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定坤丹对多囊卵巢综合征患者性激素水平、胰岛素抵抗及妊娠情况的影响 *

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摘要 目的:探讨定坤丹对多囊卵巢综合征患者性激素水平、胰岛素抵抗及妊娠情况的的影响。**方法:**选择 2016 年 5 月至 2018 年 5 月我院收治的 210 例多囊卵巢综合征患者,根据随机化原则将其分为两组,每组 105 例。对照组患者接受达英 -35 与二甲双胍治疗,研究组在对照组的基础上口服定坤丹治疗。连续治疗 3 个月后,比较两组治疗前后的性激素水平及胰岛各相关指标的变化。治疗结束后随访 1 年,比较两组的排卵及妊娠情况。**结果:**与治疗前相比,两组治疗后的血清睾酮(Testosterone,T)、黄体生成素(Luteinizing hormone,LH)及 LH/FSH 均明显降低,且研究组以上指标均显著低于对照组($P<0.05$)。两组治疗前后的卵泡刺激素(Follicle-stimulating hormone,FSH)水平比较无统计学差异($P>0.05$)。与治疗前相比,两组治疗后的空腹胰岛素(Fasting insulin,FINS)、餐后 2 h 胰岛素(Postprandial 2 hours insulin,2hPINS)及 β 细胞胰岛素分泌功能(Homeostasis model assessment of β cell,HOMA-β)均明显升高,胰岛素敏感指数(Homeostasis model assessment-Insulin sensitivity index,HOMA-IS)明显降低,且研究组以上指标较对照组改善更明显($P<0.05$)。研究组排卵及成功妊娠率均显著高于对照组($P<0.05$)。**结论:**定坤丹有助于改善多囊卵巢综合征患者性激素水平及胰岛素抵抗,提高排卵及妊娠率。

关键词:定坤丹;多囊卵巢综合征;性激素;胰岛素抵抗;妊娠率

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Effects of Dinkundan on the Sex Hormone Levels, Insulin Resistance and Pregnancy in Patients with PCOS*

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ABSTRACT Objective: To investigate the effect of dinkundan on sex hormone level, insulin resistance and pregnancy in patients with PCOS. **Methods:** 210 patients with PCOS were selected as objects from May 2016 to May 2018. According to the admission single and double number, 105 patients in the control group received Da-35 and metformin therapy, and 105 patients in the study group received were treated with dinkundan orally on the basis of the control group. After continuous treatment for 3 months, the changes of sex hormone levels and islet related indicators before and after treatment in the two groups were compared,The ovulation and pregnancy of the two groups were compared after 1 year follow-up. **Results:** Compared with before treatment, T, LH/FSH and LH of the two groups were significantly reduced after treatment, and the experimental group was significantly lower than the control group ($P<0.05$). There was no statistically significant difference in FSH level between the two groups before and after treatment ($P>0.05$). Compared with before treatment, FINS, 2hPINS and homa-beta of the two groups were significantly increased after treatment, while homa-is was significantly decreased. Moreover, the improvement of the research group was more significant than that of the control group($P<0.05$). The ovulation and successful pregnancy rates in the study group were significantly higher than those in the control group ($P<0.05$). **Conclusion:** Dinkundan helps improve sex hormone levels and patients' insulin resistance, increased ovulation and pregnancy rates, It has high application value in the treatment of PCOS.

Key words: Dingkundan; Polycystic ovary syndrome; Sex hormone levels; Insulin resistance; The pregnancy rate

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前言

多囊卵巢综合征(Polycystic ovarian syndrome,PCOS)是以排卵功能紊乱或丧失及高雄激素血症为特征的一种复杂性内

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分泌系统疾病，临床上常表现为月经紊乱、不孕、多毛、痤疮等。据统计，因 PCOS 所致的不孕占无排卵性不孕的 60 %左右，给患者的生育功能及身心健康造成极大的威胁[1-3]。目前，临床上治疗 PCOS 主要以降低雄激素水平、改善胰岛素抵抗以诱发排卵为治疗原则。二甲双胍与达英 -35 是临床治疗 PCOS 的常用药物，两者联合应用主要通过解除胰岛素抵抗、减少雄性激素分泌来协同性的促进排卵，改善患者的病情，但部分患者取得的治疗效果常不理想[4-6]。

中医认为 PCOS 属于 " 不孕 "、" 闭经 "、" 月经不调 " 范畴，与肝肾亏虚、气虚血瘀、脾胃不和、痰湿内滞等因素有关，辅助调补肝肾、益气养血、活血化瘀治疗对促进排卵具有积极意义[7]。定坤丹是一种中药复方制剂，调经舒郁、滋补气血作用显著，常被用于月经不调、经行腹痛、产后诸虚、崩漏下血、骨蒸潮热、围绝经期综合征等的治疗，但其在 PCOS 治疗中的报道较少。本研究选择 2016 年 5 月至 2018 年 5 月我院收治的 210 例多囊卵巢综合征患者，探讨了定坤丹对多囊卵巢综合征患者性激素水平、胰岛素抵抗及妊娠情况的的影响，以期为临床提供参考，现进行如下报道。

1 资料与方法

1.1 一般资料

选择 2016 年 5 月至 2018 年 5 月我院收治的 210 例多囊卵巢综合征患者，根据随机化原则将受试者分为两组，每组 105 例。对照组年龄 23-38 岁，平均(30.25± 3.42)岁；不孕时间 1-13 年，平均 (5.62± 2.14) 年；BMI 指数 21-26 kg/m^2，平均(24.65± 2.32)kg/m^2；月经紊乱 62 例，闭经 23 例，功能失调性子宫出血 20 例；研究组年龄 22-39 岁，平均(31.05± 3.37)岁；不孕 1-14 年，平均 (5.88± 2.24) 年；BMI 指数 21-27 kg/m^2，平均(24.59± 2.26)kg/m^2；月经紊乱 60 例，闭经 26 例，功能失调性子宫出血 19 例。两组一般资料比较差异无统计学意义(P>0.05)，具有可比性。

1.2 纳入及排除标准

纳入标准：符合 PCOS 的诊断标准，年龄 20-50 岁，已婚，在无任何避孕措施下性生活正常维持 1 年以上，自愿配合完成本次治疗。排除标准：甲状腺功能障碍及卵巢早衰等因素所致的排卵障碍、近 1 个月内服用过影响性激素及胰岛相关指标的药物、输卵管阻塞、子宫病变、先天性生理缺陷、伴有严重的器质性病变及心脑血管疾病、相关药物过敏史、治疗依从性差、临床资料不全及失访者。

1.3 方法

对照组接受达英 -35 与二甲双胍治疗，自月经第 5 d 起口服达英 -35 (拜耳医药保健有限公司广州分公司，国药准字 J20140114，规格：2 mg/ 片)，每日 1 片，连续治疗 21 d，停药后月经来潮，自月经第 5 d 起进入下一个疗程，连续治疗 3 个疗程；自月经第 5 d 起口服盐酸二甲双胍缓释片(南京亿华药业有限公司，国药准字 H20040816，规格：500 mg/ 片)，每次 250 mg，每日 3 次，餐后 0.5 h 后服用，1 个月为一疗程，连续治疗 3 个疗程。研究组在对照组的基础上口服定坤丹(山西广誉远国药有限公司，国药准字 Z14020656，规格：7 g/ 瓶)治疗，每次 7 g，每日 2 次，连续治疗 3 个月。

1.4 评价标准

比较两组的治疗前后的性激素水平及胰岛各相关指标变化，治疗结束后随访 1 年，比较两组的排卵及妊娠情况。

治疗前后均取患者的空腹条件下外周静脉血 5 mL，静置 30 min 后使用离心分离出血清于 -30℃冰箱中保存，采用化学发光法检测血清中黄体生成素(LH)、睾酮(T)、卵泡刺激素(FSH)水平，并采用全自动分析仪检测空腹胰岛素(FINS)、餐后 2h 胰岛素(2hPINS)及 β 细胞胰岛素分泌功能(HOMA-β)水平，计算胰岛素敏感指数(HOMA-IS)[8-10]。

1.5 统计学方法

采用 SPSS19.0 进行数据分析，计量资料采用均数± 标准差($\bar{x}$± s)表示，组内及组间比较行独立样本 t 检验，计数资料采用百分数(%)表示，组间比较行独立样本 x^2 检验，以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组治疗前后各性激素水平变化的比较

与治疗前相比，两组治疗后血清的 T、LH/FSH 及 LH 水平均明显降低，且研究组以上指标均显著低于对照组(P＜0.05)，两组治疗前后的血清 FSH 水平比较无统计学差异(P>0.05)，见表 1。

表 1 两组治疗前后各性激素水平变化的比较($\bar{x}$± s)

Table 1 Comparison of the changes of sex hormone levels before and after treatment between two groups($\bar{x}$± s)

Groups	Time	T(μg/L)	LH/FSH	LH (IU/L)	FSH(IU/L)
Study Group(n=105)	Before treatment	1.82± 0.69	3.29± 0.98	16.31± 1.69	5.20± 0.97
	After treatment	0.79± 0.50*#	1.71± 0.65*#	8.09± 1.30*#	5.77± 1.06
Control group(n=105)	Before treatment	1.80± 0.72	3.28± 0.89	16.36± 2.12	5.19± 0.98
	After treatment	1.20± 0.68*	2.67± 0.73*	10.35± 1.48*	5.28± 1.02

Note: compared with pre-treatment and the control group, *P＜0.05, #P＜0.05.

2.2 两组治疗前后胰岛各相关指标变化的比较

与治疗前相比，两组治疗后的 FINS、2hPINS 及 HOMA-β 水平均明显升高，HOMA-IS 明显降低，且研究组以上指标改善较对照组更显著(P＜0.05)，见表 2。

2.3 两组排卵及妊娠情况的比较

研究组排卵及成功妊娠率均显著高于对照组(P＜0.05)，见表 3。

表 2 两组治疗前后胰岛各相关指标变化的比较($\bar{x}\pm s$)

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

Groups	Time	FINS(mU/L)	2hPINS(mU/L)	HOMA-IS	HOMA-β
Study Group(n=105)	Before treatment	7.41± 1.86	44.11± 6.19	3.60± 0.81	31.20± 13.75
	After treatment	11.59± 1.61*#	58.52± 7.16*#	2.85± 0.49*#	61.92± 16.26*#
Control group(n=105)	Before treatment	7.33± 1.54	44.08± 6.42	3.59± 0.80	30.87± 14.05
	After treatment	8.91± 1.46*	50.21± 7.65*	3.25± 0.54*	41.26± 15.34*

Note: compared with pre-treatment and the control group, *$P<0.05$, #$P<0.05$.

表 3 两组排卵及妊娠情况的比较(例,%)

Table 3 Comparison of the ovulation and pregnancy status between two groups(n, %)

Groups	NNT	Ovulation	Pregnancy
Study Group	105	94(89.52)	75(71.43)
Control group	105	80(76.19)	60(57.14)
x^2		6.571	4.667
P		<0.05	<0.05

3 讨论

PCOS 是育龄期妇女的常见病、多发病,病因复杂多样,发病机制尚不完全明确,大多学者认为其病机可能为下丘脑 - 垂体 - 卵巢轴失调、生长激素与类胰岛素样生长因子及受体分泌失常、胰岛素抵抗等[11]。研究表明 PCOS 是 II 型糖尿病、心血管疾病、妊娠期并发症及子宫内膜癌的重要危险因素,不仅会增加患者自然受孕的难度,影响生育功能,还会增加以上疾病的发生风险,危害性较大[12]。

针对 PCOS 目前临床上无标准的治疗方案,主要通过口服药物来提高胰岛素的敏感性, 降低雄激素水平以促进排卵[17]。二甲双胍作为一种胰岛素增敏剂,可促进外周组织对葡萄糖的吸收利用来改善糖代谢,并抑制肝糖原医生来增强外周组织对胰岛素的敏感性,改善高胰岛素血症,促进排卵,提高妊娠率[18]。达英 -35 是临床上常用的一种口服避孕药, 可有效抑制 LH 水平,恢复 LH/FSH 的正常比值,减少雄激素的生成,有效缓解高雄激素血症,与二甲双胍联合应用可协同性的纠正高雄激素血症,增强胰岛素的敏感性,促进月经周期的恢复及排卵,提高治疗效果[19]。还有研究表明,二甲双胍联合达英 -35 还有助于改善患者的血脂水平,预防心脑血管疾病的发生风险。临床实践证实,大多患者长时间应用二甲双胍联合达英 -35 治疗后仍无法完全巩固病情使其受孕[20]。

中医认为肾虚血瘀、瘀痰互结为 PCOS 的基本病机,因此应以补益肾气、滋补卵巢为主治[21]。定坤丹方中人参、白术补气,鹿茸、鹿角霜壮阳益精,当归、熟地、白芍、阿胶补血,枸杞滋阴补肾,川芎、西红花、鸡血藤、茺蔚子、延胡索、三七等活血行气止痛。既补气补血、壮阳益精,又活血止痛、益气养血[22]。现代药理研究表明定坤丹可有效降低血清雄激素水平,提高子宫内膜 HOXA10 表达,进而保证胚胎着床及发育[23];还可调节下丘脑 - 垂体 - 卵巢轴, 改善性激素水平及卵巢血流, 提高卵泡质量,促进排卵[24]。此外,定坤丹还具有降低毛细血管通透性,改善微血流,调节免疫和抗炎作用[25,26]。定坤丹在二甲双胍与达英 -35 的基础上联合应用可充分发挥各自优势, 恢复月经的正常周期,增强胰岛素的敏感性,缓解高胰岛素血症,促进排卵,提高妊娠率[27-29]。

LH 是由垂体产生的激素,与 FSH 可协同性的刺激卵巢雌激素分泌,促进卵泡成熟及排卵,是预测排卵时间的主要指标,而 FSH 可刺激受精卵的成熟,LH/FSH 升高是 PCOS 的重要特征之一[13]。T 可通过增强胰岛 B 细胞内 DNA 的合成,提高细胞内胰岛素的含量而保护胰岛细胞,其分泌受 LH 的调节,对下丘脑和垂体起负反馈作用[14]。胰岛素抵抗是 PCOS 发生的重要环节,当外周组织对胰岛素敏感性降低或丧失,机体则会促进胰岛素分泌引发高胰岛素血症,进而导致卵泡发育障碍,最终导致无排卵,影响受孕[15]。HOMA-IS 指数随着胰岛素敏感性水平的升高而升高,常被临床作为评价胰岛素敏感性水平的另一指标[16]。本研究结果显示与治疗前相比,治疗后两组患者的 T、LH/FSH 及 LH 均明显降低,且研究组显著低于对照组,提示定坤丹可协同二甲双胍与达英 -35 改善患者的性激素水平,促进排卵,保护胰岛细胞。与治疗前相比,治疗后两组患者的 FINS、2hPINS 及 HOMA-β 均明显升高,HOMA-IS 明显降低,且研究组较对照组改善更为显著,提示定坤丹可有效降低血清雄激素水平,提高子宫内膜容受性,协同性的改善胰岛素抵抗,进而促进排卵。此外,研究组患者排卵及成功妊娠率均显著高于对照组。以上结果提示定坤丹可有效降低血清雄激素水平,协同性的提高卵泡质量,促进排卵;提高子宫内膜容受性,保证胚胎着床及发育,提高妊娠率[30]。

综上所述,定坤丹有助于改善多囊卵巢综合征患者性激素水平及胰岛素抵抗,提高排卵及妊娠率。

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