doi: 10.13241/j.cnki.pmb.2017.23.028

来曲唑联合 GnRH-a 对多囊卵巢综合征患者雌激素水平及对排卵质量的影响 *

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摘要 目的：研究来曲唑(Letrozole，LE)联合醋酸曲普瑞林(GnRH-a)治疗多囊卵巢综合征(PCOS)的临床疗效及对排卵质量的影响。**方法：**选取我院 2014 年 8 月到 2016 年 1 月收治的 PCOS 患者 112 例，随机将其分为对照组(50 例)和观察组(62 例)。在月经周期第 3~7 天时，观察组患者口服 LE，2.5 mg/d；对照组患者肌肉注射人绝经期促性腺素(HMG)，75 IU/d。当最大卵泡直径(MFD)≥ 18 mm 时，观察组患者皮下注射 0.1 mg 醋酸曲普瑞林诱发排卵，对照组患者肌肉注射 6000~10000 IU 人绒毛膜促性腺激素(HCG)诱发排卵。比较两组患者诱发排卵日的排卵效果和血清各激素水平，并统计妊娠结局。**结果：**诱发排卵日，两组患者的子宫内膜厚度、成熟卵泡数目、血清黄体生成激素(LH)和孕酮(P)水平、排卵率、妊娠率及黄体功能不全发生率比较差异均无统计学意义(P>0.05)，观察组的优势卵泡数目、血清 E2 和 T 水平、多胎率、OHSS 发生率及卵巢囊肿发生率均明显低于对照组(P<0.05)。**结论：**LE 联合 GnRH-a 可有效提高 PCOS 患者的排卵质量，降低血清雌激素水平，并能预防 OHSS 发生，改善妊娠结局。

关键词：来曲唑；醋酸曲普瑞林；多囊卵巢综合征；雌激素；排卵质量

中图分类号：R711.6；R711.75 **文献标识码：**A **文章编号：**1673-6273(2017)23-4521-04

Effect of Letrozole Combined with GnRH-a on Serum Estrogen Levels and Ovulation Quality of Patients with Polycystic Ovary Syndrome*

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ABSTRACT Objective: To study the clinical effect of letrozole combined with triptorelin acetate (GnRH-a) on the serum estrogen level and ovulation quality of patients with polycystic ovary syndrome(PCOS). **Methods:** 112 cases of PCOS patients in our hospital from August 2014 to January 2016 were selected and randomly divided into the control group (50 cases) and the observation group (62 cases) according to the wishes of patients. During the first 3~7 days of the menstrual cycle, the patients in the observation group were treated by LE, 2.5 mg/d; the patients in the control group were given intramuscular injection of human menopausal gonadotropin (HMG), 75 IU/d. when the diameter of the largest follicle (MFD)≥ 18 mm, the patients in the observation group were were given subcutaneous injection of 0.1 mg triptorelin acetate induced ovulation, patients in the control group were given intramuscular injection of Human chorionic gonadotropin HCG6000~10000IU induced ovulation. The ovulation induced ovulation effect and the serum hormone levels and pregnancy outcome were compared between two groups. **Results:** On the induced ovulation day, no significant difference was found in the endometrial thickness, the number of mature follicles, serum LH and P levels, rate of pregnancy and the luteal function between two groups of patients (P>0.05), the number of dominant follicles, serum E2 and T levels, multiple pregnancy rate, the incidence of OHSS and ovarian cyst in observed group were significantly lower than those of the control group (P<0.05). **Conclusion:** LE combined with GnRH-a could effectively improve the quality of ovulation in patients with PCOS, reduce the serum level of estrogen, and prevent the occurrence of OHSS, improve the outcome of pregnancy.

Key words: Letrozole; GnRH-a; PCOS; Estrogen; Ovulation quality

Chinese Library Classification(CLC): R711.6; R711.75 Document code: A

Article ID: 1673-6273(2017)23-4521-04

前言

多囊卵巢综合征(polycystic ovarian syndrome，PCOS)是育龄期妇女高发的内分泌代谢紊乱性疾病，以持续性无排卵、高雄激素血症为主要特征，是导致妇女不孕的主要疾病。据统计显示，PCOS 目前发病率为 5.0%~10.0%[1]，其中高达 90.0%以上

* 基金项目：陕西省教育厅科研计划项目 2013JK0782

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(收稿日期：2016-12-20 接受日期：2017-01-15)

无排卵型不孕症因 PCOS 所致,严重威胁女性的生殖健康。促排卵药物 LE 或 HMG 是目前治疗 PCOS 的主要治疗手段,能有效改善机体激素水平,提高排卵质量,进而提高妊娠成功率[2]。但研究显示,HMG 在促排卵过程中因其较强的药效易引起多胎、卵巢过度刺激症(OHSS)等并发症,限制其临床应用[3]。LE 属于第三代芳香化酶抑制剂,能有效促进卵泡发育及释放,目前广泛应用于治疗 PCOS,被证实具有较高的疗效及安全性[4]。大量研究显示[5,6]在促排卵治疗过程中辅以 GnRH-a 诱发排卵,较单独应用具有更优的促排卵效果。人绒毛膜促性腺激素(HCG)既往常被用于替代内源性 LH 峰,以促进卵泡发育及排出,但存在诱发低体重胎儿、早产儿以及 OHSS 风险[7]。近年来研究显示[8]使用 GnRH-a 替代 HCG 用于诱发排卵不仅可取得较高的效果,且安全性更高。因此,本研究采用 LE 联合GnRH-a 治疗 PCOS,探究其促排卵效果,旨在为临床提供参考。

1 资料与方法

1.1 一般资料

研究对象选取我院 2014 年 8 月到 2016 年 1 月收治的 POCS 患者 112 例,纳入标准:① 均符合 2003 年鹿特丹修正的 PCOS 诊断标准[9];② 在排除男方不孕因素后,正常性生活一年以上未孕者;③ 无合并严重心脑血管、肝肾肺等器官组织疾病;④ 超声检查证实至少一侧输卵管通畅;⑤ 均自愿参加本研究并签署知情同意书。排除标准:① 对本研究药物过敏者;② 严重内分泌系统、血液系统或免疫系统疾病者;③ 其他妇科疾病所致不孕者;④ 合并甲状腺功能异常者。将其随机分为对照组(50 例)和观察组(62 例),对照组患者年龄在 23~38 岁,平均年龄为(28.75± 2.61)岁,不孕年限在 2~8 年,平均时间为(3.64± 1.82)年,体重指数(BMI)在 22~25 kg/m^2,平均 BMI 为(23.16± 0.77) kg/m^2;观察组患者年龄在 23~37 岁,平均年龄为(28.59± 2.72)岁,不孕年限在 3~8 年,平均时间为(3.86± 1.90)年,体重指数(BMI)在 22~24 kg/m^2,平均 BMI 为(23.25± 0.81)kg/m^2。两组患者在年龄、不孕时间及 BMI 等一般资料比较差异均无统计学意义(P>0.05),具可比性。本研究经院内伦理委员会审核批准。

1.2 治疗方法

所有患者治疗前需疏通双侧输卵管,同时服用炔雌醇环丙孕酮片 (仙琚制药股份有限公司,H20065479, 2 mg) 治疗 1~3 月,改善患者内分泌。在征得患者意愿后,观察组患者于月经周期的第 3~7 天口服 LE (江苏恒瑞医药股份有限公司,H19991001,2.5 mg)治疗,2.5 mg/d;对照组患者于月经周期第 3 天起,给予肌肉注射 HMG 治疗,75 IU/d。经阴道超声检查卵泡直径,当最大卵泡直径≥ 18 mm 时,给予观察组患者皮下注射醋酸曲普瑞林 (成都天台山制药有限公司,H20058648,0.1 mg) 0.1 mg 1 次诱发排卵,对照组患者肌肉注射 HCG 诱发排卵,剂量为 6000~10000 IU,于注射 24 h 后,均进行指导同房,同时排卵后均口服黄体酮胶丸 (湖北葛店人福药业有限责任公司,H20066109,200 mg),200 mg/ 次,1 次 /d,连续治疗 12 d。

1.3 观察指标

① 两组患者诱发排卵日的子宫内膜厚度、成熟卵泡数目、优势卵泡(≥ 14 mm)数目,均采用经阴道超声检查;② 两组患者诱发排卵日的血清黄体生成素(LH)、雌激素(E2)、孕激素(P)水平,采用放射免疫法(罗氏 e411 检测仪)进行检测[10];③ 两组患者的排卵率、妊娠率、多胎率、OHSS 发生率、黄体功能不全以及卵巢囊肿发生率。

1.4 统计学方法

所有统计学资料都采用 SPSS21.0 专业统计学软件进行数据分析,计量资料以均数± 标准差表示,进行 t 检验。而所有的计数资料用 x^2 检验,P<0.05 为差异具有统计学意义。

2 结果

2.1 两组患者在诱发排卵日的促排卵效果指标比较

两组患者在诱发排卵日的子宫内膜厚度和成熟卵泡数目比较均无明显差异(P>0.05),观察组患者的优势卵泡数目明显低于对照组(P<0.01),详情见表 1。

表 1 两组患者在诱发排卵日的促排卵效果指标比较($\bar{x}$± s)

Table 1 Comparison of the ovulation promoting effect index between two groups of patients on the induction ovulation day($\bar{x}$± s)

Groups	Endometrial thickness(mm)	Number of mature follicles	Dominant follicle number
Control group(n=50)	9.27± 0.71	2.64± 0.46	3.12± 0.68
Observation group (n=62)	9.86± 0.75	3.01± 0.53	1.87± 0.56
P	0.95	0.45	0.00

2.2 两组患者在诱发排卵日的血清激素水平比较

两组患者在诱发排卵日的血清 LH 和 P 水平比较无明显差异(P>0.05);观察组患者在诱发排卵日的血清 E2 和 T 水平明显低于对照组(P<0.01),详情见表 2。

表 2 两组患者在诱发排卵日的血清激素水平比较($\bar{x}$± s)

Table 2 Comparison of the serum hormone levels between two groups of patients on the ovulation induction day($\bar{x}$± s)

Groups	LH(mIU/mL)	E2(pg/L)	P(ng/mL)	T(ng/dL)
Control group(n=50)	10.74± 1.91	1185.46± 206.38	0.65± 0.37	0.91± 0.43
Observation group(n=62)	9.68± 1.50	381.09± 83.51	0.61± 0.34	0.65± 0.31
P	0.17	0.00	0.57	0.00

2.3 两组患者的妊娠结局比较

两组患者的排卵率、妊娠率及黄体功能不全发生率比较均无明显差异(P>0.05),观察组患者的多胎率、OHSS 发生率及卵巢囊肿发生率比较均明显低于对照组(P<0.05),详情见表 3。

表 3 两组患者的妊娠结局比较[例(%)]

Table 3 Comparison of the pregnancy outcome between two groups of patients[n(%)]

Groups	Ovulation rate	Pregnancy rate	Polyembryony rate	Incidence rate of OHSS	Oophoritic cyst	Insufficiency of corpus corpus
control group(n=50)	44(88.00)	12(24.00)	7(14.00)	8(16.00)	11(22.00)	0(0.00)
observation group(n=62)	56(90.32)	17(27.41)	1(1.61)	0(0.00)	2(3.22)	3(4.84)
P	0.69	0.66	0.01	0.00	0.00	0.11

3 讨论

PCOS 是一种复杂性内分泌紊乱综合征,其病因目前尚未明确阐述,可能与遗传、环境等因素有关[11],以持续无排卵和高雄激素血症以及胰岛素抵抗为主要病理生理特征。研究证实[12]无排卵是引起 PCOS 患者不孕的主要原因,因此促排卵是其主要的治疗方法,且注重单卵泡的发育,以减少多胎及其他并发症发生。LE 和 HMG 是目前治疗 PCOS 最常见的两种促排卵药物。HMG 主要由 FSH 和 LH 组成,其中 FSH 能促进卵泡发育并分泌雌激素,而 LH 则可刺激卵巢黄体分泌孕激素,促进子宫内膜细胞增生。但研究显示[13]其较强的药理作用易引起多胎、OHSS 等并发症,治疗安全性存在较大争议。LE 属于第三代非甾体类芳香化酶抑制剂,既往常用以治疗乳腺癌,近年来在促排卵治疗中有着广泛应用。药理学研究显示[14]LE 可有效抑制芳香化酶活性,减少雄激素向雌激素的转化,从而降低血清雌激素浓度, 消除内源性雌激素对下丘脑 - 垂体 - 性腺轴的负反馈抑制,进而促进垂体分泌促性腺激素,刺激卵泡的发育及成熟。同时阻碍雄激素的转化,使卵巢局部暂时性雄激素浓度升高, 还可促进 FSH 受体表达及增强胰岛素样生长因子作用,提高卵泡对 FSH 敏感性和机体对药物敏感性,进而促进卵泡的成熟及排出[15]。且 LE 还具有半衰期短、无结合雌激素受体作用,促进卵泡晚期雌激素与雌激素受体结合,改善宫颈粘液状态以及子宫内血流, 促进子宫内膜间质及上皮细胞增殖,为受精卵着床提供有利条件。

Layeequr RR 等[16]研究表明 LE 和 LMG 均可取得较好的促排卵效果,但 LE 能明显降低血清 E2 水平,减少 OHSS、卵巢囊肿等并发症风险。本研究结果显示两组患者在促排卵日在子宫内膜厚度、成熟卵泡数以及血清 LH 和 P 水平均无明显差异,表明两种药物均可取得较好的促排卵效果,但 LE 治疗的优势卵泡数更少,且血清 E2 和 T 水平更低,与 Kruljac I 等[17]研究一致。诱发排卵是治疗 PCOS 的重要环节,既往临床多采用 HCG 治疗,是从孕妇尿液中所提取出的生物制剂,化学结构及生物学性能与 LH 相似, 其效能是自然排卵周期前 LH 峰值的 20 倍[18],但也明显增加 OHSS、多胎及卵巢囊肿发生率。近年来,GnRH-a 在诱发排卵中得到广泛应用,醋酸曲普瑞林属于短效 GnRH-a,与 GnRH 受体有着高度亲和力,通过结合激素受体复合物,使 FSH 和 LH 在短期内急剧增加,其激发的 LH 和 FSH 峰值更接近于正常内源性周期,并可作用于卵巢增加颗粒细胞前列素的合成,激活卵巢组织型纤维蛋白溶解酶原激活因子活性,从而诱发卵泡发育及排出[19]。本研究结果显示两组患者在排卵率和妊娠率虽无明显差异, 但观察组患者的多胎率、OHSS 发生率以及卵巢囊肿率明显低于对照组, 证实 LE 联合醋酸曲普瑞林治疗 PCOS 的安全性更高,与目前研究结果一致[20]。其原因可能与 LE 无雌激素结合作用,优势卵泡生长机雌激素水平上升时,FSH 可通过负反馈作用抑制部分小的卵泡闭锁,有更利优势卵泡形成,且醋酸曲普瑞林诱发排卵时的作用更接近与正常周期的激素水平,进而减少 OHSS、卵巢囊肿等并发症发生。但本研究结果显示观察组患者存在黄体功能不全发生危险, 这与 GnRH-a 对黄体期雌激素和孕激素降低有关。因此,在诱发排卵过程中需注意优化黄体支持方案,同时雄激素水平过高患者需谨慎使用 LE。

综上所述,LE 联合 GnRH-a 治疗可有效提高 PCOS 患者排卵的质量,降低血清雌激素水平,并能预防 OHSS 发生,改善妊娠结局。

参 考 文 献(References)

[1] Wang Y Q, Yu N, Xu W M, et al. Cetrotide administration in the early luteal phase in patients at high risk of ovarian hyperstimulation syndrome: A controlled clinical study [J]. Experimental & Therapeutic Medicine, 2014, 8(8): 1855-1860

[2] Farag A H, El-Deen M H N, Hassan R M. Triggering ovulation with gonadotropin-releasing hormone agonist versus human chorionic gonadotropin in polycystic ovarian syndrome. A randomized trial [J]. Middle East Fertility Society Journal, 2015, 123(4): 217-223

[3] Siebert T I, Kruger T F, Grieve C L, et al. Is the use of a GnRH antagonist effective in patients with polycystic ovarian syndrome? A South African perspective[J]. South African Journal of Obstetrics & Gynaecology, 2012, 18(1): 11-14

[4] Marci R, Graziano A, Lo M G, et al. GnRH antagonists in assisted reproductive techniques: a review on the Italian experience [J]. European Review for Medical & Pharmacological Sciences, 2013, 17(7): 853-873

[5] Wang L, Li H, Ai J, et al. Attenuated AMH signaling pathway plays an important role in the pathogenesis of ovarian hyperstimulation syndrome [J]. American Journal of Translational Research, 2015, 7(10): 1925-1938

[6] Huang P X, Wei J H, Wei L H. Gonadotropin-releasing hormone agonist for oocyte triggering in endometrial preparation of letrozole stimulation protocols does not affect clinical outcome of frozen-thawed embryo transfer [J]. International Journal of Clinical & Experimental Medicine, 2015, 8(10): 411-437

[7] Panday K, Gona A, Humphrey M B. Medication-induced osteoporosis: screening and treatment strategies [J]. Therapeutic Advances in Musculoskeletal Disease, 2014, 6(5): 185-202

[8] Hu Y J, Chen Y Z, Zhu Y M, et al. Letrozole stimulation in endometrial preparation for cryopreserved-thawed embryo transfer in women with polycystic ovarian syndrome: a pilot study[J]. Clinical Endocrinology,

2014, 80(2): 283-289

[9] Group. E S P C W. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome [J]. Human Reproduction, 2004, 19(1): 19-25

[10] Bodri D, Kawachiya S, Brucker M D, et al. Cumulative success rates following mild IVF in unselected infertile patients: a 3-year, single-centre cohort study [J]. Reproductive Biomedicine Online, 2014, 28(5): 572-581

[11] Zhang X J, Liu S Y, Fu W, et al. The association of serum estradiol level with outcomes of clomiphene citrate/human menopausal gonadotropin ovarian stimulation for in vitro fertilization and embryo transfer [J]. Reproductive Biology and Endocrinology, 2015, 13(1): 1-7

[12] A Ganesh M, Rahmati J, Kasius XL, et al. Session 56: Endometrial Function Determines Implantation Success[J]. Human Reproduction, 2014, 12(8): 69-71

[13] Foroozanfard F, Saberi H, Moraveji S A, et al. Pregnancy rate following luteal phase support in Iranian women with polycystic ovarian syndrome[J]. International Journal of Fertility & Sterility, 2014, 8(3): 235-242

[14] Rahman F, Mahmud N, Chowdhury T, et al. Follicular Response by using Letrozole alone or combination of Letrozole and Gonadotrophins in patients stimulated for IUI [J]. Bangladesh Journal of Obstetrics & Gynecology, 2013, 26(1): 718-724

[15] Azra A, Pejman M M, Akbari A F, et al. Effects of Letrozole-HMG and Clomiphene-HMG on Incidence of Luteinized Unruptured Follicle Syndrome in Infertile Women Undergoing Induction Ovulation and Intrauterine Insemination: A Randomised Trial[J]. Global Journal of Health Science, 2015, 8(4): 244-252

[16] Layeequr R R, Sandhya P. Chemoprevention of Breast Cancer: The Paradox of Evidence versus Advocacy Inaction [J]. Cancers, 2012, 4 (4): 1146-1160

[17] Kruljac I, Butorac D, Vrkljan M. Letrozole or clomiphene for infertility in the polycystic ovary syndrome [J]. New England Journal of Medicine, 2014, 371(15): 1462-1464

[18] Legro R S, Brzyski R G, Diamond M P, et al. Letrozole versus clomiphene for infertility in the polycystic ovary syndrome.[J]. New England Journal of Medicine, 2014, 371(2): 119-129

[19] Li D, Li C, Xu Y, et al. Differential Expression of microRNAs in the Ovaries from Letrozole-Induced Rat Model of Polycystic Ovary Syndrome[J]. Dna & Cell Biology, 2016, 35(4): 394-399

[20] Zhu X, Zhang X, Fu Y. Utrogestan as an effective oral alternative for preventing premature luteinizing hormone surges in women undergoing controlled ovarian hyperstimulation for in vitro fertilization [J]. Medicine, 2015, 94(21): 709-715

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[10] Paladini L, Fabris L, Bottai G, et al. Targeting microRNAs as key modulators of tumor immune response [J]. J Exp Clin Cancer Res, 2016, 35: 103

[11] Guo H, Li Q, Li W, et al. MiR-96 downregulates RECK to promote growth and motility of non-small cell lung cancer cells [J]. Mol Cell Biochem, 2014, 390(1-2): 155-160

[12] Teng Y, Mei Y, Hawthorn L, et al. WASF3 regulates miR-200 inactivation by ZEB1 through suppression of KISS1 leading to increased invasiveness in breast cancer cells [J]. Oncogene, 2014, 33 (2): 203-211

[13] Shi L, Jackstadt R, Siemens H, et al. p53-induced miR-15a/16-1 and AP4 form a double-negative feedback loop to regulate epithelial-mesenchymal transition and metastasis in colorectal cancer [J]. Cancer Res, 2014, 74(2): 532-542

[14] Fisher JN, Terao M, Fratelli M, et al. MicroRNA networks regulated by all-trans retinoic acid and Lapatinib control the growth, survival and motility of breast cancer cells [J]. Oncotarget, 2015, 6 (15): 13176-13200

[15] Nam EJ, Kim S, Lee TS, et al. Primary and recurrent ovarian high-grade serous carcinomas display similar microRNA expression patterns relative to those of normal ovarian tissue [J]. Oncotarget, 2016 [Epub ahead of print]

[16] Pizzimenti S, Ferracin M, Sabbioni S, et al. MicroRNA expression changes during human leukemic HL-60 cell differentiation induced by 4-hydroxynonenal, a product of lipid peroxidation [J]. Free Radic Biol Med, 2009, 46(2): 282-288

[17] Lee JE, Hong EJ, Nam HY, et al. Molecular signatures in response to Isoliquiritigenin in lymphoblastoid cell lines [J]. Biochem Biophys Res Commun, 2012, 427(2): 392-397

[18] Gu H, Yang T, Fu S, et al. MicroRNA-490-3p inhibits proliferation of A549 lung cancer cells by targeting CCND1[J]. Biochem Biophys Res Commun, 2014, 444(1): 104-108

[19] Ye XW, Yu H, Jin YK, et al. miR-138 inhibits proliferation by targeting 3-phosphoinositide-dependent protein kinase-1 in non-small cell lung cancer cells[J]. Clin Respir J, 2015, 9(1): 27-33

[20] Nardelli C, Iaffaldano L, Ferrigno M, et al. Characterization and predicted role of the microRNA expression profile in amnion from obese pregnant women[J]. Int J Obes (Lond), 2014, 38(3): 466-469

[21] Broustas CG, Gokhale PC, Rahman A, et al. BRCC2, a novel BH3-like domain-containing protein, induces apoptosis in a caspase-dependent manner[J]. J Biol Chem, 2004, 279(25): 26780-26788

[22] Yu X, Li Z. BLID: A Novel Tumor-Suppressor Gene [J]. Oncol Res, 2014, 22(5-6): 333-338

[23] Zhao F, Bai J, Chen W, et al. Evaluation of BLID and LOC399959 as candidate genes for high myopia in the Chinese Han population [J]. Mol Vis, 2010, 16: 1920-1927