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麒麟丸联合炔雌醇环丙孕酮对多囊卵巢综合征致不孕症患者子宫内膜容受性、血清性激素和氧化应激水平的影响*

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摘要 目的:探讨麒麟丸联合炔雌醇环丙孕酮对多囊卵巢综合征(PCOS)致不孕症患者子宫内膜容受性、血清性激素和氧化应激水平的影响。**方法:**选取我院于2018年1月~2020年1月期间收治的PCOS致不孕症患者460例,符合要求的患者按照随机数字表法分为对照组和研究组,各为230例。对照组患者予以炔雌醇环丙孕酮治疗,研究组予以麒麟丸联合炔雌醇环丙孕酮治疗,对比两组疗效、子宫内膜容受性、性激素、氧化应激、排卵率、妊娠率和不良反应。**结果:**研究组的临床总有效率较对照组更高(P<0.05)。研究组治疗后子宫动脉搏动指数(PI)、子宫动脉血流阻力指数(RI)低于对照组,子宫内膜厚度大于对照组(P<0.05)。研究组治疗后促卵泡激素(FSH)和黄体生成素(LH)低于对照组,雌二醇(E2)高于对照组(P<0.05)。研究组治疗后丙二醛(MDA)、活性氧物质(ROS)低于对照组,过氧化物歧化酶(SOD)高于对照组(P<0.05)。随访6个月后,研究组的妊娠率、排卵率明显高于对照组(P<0.05)。两组不良反应发生率组间对比无差异(P>0.05)。**结论:**麒麟丸联合炔雌醇环丙孕酮治疗PCOS致不孕症患者,可以有效改善患者子宫内膜容受性、血清性激素和氧化应激状态,提高妊娠率、排卵率,安全有效。

关键词:麒麟丸;炔雌醇环丙孕酮;多囊卵巢综合征;不孕症;子宫内膜容受性;性激素;氧化应激
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Effects of Qilin Pill Combined with Ethinylestradiol and Cyproterone on Endometrial Receptivity, Serum Sex Hormones and Oxidative Stress Levels in Infertile Patients with Polycystic Ovary Syndrome*

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ABSTRACT Objective: To investigate the effects of Qilin pill combined with ethinylestradiol and cyproterone on endometrial receptivity, serum sex hormones and oxidative stress levels in infertile patients with polycystic ovary syndrome (PCOS). **Methods:** A total of 460 infertility patients with PCOS in our hospital from January 2018 to January 2020 were selected. The patients who met the requirements were randomly divided into control group and study group, 230 cases in each group. The control group was treated with ethinylestradiol and cyproterone, while the study group was treated with Qilin pill combined with ethinylestradiol and cyproterone. The efficacy, endometrial receptivity, sex hormone, oxidative stress, ovulation rate, pregnancy rate and adverse reactions of the two groups were compared. **Results:** The total effective rate of the study group was higher than that of the control group(P<0.05). After treatment, the uterine artery pulsatility index(PI) and uterine artery resistance index (RI) of the study group were lower than those of the control group, and the endometrial thickness was greater than that of the control group (P<0.05). After treatment, the follicle stimulating hormone (FSH) and luteinizing hormone (LH) of the study group were lower than those of the control group, and the estradiol (E_2) of the study group was higher than that of the control group (P<0.05). After treatment, malondialdehyde (MDA) and reactive oxygen species (ROS) of the study group were lower than those of the control group, while superoxide dismutase (SOD) was higher than that of the control group (P<0.05). After 6 months of follow-up, the pregnancy rate and ovulation rate of the study group were significantly higher than those of the control group(P<0.05). There was no difference in the incidence rate of adverse reactions between the two groups(P>0.05). **Conclusion:** Qilin pill combined with ethinylestradiol and cyproterone in the treatment of infertility patients with PCOS, can effectively improve the endometrial receptivity, serum sex hormone and oxidative stress state of patients, improve pregnancy rate, ovulation rate, safe and effective.

Key words: Qilin pill; Ethinylestradiol and cyproterone; Polycystic ovary syndrome; Infertile; Endometrial receptivity; Sex hormone; Oxidative stress

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前言

多囊卵巢综合征(PCOS)是育龄期女性常见的妇科内分泌疾病,其发病与基因多态性、环境、遗传、代谢综合征等因素紧密相关,是导致女性不孕的主要原因之一,给患者及其家庭带来严重影响[1-3]。现临床针对 PCOS 致不孕症患者的治疗尚无特效方案,多以促进排卵、降低高雄激素血症和胰岛素增敏剂进行治疗[4]。炔雌醇环丙孕酮是常见的口服避孕药物,既往应用于 PCOS 致不孕症可获得一定的效果[5],但长期用药也存在子宫内膜发育欠佳、卵巢过度刺激、卵泡黄素化等多种并发症,疗效尚不十分理想[6]。麒麟丸对女子不孕患者具有辅助治疗效果,主要成分包括锁阳、覆盆子、淫羊藿、制首乌、菟丝子、丹参、郁金、白芍、桑椹等组成,具有益气养血、补肾填精的功效[7]。本研究对我院收治的部分 PCOS 致不孕症患者给予麒麟丸联合炔雌醇环丙孕酮治疗,疗效较好,整理报道如下。

1 资料与方法

1.1 临床资料

本研究为前瞻性研究，选取我院于 2018 年 1 月 ~2020 年 1 月期间收治的 PCOS 致不孕症患者 460 例,所有入选患者均符合《多囊卵巢综合征中国诊疗指南》[8]、《中华妇产科学》[9]中的相关诊断标准:高雄激素的临床表现和(或) 高雄激素血症,超声表现为多囊卵巢,稀发排卵或无排卵,不孕症诊断标准参照《中华妇产科学》相关标准确诊。纳入标准:(1)患者及其家属知情本研究并签署了同意书;(2)治疗期间,有正常的夫妻生活且配偶的生殖功能正常。排除标准:(1)过敏体质或对药物所含成分过敏者;(2)伴有精神疾病,不能配合治疗者;(3)合并其他内分泌疾病者;(4)正在接受其他方案治疗者;(5)有先天生理缺陷或畸形导致月经不调及不孕者。病例脱落标准: (1)在试验过程中发生过敏反应;(2)受试者自行退出。将符合要求的患者按照随机数字表法分为研究组、对照组。其中对照组 230 例,年龄 20~40 岁，平均（29.86± 3.35）岁；不孕年限 1~10 年，平均(5.34± 0.72)年;体质量指数 20~27 kg/m^2,平均(23.59± 0.86) kg/m^2。研究组 230 例,年龄 21~39 岁,平均(29.48± 2.93)岁;不孕年限 2~8 年,平均(5.26± 0.63)年;体质量指数 21~27 kg/m^2,平均(23.36± 0.77)kg/m^2。两组一般资料均衡可比(P>0.05),具有可比性。本研究已通过我院伦理学委员会批准进行。

1.2 方法

对照组给予炔雌醇环丙孕酮(国药准字 H20094005,上海信谊天平药业有限公司,)治疗,口服,于月经自然周期第 5 d 开始服药,1 片 / 次,1 次 /d。研究组则在对照组的基础上给予麒麟丸(国药准字 Z10930034,广东太安堂药业股份有限公司)治疗,口服,6 g/ 次,3 次 /d 。两组均连续治疗 3 个月经周期。

1.3 观察指标

(1)观察两组治疗 3 个月经周期后(治疗后)的疗效。经治疗后,患者的排卵、月经周期及性激素水平均恢复正常或妊娠为痊愈。经治疗后,患者的排卵、月经周期及性激素水平基本恢复正常或者妊娠为显效。经治疗,患者的性激素、排卵水平较治疗前明显改善,或月经周期恢复正常为有效。未达到上述标准为无效。总有效率＝(痊愈＋显效＋有效)/ 总例数× 100%[8]。(2)全部患者进行 6 个月的随访,记录自发排卵和妊娠例数并进行组间比较。其中排卵率 = 6 个月随访期排卵正常例数 / 总例数。妊娠率 = 6 个月随访期妊娠例数 / 总例数。(3)于治疗前后采用阴道超声测定患者的子宫内膜厚度、子宫动脉搏动指数(PI)、子宫动脉血流阻力指数(RI)。(4)于治疗前后抽取患者清晨空腹肘静脉血 4 mL，采用邻苯三酚自氧化比色法测定丙二醛(MDA)、过氧化物歧化酶(SOD)含量。采用酶联免疫吸附法测定其中活性氧物质(ROS)水平。采用化学发光法测量血清雌二醇(E_2)、促卵泡激素(FSH)和黄体生成素(LH)水平。检测过程中所用试剂盒均采购自丹麦 Dako 公司，严格按照试剂盒说明书进行操作。(5)记录两组用药安全性情况。

1.4 统计学方法

采用 SPSS25.0 对研究数据进行统计分析，计量资料以($\bar{x}\pm s$)表示,比较采用 t 检验。计数资料以率表示,采用 x^2 检验,以 α=0.05 为检验标准。

2 结果

2.1 两组疗效对比

研究组的临床总有效率较对照组更高,组间对比有统计学差异(P<0.05),具体如表 1 所示。

表 1 两组疗效对比 例(%)

Table 1 Comparison of curative effect between the two groups n(%)

Groups	Cure	Remarkable effect	Effective	Invalid	Total effective rate
Control group(n=230)	41(17.83)	69(30.00)	77(33.48)	43(18.70)	187(81.30)
Study group(n=230)	58(25.22)	82(35.65)	74(32.17)	16(6.96)	214(93.04)
x^2					14.174
P					0.000

2.2 两组子宫内膜容受性指标对比

两组治疗前 PI、子宫内膜厚度、RI 组间对比无差异(P>0.05),两组治疗后 PI、RI 降低,子宫内膜厚度增加(P<0.05),研究组治疗后 PI、RI 低于对照组，子宫内膜厚度大于对照组(P<0.05),具体如表 2 所示。

2.3 两组血清性激素指标对比

两组治疗前 E_2、FSH、LH 组间对比无差异(P>0.05),两组治疗后 E_2 升高,FSH、LH 降低（P<0.05），研究组治疗后 FSH、LH 低于对照组,E_2 高于对照组(P<0.05),具体如表 3 所示。

2.4 两组氧化应激指标对比

两组治疗前 MDA、SOD、ROS 组间对比无差异(P>0.05),两组治疗后 SOD 升高,MDA、ROS 降低(P<0.05),研究组治疗后 MDA、ROS 低于对照组,SOD 高于对照组(P<0.05),具体如表 4 所示。

表 2 两组子宫内膜容受性指标对比($\bar{x}\pm s$)

Table 2 Comparison of endometrial receptivity between the two groups($\bar{x}\pm s$)

Groups	PI		Endometrial thickness(mm)		RI	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=230)	2.87± 0.41	2.37± 0.38[a]	7.58± 0.96	9.02± 1.27[a]	0.93± 0.12	0.78± 0.08[a]
Study group (n=230)	2.81± 0.43	1.69± 0.29[a]	7.51± 0.83	11.39± 0.93[a]	0.91± 0.11	0.59± 0.06[a]
t	1.532	21.754	0.837	22.834	1.863	28.815
P	0.126	0.000	0.403	0.000	0.063	0.000

Note: compared with before treatment, [a]*P*<0.05.

表 3 两组血清性激素指标对比($\bar{x}\pm s$)

Table 3 Comparison of serum sex hormone indexes between the two groups($\bar{x}\pm s$)

Groups	E_2(ng/L)		FSH(IU/L)		LH(U/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=230)	45.91± 5.49	51.52± 6.38[a]	7.41± 0.57	6.52± 0.61[a]	15.23± 2.64	11.97± 1.15[a]
Study group (n=230)	45.53± 6.55	56.59± 7.44[a]	7.48± 0.56	5.99± 0.68[a]	15.17± 2.88	7.96± 1.03[a]
t	0.674	7.845	1.329	8.799	0.233	19.428
P	0.500	0.000	0.185	0.000	0.816	0.000

Note: compared with before treatment, [a]*P*<0.05.

表 4 两组氧化应激指标对比($\bar{x}\pm s$)

Table 4 Comparison of oxidative stress indexes between the two groups($\bar{x}\pm s$)

Groups	MDA(nmoL/mL)		SOD(U/mL)		ROS(μmoL/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=230)	19.62± 3.57	14.22± 2.89[a]	118.39± 15.84	137.23± 25.35[a]	12.94± 2.87	8.35± 2.07[a]
Study group (n=230)	18.55± 2.46	9.38± 2.83[a]	119.17± 16.72	181.64± 31.36[a]	13.03± 2.83	5.24± 1.29[a]
t	0.245	18.147	0.145	16.702	0.339	13.452
P	0.807	0.000	0.885	0.000	0.735	0.000

Note: compared with before treatment, [a]*P*<0.05.

2.5 两组妊娠率、排卵率对比

随访 6 个月后，研究组的妊娠率、排卵率明显高于对照组（*P*<0.05），详细见表 5。

2.6 两组不良反应发生率对比

两组不良反应发生率组间对比无差异（*P*>0.05），具体见表6。

表 5 两组妊娠率、排卵率对比 [例(%)]

Table 5 Comparison of pregnancy rate and ovulation rate between the two groups [n(%)]

Groups	Ovulation rate	Pregnancy rate
Control group(n=230)	162(70.43)	89(38.70)
Study group(n=230)	208(90.43)	134(58.26)
x^2	44.160	17.625
P	0.000	0.000

3 讨论

PCOS 致不孕症是由于 PCOS 导致的不孕症，其突出的临床症状为雄激素水平过高、持续的无排卵，同时患者并无其他

表 6 两组不良反应发生率对比 [例(%)]

Table 6 Comparison of the incidence rate of adverse reactions between the two groups [n(%)]

Groups	Nausea	Vomit	Gastrointestinal discomfort	Fever	Total incidence rate
Control group(n=230)	8(3.48)	6(2.61)	10(4.35)	3(1.30)	27(11.74)
Study group(n=230)	7(3.04)	4(1.74)	11(4.78)	3(1.30)	25(10.87)
x^2					0.690
P					0.406

明显症状,多数患者是由于长期不孕而被检出[10,11]。PCOS 致不孕症若是未能接受及时有效的治疗，或者盲目的促进排卵,可能会加速卵巢衰老,引起终身不孕等严重危害[12]。现临床有关 PCOS 致不孕症的发病机制尚不十分明确,既往多认为与下丘脑 - 垂体 - 卵巢轴功能失常、肾上腺功能紊乱,进而引起内分泌系统功能紊乱有关[13]。PCOS 患者的下丘脑促性腺激素释放可引起垂体释放大量的 LH,高水平的 LH 可引起高雄激素血症、胰岛素抵抗、高胰岛素血症,而这些又可进一步负反馈作用于下丘脑 - 垂体 - 性激素轴发生紊乱[14,15]。此外,PCOS 能引起患者的子宫内膜发生缺陷,排卵率、妊娠率明显降低,即使妊娠,也会增加流产的发生率[16,17]。随着研究的深入,学者们发现氧化应激与 PCOS 的发病也有着密切的关系,体内生理浓度的氧化状态能介导多种反应,在女性生育方面可促进胚泡的形成和植入、卵母细胞的发育成熟和排卵以及妊娠黄体的维持等,但是氧化应激失衡可导致蛋白质、DNA 和脂质等氧化损伤,对卵巢的诸多功能产生不利影响[18-20]。

炔雌醇环丙孕酮由乙炔雌二醇、醋酸环丙孕组成,其中醋酸环丙孕能反馈性抑制 LH 的过度分泌，发挥抗雄激素效应,乙炔雌二醇可增强醋酸环丙孕抑制促性腺激素的效应,降低循环中游离 FSH 水平[21,22],同时炔雌醇环丙孕酮还可抑制双氢睾酮与雄激素受体的结合,对 PCOS 致不孕症具有显著的治疗效果,但单纯的炔雌醇环丙孕酮治疗仍存在妊娠率、排卵率一般的情况[23]。麒麟丸具有益气养血、补肾填精、滋阴补阳之功效,此外,麒麟丸可以提高血液中雌激素水平,改善患者垂体内分泌功能,增加患者子宫内膜厚度[24,25]。本次研究结果显示,研究组的临床总有效率较对照组更高,可能是由于麒麟丸可协助炔雌醇环丙孕酮全面提高生殖系统功能功能，进而调节整体,促进机体恢复有关。机体内过多的氧自由基可致卵子膜及 DNA 损伤导致女性不孕,本次研究结果显示,相对于单用炔雌醇环丙孕酮治疗而言,麒麟丸联合炔雌醇环丙孕酮治疗 PCOS 致不孕症患者,可以有效提升患者子宫内膜容受性,改善血清性激素分泌和氧化应激失衡,提高妊娠率、排卵率。现代药理研究学表明,麒麟丸中的提取物中有淫羊藿苷、维生素 E、淫羊藿多糖成分,其中淫羊藿苷具有类性激素的作用,进而改善附属性腺的分泌功能;维生素 E 可促进 α- 葡糖苷酶、锌、果糖等分泌,调节人体内分泌功能;淫羊藿多糖可增加垂体、卵巢和子宫的质量,提高性激素水平[26]。覆盆子能促进生殖系 统发育,改善肾虚排卵障碍,能促进排卵;制首乌可减少脂质过氧化,改善自由基代谢,抑制氧化应激;菟丝子作用于下丘脑 - 垂体 - 性腺轴来调节机体的生殖内分泌,具有明显调节生殖内分泌腺轴的作用,促进睾酮的生成,同时能抑制生殖细胞凋亡、抗氧化从而提高卵子质量[27-29]。两组不良反应发生率组间对比无差异,提示麒麟丸联合炔雌醇环丙孕酮治疗是一种较为安全可靠的治疗方案。

综上所述,麒麟丸联合炔雌醇环丙孕酮治疗 PCOS 致不孕症患者,可以有效改善患者子宫内膜容受性、血清性激素和氧化应激状态,提高妊娠率、排卵率,安全有效。

参 考 文 献(References)

[1] Zhang J, Bao Y, Zhou X, et al. Polycystic ovary syndrome and mitochondrial dysfunction[J]. Reprod Biol Endocrinol, 2019, 17(1): 67

[2] Wolf WM, Wattick RA, Kinkade ON, et al. Geographical Prevalence of Polycystic Ovary Syndrome as Determined by Region and Race/Ethnicity[J]. Int J Environ Res Public Health, 2018, 15(11): 2589

[3] Chen ZJ, Shi Y, Sun Y, et al. Fresh versus Frozen Embryos for Infertility in the Polycystic OvarySyndrome[J]. N Engl J Med, 2016, 375(6): 523-533

[4] Balen AH, Morley LC, Misso M, et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance[J]. Hum Reprod Update, 2016, 22(6): 687-708

[5] 李红云, 丁慧青, 刘长青, 等. 炔雌醇环丙孕酮联合雷洛昔芬治疗多囊卵巢综合征不孕的疗效以及对性激素与子宫内膜容受性的影响[J].中国妇幼保健, 2020, 35(10): 1890-1893

[6] Cui N, Feng X, Zhao Z, et al. Restored Plasma Anandamide and Endometrial Expression of Fatty Acid Amide Hydrolase in Women With Polycystic Ovary Syndromeby the Combination Use of Diane-35 and Metformin[J]. Clin Ther, 2017, 39(4): 751-758

[7] 赵丽萍, 杨敏, 张云杰. 麒麟丸联合炔雌醇环丙孕酮治疗多囊卵巢综合征不孕患者的疗效及安全性[J]. 临床药物治疗杂志, 2020, 18(6): 44-48

[8] 中华医学会妇产科学分会内分泌学组及指南专家组. 多囊卵巢综合征中国诊疗指南[J]. 中华妇产科杂志, 2018, 53(1): 2-6

[9] 曹泽毅. 中华妇产科学[M]. 北京:人民卫生出版社, 2014: 159-160

[10] Jin P, Xie Y. Treatment strategies for women with polycystic ovary syndrome[J]. Gynecol Endocrinol, 2018, 34(4): 272-277

[11] 毕艳慧, 高新源, 向阳, 等. 二甲双胍联合枸橼酸氯米芬对多囊卵巢综合征不孕患者性激素和胰岛素水平的影响[J]. 现代生物医学进展, 2020, 20(5): 927-930

[12] Costello MF, Misso ML, Balen A, et al. A brief update on the evidence supporting the treatment of infertility in polycystic ovary syndrome[J]. Aust N Z J Obstet Gynaecol, 2019, 59(6): 867-873

[13] Otto-Buczkowska E, Grzyb K, Jainta N. Polycystic ovary syndrome (PCOS) and the accompanying disorders of glucose homeostasis

among girls at the time of puberty [J]. Pediatr Endocrinol Diabetes Metab, 2018, 24(1): 40-44

[14] Osibogun O, Ogunmoroti O, Michos ED. Polycystic ovary syndrome and cardiometabolic risk: Opportunities for cardiovas cular disease prevention[J]. Trends Cardiovasc Med, 2020, 30(7): 399-404

[15] Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome[J]. Hum Reprod, 2018, 33(9): 1602-1618

[16] Cunha A, Póvoa AM. Infertility management in women with polycystic ovary syndrome: a review[J]. Porto Biomed J, 2021, 6(1): e116

[17] Akbari Sene A, Tahmasbi B, Keypour F, et al. Differences in and Correlates of Sexual Function in Infertile Women with and without Polycystic Ovary Syndrome[J]. Int J Fertil Steril, 2021, 15(1): 65-72

[18] Neven ACH, Laven J, Teede HJ, et al. A Summary on Polycystic Ovary Syndrome: Diagnostic Criteria, Prevalence, Clinical Manifestations, and Management According to the Latest International Guidelines[J]. Semin Reprod Med, 2018, 36(1): 5-12

[19] Jamilian M, Mansury S, Bahmani F, et al. The effects of probiotic and selenium co-supplementation on parameters of mental health, hormonal profiles, and biomarkers of inflammation and oxidative stress in women with polycystic ovarysyndrome [J]. J Ovarian Res, 2018, 11(1): 80

[20] Advani K, Batra M, Tajpuriya S, et al. Efficacy of combination therapy of inositols, antioxidants and vitamins in obese and non-obese women with polycystic ovarysyndrome: an observational study [J]. J Obstet Gynaecol, 2020, 40(1): 96-101

[21] Liu Z, Song Y, Xu Y, et al. The comparison of the effectiveness and safety of drospirone ethinylestradiol and ethinyl estradiol cyproterone in the treatment of polycystic ovarian syndrome: A protocol for systematic review and meta-analysis[J]. Medicine (Baltimore), 2020, 99 (51): e23811

[22] Li Y, Ruan X, Wang H, et al. Comparing the risk of adverse pregnancy outcomes of Chinese patients with polycystic ovary syndrome with and without antiandrogenic pretreatment [J]. Fertil Steril, 2018, 109 (4): 720-727

[23] Fonseka S, Wijeyaratne CN, Gawarammana IB, et al. Effectiveness of Low-dose Ethinylestradiol/Cyproterone Acetate and Ethinylestradiol/Desogestrel with and without Metformin on Hirsutism in Polycystic Ovary Syndrome: A Randomized, Double-blind, Triple-dummy Study[J]. J Clin Aesthet Dermatol, 2020, 13(7): 18-23

[24] 杨银. 麒麟丸联合二甲双胍对多囊致不孕女性 MMP-9、VEGF 和 HGF 影响及临床疗效研究[J]. 辽宁中医杂志, 2016, 43(4): 765-767

[25] 刘萌, 高庆红. 麒麟丸治疗多囊卵巢综合征不孕症疗效观察[J]. 现代中西医结合杂志, 2019, 28(17): 1882-1884, 1897

[26] 吴海霞. 麒麟丸联合炔雌醇环丙孕酮治疗多囊卵巢综合征致不孕症的临床研究[J]. 现代药物与临床, 2018, 33(10): 2696-2699

[27] 周延春. 麒麟丸联合氯米芬治疗多囊卵巢综合征不孕的疗效及对患者血清激素水平的影响[J]. 河北医药, 2018, 40(4): 570-573

[28] 黄永俐, 沈洁. 麒麟丸联合二甲双胍对多囊卵巢致不孕患者相关指标的影响[J]. 中国中西医结合杂志, 2016, 36(9): 1042-1045

[29] 戴清. 麒麟丸联合烯丙雌醇片治疗黄体功能不全所致不孕临床观察[J]. 新中医, 2017, 49(4): 75-77

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[22] Chen L, Nan A, Zhang N, et al. Circular RNA 100146 functions as an oncogene through direct binding to miR-361-3p and miR-615-5p in non-small cell lung cancer[J]. Mol Cancer, 2019, 18(1): 13

[23] Zhang R, Xia Y, Wang Z, et al. Serum long non coding RNA MALAT-1 protected by exosomes is up-regulated and promotes cell proliferation and migration in non-small cell lung cancer[J]. Biochem Biophys Res Commun, 2017, 490(2): 406-414

[24] Wang HL, Liu YC, Long MP, et al. Blocking ROR1 enhances the roles of erlotinib in lung adenocarcinoma cell lines [J]. Oncol Lett, 2019, 18(3): 2977-2984

[25] Karachaliou N, Codony-Servat J, Bracht JWP, et al. Characterising acquired resistance to erlotinib in non-small cell lung cancer patients [J]. Expert Rev Respir Med, 2019, 13(10): 1019-1028

[26] White JT, Cross EW, Kedl RM. Antigen-inexperienced memory $CD8^+$T cells: where they come from and why we need them [J]. Nat Rev Immunol, 2017, 17(6): 391-400

[27] 李洪伟, 宋言峥. 新福菌素胸腔灌注治疗非小细胞肺癌患者的效果及对患者血清免疫球蛋白的影响 [J]. 肿瘤药学, 2017, 7(05): 551-555

[28] 张纪良, 肖昕, 邹金金, 等. 分子靶向药(特罗凯)治疗晚期非小细胞肺癌男性患者的临床疗效 [J]. 实用癌症杂志, 2015, 30(12): 1840-1842

[29] Choi HD, Chang MJ. Eye, hepatobiliary, and renal disorders of erlotinib in patients with non-small-cell lung cancer: A meta-analysis [J]. PLoS One, 2020, 15(7): e0234818

[30] Kimura T, Kawaguchi T, Chiba Y, et al. Phase I/II study of intermitted erlotinib in combination with docetaxel in patients with recurrent non-small cell lung cancer (WJOG4708L)[J]. Jpn J Clin Oncol, 2019, 49(10): 947-955