg值都明显低于治疗前,中药组与对照组相比也明显降低,表明加减黄芪丹参饮联合优思悦治疗多囊卵巢综合征能有效改善患者的免疫功能。分析可知,多囊卵巢综合征的发生与机体的免疫功能存在相关性,Th17细胞是免疫炎症反应的效应细胞,Treg细胞可介导免疫耐受,Th17/Treg平衡的破坏可能是多囊卵巢综合征发生和发展的原因^[23]。例如IL-6可抑制CD4⁺T淋巴细胞分化为Treg细胞,IL-2是对维持Treg细胞功能正常起着重要作用,但具有抑制Th17细胞分化的功能^[24]。加减黄芪丹参饮可促雌激素的分泌,还具有预防外源性的胰岛素拮抗作用。现代药理研究表明,加减黄芪丹参饮的提取物对纤溶系统有活化作用,有类雌激素样作用,与优思悦的联合使用可发挥协同效应,从而提高患者的免疫功能^[25]。

随着研究的深入,临床上单纯应用优思悦治疗多囊卵巢综合征存在一定的不足,并且长期使用优思悦容易过度刺激卵

巢,损伤机体的肝肾功能与肾功能^[26,27]。本研究显示两组治疗后的血清E2含量明显高于治疗前,血清PRL含量明显低于治疗前,治疗后中药组与对照组都有明显差异,表明加减黄芪丹参饮联合优思悦治疗多囊卵巢综合征能改善患者的性激素水平。分析可知,中医认为血液运行依赖于肾气推动,补肾与活血相辅相成,肾气衰弱,在治疗上应从补肾着手。加减黄芪丹参饮可补肝益肾,全方具有标本兼治、配伍得当的特点,可以降低血清中微炎症水平,还能完善胰岛素的生理需求量,从而维持机体的性激素分泌平衡^[28]。但本研究未对加减黄芪丹参饮的具体中药组方进行分析,且分组与纳入例数都较少,将在后续研究中探讨。

综上所述,加减黄芪丹参饮联合优思悦治疗多囊卵巢综合征能有效调节外周血Th17/Treg免疫失衡,促进性激素分泌正常,提高患者的子宫内膜厚度与最大卵泡直径,提高患者的总体治疗效果。

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