

doi: 10.13241/j.cnki.pmb.2022.15.020

B超配合金匮温经汤治疗卵巢早衰患者疗效及其生殖功能、血清雌激素的影响*

张祁红¹ 李娜^{2△} 肖风娟¹ 王瑛¹ 胡梦迪¹

(1 陕西省中医药研究院(陕西省中医医院)B超室 陕西 西安 710003;

2 陕西省中医药研究院(陕西省中医医院)妇科 陕西 西安 710003)

摘要 目的:探讨B超配合金匮温经汤治疗卵巢早衰患者疗效及其生殖功能、血清雌激素的影响。**方法:**选择2018年5月到2020年12月选择在本院诊治的96例卵巢早衰患者作为研究对象,根据1:1随机数字表法把患者分为研究组与对照组各48例。对照组给予激素替代疗法治疗,研究组在对照组治疗的基础上给予金匮温经汤治疗,所以患者在治疗前后进行B超观察。**结果:**治疗后研究组的总有效率为97.9%,高于对照组的85.4%(P<0.05),两组在治疗期间无严重不良反应发生。两组治疗后的血清卵泡生成激素(FSH)、黄体生成激素(LH)含量都低于治疗前,研究组低于对照组(P<0.05);血清雌二醇(E2)含量都高于治疗前,研究组高于对照组(P<0.05)。两组治疗后的改良Kupperman评分都低于治疗前,研究组低于对照组(P<0.05)。两组治疗后的卵泡数目与卵泡大小都高于治疗前,研究组高于对照组(P<0.05)。**结论:**金匮温经汤治疗卵巢早衰患者能提高治疗效果,改善患者的血清雌激素分泌与生殖功能,也有利于抑制炎症因子的表达,与B超配合使用可反映患者的卵泡情况,更有利于指导临床治疗与预后预测。

关键词:金匮温经汤;卵巢早衰;雌激素;生殖功能;B超

中图分类号:R271;R711.75 文献标识码:A 文章编号:1673-6273(2022)15-2903-05

The Effect of B-ultrasound Combined with Jinkui Wenjing Decoction in the Treatment of Patients with Premature Ovarian Failure and the Effect of Reproductive Function and Serum Estrogen*

ZHANG Qi-hong¹, LI Na^{2△}, XIAO Feng-juan¹, WANG Ying¹, HU Meng-di¹

(1 Department of B ultrasonic, Shaanxi Academy of Traditional Chinese Medicine (Shaanxi Hospital of Traditional Chinese Medicine), Xi'an, Shaanxi, 710003, China; 2 Department of Gynecology, Shaanxi Academy of Traditional Chinese Medicine (Shaanxi Hospital of Traditional Chinese Medicine), Xi'an, Shaanxi, 710003, China)

ABSTRACT Objective: To investigate the effect of B-ultrasound combined with Jinkui Wenjing Decoction in the treatment of patients with premature ovarian failure and the effects of reproductive function and serum estrogen. **Methods:** From May 2018 to December 2020, 96 cases of patients with premature ovarian failure who were diagnosed and treated in this hospital were selected as the research objects. All the cases were divided into the study group and the control group with 48 cases each groups accorded to the 1:1 random number table method. The control group were treated with hormone replacement therapy, and the study group were treated with Jinkui Wenjing Decoction on the basis of the treatment of the control group, so the patients underwent B-ultrasound observation before and after treatment. **Results:** After treatment, the total effective rate of the study group were 97.9%, which were higher than 85.4% of the control group ($P<0.05$). There were no serious adverse reactions in the two groups during the treatment. The serum Follicle-stimulating Hormone (FSH) and Luteinising Hormone (LH) levels after treatment in the two groups were lower than before treatment ($P<0.05$), and the study group were lower than the control group ($P<0.05$). The serum estradiol (E2) levels were higher than before treatment, and the study group were higher than the control group ($P<0.05$). The modified Kupperman scores of the two groups after treatment were lower than those before treatment, and the study group were lower than the control group ($P<0.05$). The number and size of follicles after treatment in the two groups were higher than before treatment ($P<0.05$), and the study group were higher than that in the control group ($P<0.05$). **Conclusion:** Jinkui Wenjing Decoction can improve the treatment effect of patients with premature ovarian failure, improve the patient's serum estrogen secretion and reproductive function, and also help to inhibit the expression of inflammatory factors. The use of combined with B-ul-

* 基金项目:陕西省自然科学基础研究计划项目(2020JM-669)

作者简介:张祁红(1978-),女,本科,主治医师,研究方向:腹部及小器官的超声诊断研究,

电话:13319208638, E-mail:zqh197812@163.com

△ 通讯作者:李娜(1983-),女,硕士,主治医师,研究方向:生殖与不孕症,电话:15686459965, E-mail:linana19830213@163.com

(收稿日期:2022-01-26 接受日期:2022-02-21)

trasound can reflect the patient's follicular condition, and more Conducive to guiding clinical treatment and prognosis prediction.

Key words: Jinkui Wenjing Decoction; Premature ovarian failure; Estrogen; Reproductive function; B-ultrasound

Chinese Library Classification(CLC): R271; R711.75 **Document code: A**

Article ID: 1673-6273(2022)15-2903-05

前言

卵巢早衰(Premature ovarian failure, POF)是指40岁以前的妇女因某种原因引起卵巢功能衰竭而导致不孕、闭经、雌激素水平降低及促性腺激素水平升高等疾病的疾病,多伴随有情绪激动、焦虑抑郁、性欲减退、有面色潮红、烘热汗出等症状,有时甚至使患者呈现自杀倾向^[1,2]。卵巢早衰的具体发病机制还不明确,具体病因包括病毒感染、细菌感染、特异性感染等,各种炎症因子也共同参与卵巢早衰的形成^[3,4]。西医治疗卵巢早衰多采用对症治疗,见效虽快,但是停药后容易复发,且存在药物依赖性^[5]。其中激素替代疗法(Hormone Replacement Therapy, HRT)通过周期性地序贯补充雌孕激素以改善患者的低雌激素水平,可防止降低血管舒张过度与缓解生殖器萎缩退化等,但长期应用激素替代疗法也会产生一定的不良反应^[6,7]。中医认为五脏功能失常在卵巢早衰发生中发挥着重要影响,肾阴不足以上济心阴以制约亢火,不能下助肾阳以温肾水,致肾水寒而凝涩不用,渐至卵巢功能衰退,则心主神明的功能失常,出现烦怒抑郁、心烦神乱等不适症状^[8,9]。中医治疗卵巢早衰也具有重要的作用,特别是金匮温经汤具有疏肝健脾、补血调经、调理冲任等作用,并且可达到强肾作用,以恢复正常卵巢功能、促进正常排卵^[10]。

同时当前卵巢早衰早期诊断难度大,不过B超的应用具有很好的优势^[11,12]。本文具体探讨了B超配合金匮温经汤治疗卵巢早衰患者疗效及其生殖功能、血清雌激素的影响,并阐述了相关机制。现报道如下。

1 资料与方法

1.1 研究对象

选择2018年5月到2020年12月选择在陕西省中医医院诊治的96例卵巢早衰患者作为研究对象。

纳入标准:符合卵巢早衰的诊断标准^[13](超声检查时小卵泡(直径<6 mm)数量<6个或早期卵巢一侧体积(V)<3 m³),病程≥4个月;年龄≤35岁,具有生育需求;配偶身心健康;医院伦理委员会批准了此次研究;入院前3个月内未服用相关激素类药物及免疫抑制剂;患者签署知情同意书,能积极配合完成试验及随访过程。

排除标准:由于智力或行为障碍,无法配合完成临床观察者;生殖器官先天性发育异常者;合并多囊卵巢综合征、子宫病变等患者;肾上腺疾病患者;有卵巢手术史患者。

根据1:1随机数字表法把患者分为研究组与对照组各48例,两组患者等对比无差异($P>0.05$)。见表1。

表1 一般资料对比

Table 1 Comparison of general data

Groups	n	Course of disease (years)	Body mass index (kg/m ²)	Yield (times)	Pregnancy (n)	Age (years)
Research group	48	2.90± 0.10	22.88± 1.82	1.25± 0.33	2.86± 0.46	31.40± 2.30
Control group	48	2.78± 0.30	22.32± 2.84	1.26± 0.14	2.85± 0.17	31.80± 1.80

1.2 治疗方法

对照组:给予激素替代疗法治疗,月经周期的第5 d起,每次口服戊酸雌二醇片/雌二醇环丙孕酮1片(国药准字J20030112,Schering S.A公司,每片含戊酸雌二醇2 mg、醋酸环丙孕酮1 mg),1次/d,每周无间断服用21 d后停药第8 d继续下一周期用药,疗程为3个周期。

研究组:在对照组治疗的基础上给予金匮温经汤治疗,组方:吴茱萸9克、当归6克、芍药6克、人参6克、桂枝6克、阿胶6克、牡丹皮6克、生姜6克、甘草6克、半夏3克、麦门冬3克,水煎300 mL,中饭与晚饭后1 h各服用150 mL,疗程为3个周期。

1.3 观察指标

1.3.1 疗效指标^[14] 痊愈:月经周期、经量、经期恢复正常,或不孕患者妊娠。显效:从治疗开始6个月内月经来潮1-2次以上,经色、质、量明显改善。无效:月经未见来潮,临床症状生活恶化。总有效率=(痊愈数+显效数)÷组内例数×100%。

1.3.2 FSH、LH、E2含量测定 于治疗前后,抽取患者空腹静

脉血,4℃低温,离心10 min分离上层血清,平分为两份,其中一份采用全自动生化分析仪测定卵泡生成激素(Follicle-stimulating Hormone, FSH)、黄体生成激素(Luteinising Hormone, LH)、雌二醇(Estradiol, E2)含量。

1.3.3 评估患者的临床症状^[15] 在治疗前后采用改良Kupperman评分系统评估患者的临床症状(腰骶酸软疼痛、胸闷失眠、烦躁易怒、阴道干涩、性欲下降、两胁胀痛),分数越高,卵巢早衰症状越显著。

1.3.4 卵泡数目和大小 在治疗前后对所有患者进行B超检查,在月经周期的第6-13 d进行检查,测定与记录卵泡数目和大小。

1.4 统计方法

选择SPSS19.00进行分析,检验水准为 $\alpha=0.05$, $P<0.05$ 代表差异有统计学意义。计量数据、计数数据采用均数±标准差、n%表示,比较用t检验与卡方 χ^2 检验分析等。

2 结果

2.1 总有效率对比

治疗后研究组的总有效率为 97.9 %, 对照组为 85.4 %, 研

究组较对照组高($P<0.05$)。见表 2。

表 2 治疗总有效率对比(n)

Table 2 Comparison of total effective rates (n)

Groups	n	Recovery	Excellent	Invalid	Total effective rate
Research group	48	43	4	1	47(97.9)%#
Control group	48	28	13	7	41(85.4%)

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

2.2 血清生殖功能指标及雌激素含量变化对比

与治疗前相比, 两组治疗后的血清 FSH 与 LH 含量均降

低, 研究组较对照组低($P<0.05$); 两组治疗后的血清 E2 含量均

升高, 研究组较对照组高($P<0.05$); 见表 3。

表 3 血清生殖功能指标及雌激素含量变化对比(IU/L, 均数± 标准差)

Table 3 Comparison of serum reproductive function index and estrogen content (IU/L, mean ± standard deviation)

Groups	n	FSH		LH		E2	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment	Pretherapy	Post-treatment
Research group	48	78.29± 11.49	32.10± 3.10**	40.68± 5.92	20.47± 4.13**	16.22± 2.15	33.28± 1.55**
Control group	48	78.10± 10.77	44.20± 4.91*	40.88± 5.13	28.19± 3.32*	16.21± 1.44	25.48± 2.28*

Note: compared with control group, ** $P<0.05$; compared with control group, * $P<0.05$, the same below.

2.3 Kupperman 评分变化对比

与治疗前相比, 两组治疗后的改良 Kupperman 评分均降

低, 研究组较对照组低($P<0.05$)。见表 4。

表 4 Kupperman 评分对比(分, 均数± 标准差)

Table 4 Comparison of Kupperman score (score, mean ± standard deviation)

Groups	n	Pretherapy		Post-treatment	
		32.82± 3.10		14.41± 2.82	
Research group	48				
Control group	48				

2.4 B 超指标变化对比

与治疗前相比, 两组治疗后的卵泡数目与卵泡大小均升

高, 研究组较对照组高($P<0.05$)。见表 5。

表 5 B 超指标变化对比(均数± 标准差)

Table 5 Comparison of b-ultrasound indexes (mean ± standard deviation)

Groups	n	Number of follicles (n)		Follicle size (cm)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Research group	48	1.26± 0.25	5.09± 0.16	0.54± 0.09	1.12± 0.04
Control group	48	1.25± 0.33	3.56± 0.22	0.55± 0.04	0.78± 0.06

3 讨论

卵巢早衰当前在女性中的发生率为 2.0 % 左右, 特别是当前由于女性生活节奏的加快与工作压力的增强, 使得卵巢早衰的发生率呈现逐年升高的趋势^[16,17]。中医无卵巢早衰这一病名, 但可作为 "闭经"、"月经过少" 等范畴, "冲任二脉损伤, 经漏经年不痊" 是卵巢早衰的一个重要发病机制。卵巢早衰的基本病理生理特点为囊性卵泡、间质增生等, 同时表现为雌激素水平低下和促性腺激素浓度升高^[18]。激素替代疗法具有一定的近

期疗效, 但是长期疗效不佳, 且对患者有一定的不良反应损伤^[19]。中医认为卵巢早衰发病还与功能失调的心肝脾等脏器存在相关性, 肾位北方属坎水, 心位南方为离火, 坎离相济, 功能协调。金匮温经汤能有效调节下丘脑 - 垂体 - 卵巢轴生理功能, 改善盆腔内环境, 调节内分泌功能、刺激雌激素分泌^[20]。

本研究显示治疗后研究组的总有效率高于对照组; 两组治疗后的血清 FSH 与 LH 含量较治疗前低, 研究组较对照组低; 两组治疗后的血清 E2 含量均升高, 研究组较对照组高; 与治疗前, 两组治疗后的改良 Kupperman 评分均降低, 研究组较对照

组低,该结果说明金匮温经汤治疗卵巢早衰患者可提高治疗效果,改善患者的血清雌激素分泌,提高生殖功能。该结果与Yi A等人^[21]的研究结果具有一致性。从机制上分析,金匮温经汤具有滋肾清心、交通心肾之功,特别是吴茱萸、当归能养阴,具有养阴润燥生津、清热凉血之功效;芍药、人参可清心宁神以助阴长,具有补虚固精、强筋骨等功效;桂枝、阿胶既滋补肝肾之阴血,又可填肾中之真精;牡丹皮、生姜可养血敛阴、平抑肝阳,有补肾气之功用;甘草、半夏、麦门冬可清热燥湿、清热泻火、清热解毒,还可健脾补益、滋精固肾^[22]。多数卵巢早衰患者伴随有FSH及LH水平升高,FSH可促进卵泡成熟,并进一步促进卵泡颗粒层细胞增生分化^[23]。由腺垂体嗜碱粒细胞进行分泌的LH可协同FSH共同作用,进而维持女性卵巢的月经周期^[24]。血清FSH及LH可以作为评估卵巢功能衰退的指标,主要在于卵巢早衰引起卵泡数目急剧减少,造成对垂体FSH及LH的抑制减弱,导致血清FSH及LH水平升高^[25]。而E2可反馈性抑制垂体的性功能调节轴,避免了过度的FSH或LH异常导致的患者血管舒张功能障碍的出现。因此,在B超的配合下,金匮温经汤应用于卵巢早衰患者的治疗中,其可作用于靶器官进而促进卵泡发育、排出,对垂体促性腺激素功能有调节作用,可改善雌激素缺乏以及生殖内分泌激素水平,调节患者月经周期。

卵巢早衰是指女性40岁前由于卵巢功能衰竭而发生闭经的现象,属于高发妇科病^[26]。本研究显示:与治疗前相比,两组治疗后的卵泡数目与卵泡大小均升高,研究组较对照组高,该结果表明金匮温经汤治疗卵巢早衰患者能促进卵泡数目与卵泡大小恢复情况。该结果与杨华娣等人^[27]的研究结果具有一致性。分析可知:B超检测指标可为卵巢早衰诊断提供参考,特别是其判断卵泡状况可有效区分卵巢早衰绝经期人群、月经正常人群、围卵巢早衰期人群^[28]。金匮温经汤对于子宫动脉血流动力以及血液流变具有促进作用,其可对于子宫血管痉挛进行缓解,进一步改善血液黏度以及红细胞汇集密度,使患者内分泌系统趋于一个新的稳态环境^[29]。金匮温经汤还可改善卵巢组织微环境,还具有抗细胞凋亡及雌激素样等作,从而发挥总体治疗效果^[30]。不过本研究存在一定不足,样本量有限,随访时间较短,因此可能存在一定的统计学偏差与研究偏倚,在后期进行更深入的研究。

总之,金匮温经汤治疗卵巢早衰患者能提高治疗效果,改善患者的血清雌激素分泌与生殖功能,也有利于抑制炎症因子的表达,与B超配合使用可反映患者的卵泡情况,更有利指导临床治疗与预后预测。

参考文献(References)

- [1] Yin N, Wu C, Qiu J, et al. Protective properties of heme oxygenase-1 expressed in umbilical cord mesenchymal stem cells help restore the ovarian function of premature ovarian failure mice through activating the JNK/Bcl-2 signal pathway-regulated autophagy and upregulating the circulating of CD8 (+)CD28 (-) T cells [J]. Stem Cell Res Ther, 2020, 11(1): 49
- [2] Yoon S Y, Yoon J A, Park M, et al. Recovery of ovarian function by human embryonic stem cell-derived mesenchymal stem cells in cisplatin-induced premature ovarian failure in mice[J]. Stem Cell Res Ther, 2020, 11(1): 255
- [3] Yun B S, Lee K J, Song J Y, et al. Small extracellular vesicles derived from embryonic stem cells restore ovarian function of premature ovarian failure through PI3K/AKT signaling pathway [J]. J Pers Med, 2020, 11(1): 3
- [4] Rose B I. An explanation of the mechanisms underlying fragile X-associated premature ovarian insufficiency[J]. J Ovarian Res, 2020, 37(6): 1313-1322
- [5] Shen J, Cao D, Sun J L. Ability of human umbilical cord mesenchymal stem cells to repair chemotherapy-induced premature ovarian failure [J]. World J Stem Cells, 2020, 12(4): 277-287
- [6] Garg N, Behbehani S, Kosiorek H, et al. Hormone Replacement Therapy Prescription after Premature Surgical Menopause [J]. J Minim Invasive Gynecol, 2020, 27(7): 1618-1623
- [7] Iavazzo C, Gkegkes I. Regarding "Hormone Replacement Therapy Prescription after Premature Surgical Menopause" [J]. J Minim Invasive Gynecol, 2020, 27(6): 1425
- [8] Adderley N J, Igboeli P, El Andaloussi A, et al. Intraovarian injection of autologous human mesenchymal stem cells increases estrogen production and reduces menopausal symptoms in women with premature ovarian failure: two case reports and a review of the literature[J]. Bmj, 2020, 14(1): 108
- [9] Keremu A, Yaoliwasi A, Tuerhong M, et al. Research on the establishment of chronic stress-induced premature ovarian failure the rat model and effects of Chinese medicine Muniziqi treatment[J]. Mol Reprod Dev, 2019, 86(2): 175-186
- [10] 汤传梅,沙丹.金匮温经汤对肾虚血瘀型免疫性卵巢早衰患者性激素水平及临床证候积分的影响[J].新中医,2021,53(14): 1-5
- [11] Bahmanpour S, Moradian E, Dehghani F, et al. Chemoprotective effects of plasma derived from mice of different ages and genders on ovarian failure after cyclophosphamide treatment [J]. J Ovarian Res, 2020, 13(1): 138
- [12] Bahrehbar K, Rezazadeh Valojerdi M, Esfandiari F, et al. Human embryonic stem cell-derived mesenchymal stem cells improved premature ovarian failure [J]. World J Stem Cells, 2020, 12 (8): 857-878
- [13] Sheikhan S, Aghebati-Maleki L, Nouri M, et al. Current approaches for the treatment of premature ovarian failure with stem cell therapy[J]. Biomed Pharmacother, 2018, 102(2): 254-262
- [14] Cai L, Zong DK, Tong GQ, et al. Apoptotic mechanism of premature ovarian failure and rescue effect of Traditional Chinese Medicine: a review[J]. J Tradit Chin Med, 2021, 41(3): 492-498
- [15] Wang C, Huang Q, Liang CL, et al. Effect of cimicifuga racemosa on menopausal syndrome caused by LHRH-a in breast cancer [J]. J Ethnopharmacol, 2019, 238(1): 111840
- [16] Ma Q, Tan Y, Mo G. Effectiveness of Cotreatment with Kuntai Capsule and Climen for Premature Ovarian Failure: A Meta-Analysis [J]. Evid Based Complement Alternat Med, 2020, 20(1): 4367359
- [17] 孙娜,高树苓,安朗,等.卵巢早衰患者血清抑制素B、抗苗勒管激素及性激素水平与子宫动脉血流参数的相关性研究[J].现代生物医学进展,2021,21(5): 4
- [18] Cho L, Davis M, Elgendi I, et al. Summary of Updated Recommendations for Primary Prevention of Cardiovascular Disease in Women: JACC State-of-the-Art Review [J]. J Am Coll Cardiol,

- 2020, 75(20): 2602-2618
- [19] Zhou Y, Zhou J, Xu X, et al. Matrigel/Umbilical Cord-Derived Mesenchymal Stem Cells Promote Granulosa Cell Proliferation and Ovarian Vascularization in a Mouse Model of Premature Ovarian Failure[J]. Stem Cells Dev, 2021, 30(15): 782-796
- [20] Cao XJ, Huang X, Liu J, et al. A randomized, double-blind, placebo-controlled trial of Chinese herbal medicine capsules for the treatment of premature ovarian insufficiency[J]. Menopause, 2018, 25(8): 918-926
- [21] Yi A, Qin X, Du Z, et al. Clinical Observation on the Improvement of Serum Sex Hormone and Ovarian Function in Premature Ovarian Failure Patients with Deficiency-Cold Syndrome by Combining Wenjing Decoction with Tiaobu Chongren Acupuncture and Moxibustion[J]. Evid Based Complement Alternat Med, 2021, 11(1): 3926822
- [22] 周艳艳, 刘阳阳, 任静雯, 等. 基于 "一气周流" 学说探析《金匱要略》温经汤[J]. 中国中医基础医学杂志, 2021, 27(3): 488-489
- [23] Amer Abed F, Ezzat Maroof R, Al-Nakkash UMA. Comparing the Diagnostic Accuracy of Anti-Müllerian Hormone and Follicle Stimulating Hormone in Detecting Premature Ovarian Failure in Iraqi Women by ROC Analysis [J]. Rep Biochem Mol Biol, 2019, 8(2): 126-131
- [24] Mauri D, Gazouli I, Zarkavelis G, et al. Chemotherapy Associated Ovarian Failure[J]. Front Endocrinol (Lausanne), 2020, 11(2): 572388
- [25] Brown S E, Sasaki Y, Ikeda Y, et al. Estrogen-SIRT1 Axis Plays a Pivotal Role in Protecting Arteries Against Menopause-Induced Senescence and Atherosclerosis [J]. J Assist Reprod Genet, 2020, 27(1): 47-59
- [26] Li M, Peng J, Zeng Z. Overexpression of long non-coding RNA nuclear enriched abundant transcript 1 inhibits the expression of p53 and improves premature ovarian failure [J]. Stem Cells Int, 2020, 20(5): 69-74
- [27] 杨华娣, 邵一峰, 单双双, 等. 金匱温经汤联合芬吗通治疗化疗源性卵巢早衰的临床疗效[J]. 中成药, 2019, 41(5): 3
- [28] Liang X, Yan Z, Ma W, et al. Peroxiredoxin 4 protects against ovarian ageing by ameliorating D-galactose-induced oxidative damage in mice[J]. Cell Death Dis, 2020, 11(12): 1053
- [29] Nie X, Dai Y, Zheng Y, et al. Establishment of a Mouse Model of Premature Ovarian Failure Using Consecutive Superovulation[J]. Cell Physiol Biochem, 2018, 51(5): 2341-2358
- [30] 徐丁洁, 徐洪, 张碧激, 等. 金匱温经汤对围绝经期大鼠性激素水平及卵巢凋亡相关蛋白 Bcl-2、Bax 表达的影响 [J]. 东南大学学报(医学版), 2019, 38(2): 355-357