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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素各相关指标的变化。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2h胰岛素(Postprandial 2 hours insulin, 2hPINS)及 $\beta$ 细胞胰岛素分泌功能(Homeostasis model assessment of  $\beta$  cell, HOMA- $\beta$ )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:** Dinkundan; 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<sup>[1-3]</sup>。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<sup>[4-6]</sup>。

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<sup>[7]</sup>。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<sup>2</sup>,平均(24.65±2.32)kg/m<sup>2</sup>;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<sup>2</sup>,平均(24.59±2.26)kg/m<sup>2</sup>;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  $\beta$  细胞胰岛素分泌功能(HOMA- $\beta$ )水平,计算胰岛素敏感指数(HOMA-IS)<sup>[8-10]</sup>。

### 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( $\bar{x} \pm s$ )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  $\chi^2$  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( $\bar{x} \pm s$ )

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

Groups	Time	T( $\mu$ g/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- $\beta$  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- $\beta$
Study Group(n=105)	Before treatment	7.41 $\pm$ 1.86	44.11 $\pm$ 6.19	3.60 $\pm$ 0.81	31.20 $\pm$ 13.75
	After treatment	11.59 $\pm$ 1.61* <sup>#</sup>	58.52 $\pm$ 7.16* <sup>#</sup>	2.85 $\pm$ 0.49* <sup>#</sup>	61.92 $\pm$ 16.26* <sup>#</sup>
Control group(n=105)	Before treatment	7.33 $\pm$ 1.54	44.08 $\pm$ 6.42	3.59 $\pm$ 0.80	30.87 $\pm$ 14.05
	After treatment	8.91 $\pm$ 1.46*	50.21 $\pm$ 7.65*	3.25 $\pm$ 0.54*	41.26 $\pm$ 15.34*

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

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)
$\chi^2$		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<sup>[11]</sup>。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<sup>[12]</sup>。

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<sup>[17]</sup>。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<sup>[18]</sup>。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<sup>[19]</sup>。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。临床实践证明,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<sup>[20]</sup>。

中医认为肾虚血瘀、痰瘀互结为 PCOS 的基本病机,因此应以补益肾气、滋补卵巢为主治<sup>[21]</sup>。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、菟藟子、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<sup>[22]</sup>。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<sup>[23]</sup>;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<sup>[24]</sup>。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<sup>[25,26]</sup>。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<sup>[27-29]</sup>。

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<sup>[13]</sup>。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<sup>[14]</sup>。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<sup>[15]</sup>。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<sup>[16]</sup>。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- $\beta$  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<sup>[30]</sup>。

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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