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自拟柴郁寄生汤治疗高泌乳素血症伴不孕症的前瞻性 随机对照研究

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[摘要] **目的:** 探讨自拟柴郁寄生汤治疗高泌乳素血症伴不孕症的效果。**方法:** 采用多中心、随机、双盲、双模拟与平行对照前瞻性方式对2016年10月至2019年9月廊坊市妇幼保健院收治的106例高泌乳素血症伴不孕症的患者进行研究。以随机数字表法将106例患者分为对照组与研究组各53例。对照组服用甲磺酸溴隐亭片治疗, 研究组在此基础上加用自拟柴郁寄生汤治疗。对比两组治疗的总有效率、治疗前后血清内分泌激素指标[血清催乳素(prolactin, PRL)、促卵泡激素(follicle-stimulating hormone, FSH)与孕酮(progesterone, P)]的变化、优势卵泡数、排卵数、随访6个月的妊娠率、妊娠时间, 以及不良反应的发生率。**结果:** 研究组治疗的总有效率为94.34%, 高于对照组(79.25%), 差异有统计学意义($P < 0.05$)。治疗后, 研究组PRL值低于对照组($P < 0.01$), FSH与P值高于对照组, 差异有统计学意义($P < 0.01$)。研究组患者优势卵泡、排卵率均高于对照组, 差异有统计学意义($P < 0.01$ 或 $P < 0.05$)。随访6个月, 研究组妊娠率(35.85%)高于对照组(16.98%), 差异有统计学意义($P < 0.05$)。生存曲线数据分析表明: 与对照组相比, 研究组患者妊娠时间更短, 差异具有统计学意义($P < 0.01$)。研究组不良反应发生率为3.77%, 与对照组(5.66%)比较差异无统计学意义($P > 0.05$)。**结论:** 自拟柴郁寄生汤治疗高泌乳素血症伴不孕症疗效确切, 可以有效改善患者的内分泌激素水平, 提高妊娠率, 且安全可靠, 值得临床推广。

[关键词] 自拟柴郁寄生汤; 中医; 高泌乳素血症; 不孕症

A prospective randomized control study of self-made Chaiyujisheng Decoction in the treatment of hyperprolactinemia with infertility

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Abstract **Objective:** To investigate the effect of self-simulated Chaiyujisheng Decoction on the treatment of hyperprolactinemia with infertility. **Methods:** A total of 106 cases of hyperprolactinemia with infertility in our hospital from October 2016 to September 2019 were studied and the prospective methods used in the research

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were multicenter, randomized, double-blind in addition to double simulation and parallel control. Totally 106 patients were randomly divided into a control group and a study group, with the table of random number 53 cases in each group. The control group was treated with bromocryptine mesilate tablets, and the study group was treated with Chaiyujisheng Decoction. The total effective rates of treatment, the changes of serum endocrine hormone indexes [serum prolactin (PRL), follicle-stimulating hormone (FSH), and progesterone (P)], predominance of follicles, ovulation, pregnancy rates, of follow-up for 6 months, pregnancy time, and the incidence of adverse reactions were compared between the 2 groups before and after the treatment. **Results:** The total effective rate of treatment in the study group was 94.34% higher than that in the control group 79.25%, and the difference was statistically significant ($P<0.05$). After the treatment, the PRL of the study group was lower than those of the control group (all $P<0.01$), and its FSH and P were higher than those of the control group with the statistically significant differences ($P<0.01$). The dominant follicles and ovulation rate of the study group were higher than those of the control group, and the differences were statistically significant ($P<0.01$ or $P<0.05$). After follow-up for 6 months, the pregnancy rate in the study group was 35.85% higher than that in the control group (16.98%) ($P<0.05$). Survival curve showed that compared with the control group, the pregnancy time of the study group was shorter, and the difference was statistically significant ($P<0.01$). The incidence of adverse reactions in the study group was 3.77% and the control group was 5.66%, but there was no significant difference between them ($P>0.05$). **Conclusion:** The self-designed Chaiyujisheng Decoction is effective, safe and reliable on the treatment of hyperprolactinemia with infertility, which can effectively improve the endocrine hormone levels of patients, and improve the pregnancy rate, so it is worthy of clinical promotion.

Keywords self-imitating Chaiyujisheng Decoction; traditional Chinese medicine; hyperprolactinemia; infertility

高泌乳素血症又称为高泌催乳素血症，主要表现为泌乳、闭经、月经稀少、月经频发、不孕、头痛、性功能减退、肥胖等症状^[1]。目前，多巴胺受体激动剂是治疗高泌乳素血症伴不孕症的主要药物，但该药在治疗期间易出现不良反应，且复发率高，所以整体疗效不够理想^[2]。中医认为：高泌乳素血症伴不孕症属于“闭经”“乳泣”“不孕”的范畴，主要与肝气郁结、肾虚肝郁，致使疏泄失常，加之肝郁肾阴，损耗肾阳，肝肾不足，血海空虚，冲任失于濡养有关，故治疗时应取补肾调经、疏肝解郁之法^[3]。柴郁寄生汤具有补肝调冲、疏肝解郁的功效，针对高泌乳素血症伴不孕症的治疗具有独到之处。2016年10月至2019年9月廊坊市妇幼保健院对53例高泌乳素血症伴不孕症的患者应用了自拟柴郁寄生汤治疗，疗效满意，现报告如下。

1 对象与方法

1.1 对象

采用多中心、随机、双盲、双模拟与平行对照前瞻性方式对2016年10月至2019年9月廊坊市妇幼保健院收治的106例高泌乳素血症伴不孕症的患

者进行研究。以随机数字表法将106例患者分为对照组与研究组各53例。纳入标准：西医符合《妇产科学》9版^[4]中的诊断标准，并具有不同程度的溢乳、头痛、月经失调、视觉障碍、性功能改变、眼花、不孕等症状；空腹血清催乳素 (prolactin, PRL) $\geq 25 \mu\text{g/L}$ ；1年内未采取避孕措施且性生活正常的情况下没有成功妊娠。中医符合《中药新药临床研究指导原则(试行)》^[5]中的诊断标准，主症见情绪抑郁或心烦易怒，腰膝酸软，月经量少，婚后不孕，或闭经，伴有溢乳；次症见行经期小腹胀痛，乳房胀痛，拒按，性欲减退，头晕耳鸣或头痛；舌脉为苔薄白，淡红，脉弦细。男方精液常规与生殖免疫检查均为正常；本次研究经医院伦理委员会批准；研究内容已告知患者知情同意。排除标准：多囊卵巢综合征、输卵管粘连等其他原因所致的不孕症；运动、应激刺激、低血糖等原因导致的PRL升高；甲状腺功能或肾功能不全导致的PRL升高；脑垂体腺瘤等颅内占位性疾病；阴道炎、宫颈糜烂等妇科疾病；接受过输卵管结扎、子宫切除、卵巢切除等妇产科手术；有精神疾病史。对照组：年龄22~43(28.6 \pm 3.0)岁；病程2~10(4.5 \pm 0.5)年；其中闭经8例，经量过少或延后45例。研究组：

年龄22~44(28.5±2.8)岁; 病程2~9(4.4±0.6)年; 其中闭经7例, 经量过少或延后46例。2组在年龄、病程与月经情况对比中, 差异无统计学意义($P>0.05$)。研究对象纳入流程图见图1。

1.2 方法

对照组服用甲磺酸溴隐亭片(批准文号: H20160030; 生产厂家: Novartis Farma S.p.A)治疗, 初始用量为2.5 mg/次, 1次/d; 1周内增加至2.5 mg/次, 3次/d; 血清PRL降至正常水平时可根据情况减少用量; 1个月经期为1个疗程, 持续治疗3个疗程。研究组在此基础上加用自拟柴郁寄生汤治疗, 方药组成: 白芍、桑寄生各15 g, 柴胡、香附、郁金各6 g, 当归、泽兰、杜仲、川断各10 g, 甘草5 g。上述方药以水煎煮, 月经第5天时分早晚两次温服, 1个月经期为1个疗程, 持续治疗3个疗程。2组治疗期间若发现妊娠, 则立即停止用药。

1.3 观察指标

主要疗效指标: 1)根据《中药新药临床研究指导原则》与《妇产科疾病诊断治愈标准(第2版)》中的内容对比2组患者的临床疗效, 其中主要疗效指标包括PRL值、复发情况、中医证候积分; 次要疗效指标包括临床症状与体征。中医证候积分: 腰膝酸软、情绪抑郁或心烦易怒、月经稀发或闭经、月经量少、溢乳、经行小腹拒按或

胀痛、性欲减退、乳房胀痛、头晕耳鸣或头痛, 其中无症状计0分, 轻微症状计2分, 中度症状计4分, 重度症状计6分, 舌脉不计分。痊愈: PRL值恢复至正常水平, 随访6个月无复发; 临床症状与体征完全消失; 中医证候积分较治疗前改善 $>95\%$ 。显效: PRL值较治疗前降低 $>50\%$; 临床症状与体征明显好转; 中医证候积分较治疗前恢复70%~95%。有效: PRL值较治疗前降低25%~50%; 临床症状与体征有所改善; 中医证候积分较治疗前改善30%~69%。无效: PRL值较治疗前降低 $<25\%$, 临床症状与体征无好转或加重; 中医证候积分较治疗前改善 $<30\%$ 。总有效率=(痊愈例数+显效例数+有效例数)/总例数 $\times 100\%$ 。2)治疗前后分别采集患者空腹状态下肘静脉血3 mL, 其中月经规律者在月经第3天时取血, 月经稀发者通过超声明确无直径 >1 cm卵泡后取血, 血液样本在室温静置, 离心10 min, 速度为3 000 r/min, 取上清液, 再以电化学发光免疫分析仪对血清内分泌激素PRL、促卵泡激素(follicle-stimulating hormone, FSH)与孕酮(progesterone, P)进行检测。3)在治疗第3个月经周期第7~17天, 每间隔2 d采用阴道超声进行1次卵泡监测, 观察卵泡发育情况, 指导同房并记录优势卵泡与排卵。4)随访6个月, 记录患者的妊娠情况, 即妊娠率与妊娠时间。研究过程中所有患者均进行有效随访, 失访率为0。5)对比2组治疗期间的不良反应, 包括腹泻、恶心、呕吐、乏力、眩晕等。

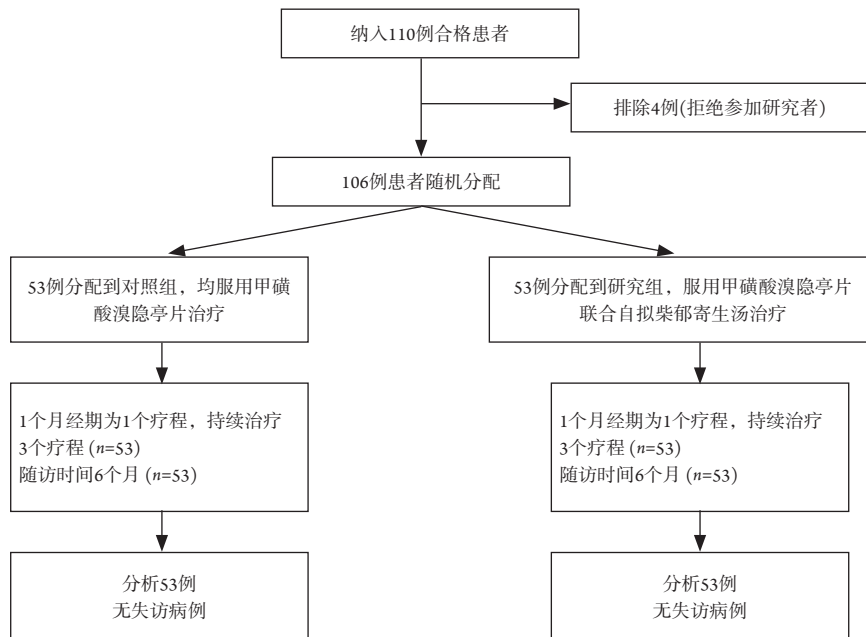


图1 研究对象纳入流程图

Figure 1 Flow chart of research object

1.4 统计学处理

采用前瞻性队列研究的设计方法设计实验流程并计算样本量。通过SPSS 20.0软件中生存函数自动生成Kaplan-Meier(K-M)生存曲线, 计量资料以均数±标准差($\bar{x}\pm s$)描述, 研究组与对照组间比较采用 t 检验; 计数资料以例数(n)与百分率(%)描述, 研究组与对照组间比较采用 χ^2 检验或Fisher精确概率计算。检验水准 $\alpha=0.05$, $P<0.05$ 为差异有统计学意义。

2 结果

2.1 2组治疗的总有效率对比

研究组治疗的总有效率为94.34%, 高于对照组(79.25%), 差异有统计学意义($P<0.05$, 表1)。

2.2 2组治疗前后血清内分泌激素水平对比

治疗前, 与对照组比较, 研究组PRL、FSH

与 P 值对比差异均无统计学意义(均 $P>0.05$); 治疗后, 研究组PRL值低于对照组($P<0.01$), FSH与 P 值高于对照组($P<0.01$, 表2)。

2.3 2组患者优势卵泡与排卵情况对比

研究组患者有优势卵泡、排卵率均高于对照组, 差异有统计学意义($P<0.01$ 或 $P<0.05$, 表3)。

2.4 2组患者妊娠情况对比

随访6个月, 研究组妊娠19例(35.85%), 对照组妊娠9例(16.98%), 研究组妊娠率高于对照组, 差异有统计学意义($\chi^2=4.854$, $P<0.05$)。K-M生存曲线数据分析表明: 与对照组相比, 研究组患者妊娠时间更短, 差异具有统计学意义($P<0.01$, 图2)。

2.5 2组患者治疗的不良反应对比

研究组不良反应发生率为3.77%, 与对照组(5.66%)对比, 差异无统计学意义($P>0.05$, 表4)。

表1 2组治疗的总有效率对比

Table 1 Comparison of total effective rates between the 2 groups

组别	n	痊愈/[例 (%)]	显效/[例 (%)]	有效/[例 (%)]	无效/[例 (%)]	总有效/[例 (%)]
研究组	53	19 (35.85)	21 (39.62)	10 (18.87)	3 (5.66)	50 (94.34)
对照组	53	13 (24.83)	16 (30.19)	13 (24.53)	11 (20.75)	42 (79.25)
P^*						0.022

*Fisher精确概率的 P 值。

表2 2组治疗前后血清内分泌激素水平对比($\bar{x}\pm s$)

Table 2 Comparison of the levels of serum endocrine hormone between the 2 groups before and after the treatment ($\bar{x}\pm s$)

组别	n	PRL/($\mu\text{g}\cdot\text{L}^{-1}$)		FSH/(IU·L ⁻¹)		P/($\mu\text{g}\cdot\text{L}^{-1}$)	
		治疗前	治疗后	治疗前	治疗后	治疗前	治疗后
研究组	53	65.3 ± 5.6	24.3 ± 2.8	7.5 ± 1.6	14.6 ± 1.5	2.2 ± 0.3	11.5 ± 2.0
对照组	53	65.0 ± 4.8	32.6 ± 3.8	7.4 ± 1.4	12.0 ± 1.8	2.1 ± 0.4	8.5 ± 1.3
t		0.296	12.804	0.342	8.078	1.456	9.156
P		0.768	<0.001	0.733	<0.001	0.148	<0.001

表3 2组患者优势卵泡与排卵情况对比

Table 3 Comparison of dominant follicles and ovulation rate between the 2 groups

组别	n	优势卵泡/[例 (%)]	排卵/[例 (%)]
研究组	53	43 (81.13)	39 (73.58)
对照组	53	30 (56.60)	20 (37.74)
χ^2		7.436	13.800
P		0.01	0.000

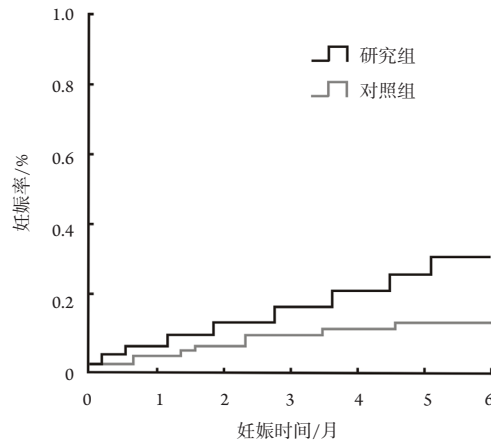


图2 2组患者妊娠时间的K-M生存曲线

Figure 2 K-M survival curves of pregnancy time in the 2 groups

表4 2组不良反应对比

Table 4 Comparison of adverse reactions between the two groups

组别	n	腹泻/[例(%)]	恶心呕吐/[例(%)]	乏力/[例(%)]	眩晕/[例(%)]	不良反应/[例(%)]
研究组	53	0 (0.00)	1 (1.82)	0 (0.00)	1 (1.82)	2 (3.77)
对照组	53	1 (1.82)	2 (3.77)	0 (0.00)	0 (0.00)	3 (5.66)
χ^2						0.210
P						0.647

3 讨论

高泌乳素血症在育龄女性中十分常见, 该病主要与机体在病理、生理、药理等多种因素的作用下, 干扰了多巴胺对PRL的分泌过程, 致使PRL分泌增加有关^[6]。据流行病学报道显示: 高泌乳素血症在育龄女性、月经异常与生殖功能异常女性中的发病率分别占0.4%、5%、17%, 这给女性的生育功能带来了严重的影响^[7]。目前, 多巴胺受体激动剂是治疗高泌乳素血症伴不孕症的主要药物, 其中以甲磺酸溴隐亭片最为常用, 其通过持久刺激泌乳细胞膜中的多巴胺, 并与其结合产生多巴胺效应, 继而有效抑制PRL的分泌与合成, 促进垂体释放FSH, 缓解溢乳、闭经等症状^[8]。部分研究发现: 虽然甲磺酸溴隐亭片具有一定的疗效, 但长期服用易发生耐药与病情反复等问题, 整体疗效不够理想^[9-10]。

近年来, 随着中医药研究的不断深入, 高泌乳素血症伴不孕症患者也有了新的治疗选择。中医认为: 高泌乳素血症伴不孕症属于“闭

经”“乳泣”“不孕”的范畴^[11]。《素问·上古天真论》^[12]中记载“女子七岁, 肾气盛……二七而天癸至, 任脉通, 太冲脉盛, 月事以时下, 故有子”, 其认为妊娠、月经与肾气盛衰具有密切的相关性。《妇人规》中有云“情志不畅, 则冲任不充, 冲任不充则胎孕不受”, 其强调肝气郁结, 冲任无法相资, 摄精成孕受阻。可见, 高泌乳素血症伴不孕症病机与肝气郁结、肾虚肝郁, 致使疏泄失常, 加之肝郁肾阴, 损耗肾阳, 肝肾不足, 血海空虚, 冲任失于濡养有关^[13]。故治疗时应取补肾调经、疏肝解郁之法^[14-15]。自拟柴郁寄生汤中柴胡解表退热、疏肝解郁、升举阳气; 当归活血止痛、补血调经; 香附宽中理气、解郁疏肝、调经止痛; 川断强筋骨、补肝肾、止崩漏; 白芍平抑肝阳、养血敛阴、柔肝止痛; 泽兰活血调经, 利水消肿^[16]; 桑寄生、杜仲养血补肝; 甘草调和诸药, 清热解毒。全方共奏补肝调冲、疏肝解郁的功效^[17]。现代中医药理学认为, 中医药主要遵循脑-肾-冲任-胞宫生殖轴线对女性生殖功能进行调节与治疗, 与现代医学中的下丘脑-垂体-

卵巢性腺轴生理功能相近^[18-19]。自拟柴郁寄生汤中白芍中白芍总苷不仅具有抗炎、镇痛、对抗应激反应与调节免疫等多种功效,还能够改善PRL水平。柴胡中活性成分三菇类中性皂甙,主要作用于丘脑下部和/或垂体,可以兴奋促肾上腺皮质激素,调节下丘脑-垂体-肾上腺轴的生理功能^[20-21]。当归中当归多糖具有抗炎、清除氧自由基、保护肾脏、提高免疫功能等作用,为卵泡发育与排卵提供了有利的条件,且改善了神经内分泌的调节机制^[22]。本研究结果显示:研究组治疗的总有效率为94.34%,高于对照组的79.25%($P<0.05$),优势卵泡、排卵与妊娠率均高于对照组($P<0.01$ 或 $P<0.05$)。可见,在甲磺酸溴隐亭片的基础上应用自拟柴郁寄生汤可以有效提高患者的整体治疗效果,促进排卵,提高妊娠率。

PRL是一种生殖激素,同时也是由脑垂体前叶泌乳细胞分泌的多肽激素,可以通过结合相关受体而发挥出促进乳腺发育、泌乳与调节免疫的作用,继而保证黄体功能,促使卵泡成熟与生长,为妊娠创造良好的微环境^[23-24]。然而,PRL水平升高后能够影响丘脑-垂体-性腺轴功能,干扰下丘脑促性腺激素释放激素(gonadotropin-releasing hormone, GnRH)合成与分泌,减少垂体对于GnRH的敏感程度,进一步降低FSH分泌量,抑制卵巢对促性腺激素的应对能力,阻碍雌激素与孕激素合成,无法形成排卵前雌激素与促黄体生成素(luteinizing hormone, LH)高峰,继而因P与LH分泌不足而影响黄体功能不全,最终导致不孕症^[25-26]。有研究^[27]显示:疏肝解郁中药可以在垂体前叶直接发挥作用,刺激多巴胺受体,继而抑制PRL分泌。同时,疏肝解郁中药可以调节内分泌,提高下丘脑GnRH分泌量,增强垂体对于GnRH的敏感程度^[28]。本研究结果显示:治疗后,研究组PRL值低于对照组($P<0.01$),FSH与P值高于对照组($P<0.01$)。可见,自拟柴郁寄生汤通过调节下丘脑-垂体-卵巢性腺轴功能,可以诱导排卵与促进卵泡发育,提高血清中P与FSH水平,继而发挥出神经内分泌系统的调节机制,纠正患者的临床症状。从安全性来看,研究组不良反应发生率为3.77%,与对照组(5.66%)对比差异无统计学意义($P>0.05$)。结果说明在甲磺酸溴隐亭片的基础上联合自拟柴郁寄生汤并未增加药物不良反应,安全性较佳。

综上,自拟柴郁寄生汤治疗高泌乳素血症伴不孕症疗效确切,可以有效改善患者的内分泌激素水平,提高妊娠率,安全可靠,值得临床推

广。需要注意的是,由于本研究中对照组未服用模拟中药制剂,所以研究结果仅提示联合用药的效果。同时,本研究样本数量与研究时间有限,关于自拟柴郁寄生汤治疗高泌乳素血症伴不孕症的具体作用机制与远期效果仍有待全方位、大样本、长时间的研究。

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