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Original Research Article

Efficacy of Kirin pill plus vitamin CE and coenzyme Q10 in the treatment of ovarian reserve hypofunction

Ling Zheng, Kuo Liu, Yue Wang*, Hui Mei
Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, Jingzhou Street, Xiangcheng District, Xiangyang City, Hubei Province, China

For correspondence:* ***Email:* *paoyueliao68629@126.com*

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Abstract

Purpose: *To investigate the efficacy of Kirin pill plus vitamin CE and coenzyme Q10 in the treatment of diminished ovarian reserve (DOR).*
Methods: *145 patients with ovarian reserve hypofunction hospitalized in Xiangyang Central Hospital, Xiangyang City, China from March 2019 to March 2022 were recruited and assigned randomly to receive either vitamin CE and coenzyme Q10 (control group), or vitamin CE and coenzyme Q10 plus Kirin pills (study group). The parameters/indices determined include menstrual recovery, clinical efficacy, sex hormone and serum anti-mullerian hormone (AMH) levels, changes in the number of ovarian sinus follicles, and levels of CD3+, CD4+ and CD8+ T cell.*
Results: *There were no significant differences ($p > 0.05$) observed among baseline data, pre-treatment sex hormones, serum AMH, ovarian antral follicle count, CD3+, CD4+, and CD8+ T cell levels. After the intervention, administration of the Kirin pill resulted in significantly lower serum follicle stimulating hormone (FSH) and FSH/luteinizing hormone (LH), elevated AMH levels, and better LH and estradiol (E2) levels in patients compared to the administration of vitamin CE and coenzyme Q10 (control group). The study group also showed superior ovarian reserve function and more ovarian basal sinus follicles than the control group ($p < 0.05$).*
Conclusion: *Kirin pill plus vitamin CE and coenzyme Q10 treatment regimen optimizes the ovarian reserve function of patients with DOR infertility by improving basal sex hormones, menstrual cycle and menstrual volume, AMH and ovarian basal sinus follicle count. Further clinical trials are required prior to application in clinical practice.*

Keywords: *Diminished ovarian reserve, Kirin pill, Vitamin CE, coenzyme Q10, Sex hormones, Anti-mullerian hormone*

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INTRODUCTION

Ovary is a sex organ that produces and expels ova, and secretes steroid hormones. The ova are stored in the ovary, and their quality determines the reserve function of the ovary [1]. Diminished ovarian reserve (DOR) is a decrease in the quality of oocytes in the ovary and their ability to produce eggs, which mainly manifests as menstrual cycle disorders, reduced menstrual volume, and decreased fertility, thereby compromising women's fertility and quality of life

[2]. The occurrence of DOR is linked to genetics, lifestyle habits, psychological state, and age, among which age is considered a primary contributor [3]. Patients with DOR have low ovum count and decreased egg quality, with suboptimal outcomes even with assisted reproductive techniques [4]. Recent studies show that age >35 years and shortened menstrual cycle are indicative of DOR. Currently, no specific clinical drugs are available for DOR, and DOR management mostly relies on hormone therapy in Western countries, which results in increased risks of endometrial cancer and cardiac diseases in the long run [5]. Coenzyme Q10, also known as ubiquinone, is a fat-soluble, natural vitamin-like substance found in many organisms. It is a natural antioxidant produced by cells, and they enhance the body's immune system. Coenzyme Q10 has been demonstrated to improve ovarian-related hormone levels, ovarian reserve function and endocrine function in patients with DOR [6]. In addition, studies have revealed that intake of micronutrients during pregnancy is closely associated with the whole course of pregnancy course - fetal growth and development, and delivery - and that excessive intake or deficiency of micronutrients interferes with the normal differentiation of the embryo and fetal growth and development, resulting in malformation of the fetus or even death. Vitamins C and E are associated with the occurrence of premature rupture of the fetal membranes [7]. Vitamin CE chewable tablets are health foods for vitamin C and vitamin E supplementation.

In traditional Chinese medicine (TCM), DOR is classified as "menorrhagia" and "amenorrhea". According to TCM, the underlying pathogenesis of DOR is "dysregulation of the ramifications and kidney deficiency" [8]. In women, the reproductive axis of *kidney qi* - *tiankui* - *Chongren* - uterus regulates fertility and the menstrual status. Therefore, the management of DOR requires the treatment of *kidney deficiencies* and *blood stasis* [9]. *Kirin* pill provides curative benefits for male and female infertility and reproductive system diseases, under the theory of "kidney is the master of reproduction" in TCM [10]. To this end, *Kirin* pill plus vitamin CE and coenzyme Q10 are used for the treatment of DOR in this study so as to investigate their efficacy.

METHODS

Participants

A total of 100 patients with ovarian reserve hypofunction hospitalized in Xiangyang Central Hospital, Xiangyang, China from March 2020 to December 2021 were recruited and assigned randomly to receive either vitamin CE and coenzyme Q10 (control group) or vitamin CE and coenzyme Q10 plus Kirin pills (study group). The study protocol was approved by Xiangyang Central Hospital's Ethics Committee (approval no. 2020-025-09), and all processes complied with the Declaration of Helsinki's Ethical Guidelines for Clinical Research [11]. The patients' profile is outlined in Table 1.

Diagnostic criteria

The diagnostic criteria for DOR was developed with reference to the descriptions of infertility and menstrual disorders in the 2nd edition of Practical Gynecologic Endocrinology [12] and the 2nd edition of Diagnosis and Differential Diagnosis of Obstetrical and Gynecologic Diseases [13].

The diagnosis criteria for the study population are as follows: (1) Female participants aged less than 40 years. (2) Participants with a history of regular menstruation in the past, followed by sporadic menstruation, shortened menstrual cycles, or significantly reduced menstrual volume. (3) Participants may or may not experience symptoms such as irritability, paroxysmal sweating, lumbar and knee tenderness, or decreased libido.

Table 1: Profile of the patients

Variable	Study group	Control group	t/χ2	*P*-value
Number of patients	73	72		
Body mass index (/kg-m-2)	23.84 ± 2.18	23.89 ± 2.21	2.364	0.234
Age (years)	33.23 ± 3.19	33.52 ± 3.18	0.223	0.961
Duration of disease (years)	1.31 ± 0.11	1.32 ± 0.12	2.164	0.356
Number of sinus follicles (pcs)				
Maximum value	8	7		
Minimum value	1	1		
	4. 21±0. 74	4. 45±0. 81	4.726	0.617

(4) Patients should have basal sex hormone levels meeting one of the following criteria: ① Follicle-stimulating hormone (FSH) between 10IU/L and 40IU/L; ② FSH to luteinizing hormone (LH) ratio greater than 2-3.6. ③ FSH less than 10IU/L and serum estradiol (E2) levels of 80pg/mL or higher. ④Anti-Müllerian hormone (AMH) less than 1.26ng/mL in two consecutive menstrual periods with an interval of more than one month. (If there is a history of sporadic menstruation or amenorrhea, AMH measurement is performed for those with menopause for more than 2 months).

(5) Ultrasonography performed on day 3 of menstruation should indicate that the number of antral follicles (AFC) in both ovaries is 6 or fewer. A person could be diagnosed with DOR if they met any one of the specified criteria.

Inclusion and exclusion criteria

Inclusion criteria

(1) Patients who met the diagnostic criteria of DOR; (2) aged between 30 - 40 years; (3) no hormonal therapy in the past 3 months, did not receive other western medicines or other Chinese medical treatment; (4) patients who consented to the treatment plan and signed an informed consent form; (5) patients without organic lesions from gynecological examinations.

Exclusion criteria

(1) Patients aged < 30 years and > 40 years; (2) with DOR caused by genetic or chromosomal factors, medical factors (radiotherapy, chemotherapy, surgery, etc); (3) patients with menstrual irregularities, abnormal menstrual flow and amenorrhea caused by congenital abnormalities in the development of reproductive organs or acquired organic lesions and injuries; (4) infertility caused by other factors such as male factor or tubal factor;

(5) patients with diseases in vital organs - the heart, brain, liver and kidneys, diseases of the hematological system, as well as psychiatric diseases and various malignant tumors; (6) patients with unexplained vaginal bleeding; (7) are allergic to multiple drugs or known to be allergic to the components of this experimental drug; (8) patients with other endocrine diseases, such as thyroid disease, congenital adrenal cortical hyperplasia, polycystic ovary syndrome, etc.; (9) patients with contraindications to estrogen, such as patients with thrombophilia and thrombotic tendencies, pregnancy or suspected pregnancy.

Treatments

Patients in the two groups received 10 mg of coenzyme Q10 tablets (Eisai Pharmaceutical Co. Ltd; Guodianzhi H10930021) orally after meals, thrice daily, for 7 days, and 0.6 g of vitamin EC chewable tablets (Beijing Haiderun Pharmaceutical Group Co., Ltd., batch number: 20171201) daily for 1 month.

Patients in the study group additionally received 6g of Kirin pill (Guangdong Taiantang Pharmaceutical Co. Ltd., State Drug Administration Z10930034) thrice daily for 2 months. Kirin Pill is composed of various ingredients, including Semen Cuscutae, mulberry, Lycii Fructus, raspberry, herba cynomorii, herba ecliptae, epimedii folium, radix codonopsis, chinese yam, astragali radix, radix polygoni multiflori, white paeony root, green tangerine peel, radix curcumae, and radix salivae miltiorrhizae.

Evaluation of parameters/outcomes

Menstrual recovery

Improvement of the menstrual cycle and menstrual volume of patients was recorded.

Efficacy

Cured: After treatment, the menstrual cycle and menstrual volume returned to normal, and various uncomfortable symptoms disappeared. The total score of symptoms decreased by ≥95 %, and the infertile patients had spontaneous pregnancy during or within 3 months after treatment [14].

Markedly effective: After treatment, the menstrual cycle and menstrual volume improved significantly, various discomfort symptoms were reduced significantly, and the total integral value of symptoms was reduced by 70 - 95 %.

Effective: Following the treatment, there was an improvement in menstrual cycle regularity and an increase in menstrual volume compared to the pre-treatment conditions. Additionally, various discomfort symptoms were alleviated, and the total symptom score decreased by 30 - 70%.

Ineffective: After treatment, the menstrual cycle and menstrual volume did not improve, various discomfort symptoms did not change or even worsened, and the total integral value of symptoms decreased by <30 %.

Sex hormone and serum anti-mullerian hormone (AMH) levels

Before treatment and after 3 cycles of treatment, 10 ml of fasting elbow venous blood was collected from the patient on D3 of the menstrual period, rested at room temperature for 30 min, and centrifuged at 3000 r/min for 15 min to obtain 2 ml of the supernatant. Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), and Estradiol (E2) were determined using photochemical method, and AMH was determined using enzyme-linked reaction adsorption test. Reagent kit: Abbott original assembly kit: batch number 73350Q100, test instrument: ARCHITECTi2000 immunoassay system manufactured by Abbott Laboratories, USA).

Changes in the number of ovarian sinus follicles

The patients received ultrasound scanning with the same ultrasound machine (GE Logiq9, GE Logiq6 color Doppler ultrasound diagnostic instrument vaginal probe frequency 5.0-7.0MHz, fan dilation angle 120) in the ultrasound department of the hospital, before and after 3 cycles of treatment on D3 of the menstrual period. Following bladder emptying, the patients were positioned in lithotomy and a vaginal probe, covered with a double layer of condoms, was gently inserted into the patients' vagina to conduct a detailed examination of the morphological size of the uterus and ovaries.

Levels of CD3+, CD4+ and CD8+ T-cell

The BD flow cytometer FACSVia (Shanghai Sanwei Medical Equipment Co., Ltd.) was used to examine changes in the serum levels of CD3+, CD4+ and CD8+ T cell before and after treatment in the patients.

Statistical analysis

The SPSS 23.0 statistical software was used for data processing. Count data are expressed as N (%) and were subjected to the chi-square ($\chi 2$) test. Measurement data are expressed as mean ± standard deviation (SD). Independent sample t-test was used for intergroup comparisons, while paired sample t-test was used for intragroup comparisons. Statistically significant difference was set at $p<0.05$.

RESULTS

Menstrual cycle changes

There was no difference in menstrual cycle between the two groups before treatment *($p > 0.05$)*. Kirin pill demonstrated significantly improved clinical efficacy in menstrual cycle when compared to the treatment with only vitamin CE and coenzyme Q10. *($p < 0.05$;* Table 2).

Changes in menstrual volume

The two groups did not differ in terms of menstrual volume prior to treatment. However, patients in the study group showed a higher menstrual volume than those in the control group *($p < 0.05$*; Table 3).

Sex hormones and serum AMH

The difference in sex hormone and serum AMH levels was not statistically significant, but after treatment, the study group showed a greater increase in sex hormone and serum AMH levels than the control group *($p <0.05$*; Table 4).

Table 2: Menstrual cycle changes

Time	Group	n	Normal	7-14 days earlier or later	>14 days earlier or later
Before treatment	Study	73	33	25	15
	Control	72	20	26	16
After treatment	Study	73	48	17	8
	Control	72	38	21	13

Table 3: Changes in menstrual volume

Time	Group	n	Normal	Reduced by 1/3	Reduced by 2/3	Extremely low volume
Before intervention	Study	73	36	15	15	7
	Control	72	31	16	17	8
After intervention	Study	73	60	46	4	3
	Control	72	51	11	6	4

Table 4: Sex hormone and serum AMH (mean ± SD, points)

Variable	Study (n = 73)		Control (n = 72)	
	Before intervention	***After intervention***	***Before intervention***	***After intervention***
FSH (IU/L)	13.34 ± 4.48	11.03 ± 3.16*#	13.13 ± 3.84	11.36 ± 3.42*
LH (IU/L)	6.74 ±2.83	6.46 ± 1.68*#	6.63 ± 2.43	6.43 ± 1.68*
FSH/LH	2.06 ± 0.41	1.74 ± 0.37*#	2.04 ± 0.32	1.78 ± 0.38*
E2 (pg/ml)	37.8 ± 18.7	37.9 ± 12.8*#	37.0 ± 18.4	37.7 ± 11.5*
AMH (ng/ml)	1.09 ± 0.72	1.21 ± 0.64*#	1.14 ± 0.66	1.19 ± 0.63*

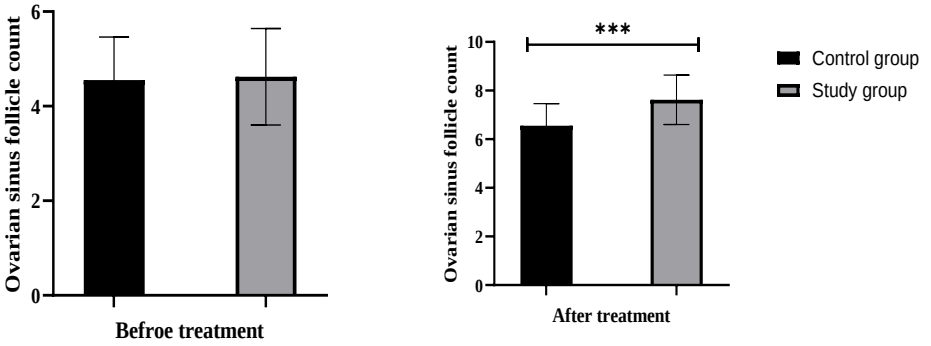

Figure 1: Ovarian sinus follicle count. ***statistically different, $p < 0.05$

Table 5: Serum CD3+, CD4+ and CD8+ T cell levels (mean ± SD, %)

Variable	Study group (n = 73)		Control group (n = 72)	
	Before intervention	***After intervention***	***Before intervention***	***After intervention***
CD3+ (%)	59.61 ± 4.76	67.28 ± 5.07*#	59.54 ± 4.71	62.85 ± 5.02*
CD4+ (%)	42.37 ± 32.24	7.25 ± 0.66*#	34.08 ± 2.15	36.42 ± 2.84*
CD8+ (%)	35.22 ± 3.19	27.03 ± 2.56*#	35.24 ± 3.21	29.37 ± 2.54*

*$P < 0.05$ compared with pre-treatment data; #$p < 0.05$ compared with the control group

Ovarian sinus follicle count

Before the intervention, there was no difference between the two groups in terms of ovarian sinus follicle count *(P>0.05)*. After treatment, the two groups of patients showed increased ovarian sinus follicle count, with higher results in the study group *($p < 0.05$*; Figure 1).

Serum levels of CD3+, CD4+ and CD8+ T cell

Before intervention, the two groups did not differ in the serum levels of CD3+, CD4+ and CD8+ T cells *(p* >0.05). After the intervention, Kirin pill plus vitamin CE and coenzyme Q10 resulted in significantly higher CD3+, CD4+ levels and lower CD8+ levels compared with the control group (*p* < 0.05; Table 5).

DISCUSSION

Factors such as life and work stress and environmental pollution result in DOR in women, so the treatment of DOR contributes to improving the quality of life of patients [15]. Western therapeutic management of DOR include hormone replacement therapy, ovulation enhancement, and assisted reproduction techniques, but long-term hormone replacement is associated with increased risks of thrombosis, uterine fibroids, endometrial cancer, and breast cancer [16]. Moreover, ovulation enhancement and assisted reproduction techniques are suboptimally effective in enhancing egg production and clinical pregnancy rates in patients with DOR [17]. Through the combination of disease identification and evidence identification, TCM regulates the function of the hypothalamic-pituitary-ovarian axis, promotes the release of monoamine neurotransmitters, boosts the production of local cytokines in the ovary and uterus, regulates autoimmune suppression, improves ovarian responsiveness to gonadotropins, and enhances endometrial tolerance, thereby enhancing ovarian reserve function [18].

In the present study, there were no statistically significant differences observed in baseline data, pre-treatment sex hormones, serum AMH,

ovarian sinus follicle count, CD3+, CD4+, and CD8+ T cell levels. The administration of Kirin pill did not significantly lower serum levels of FSH and FSH/LH, elevate AMH, and an improvement in LH and E2 levels in patients compared with the control group. The study group also showed superior ovarian reserve function and more ovarian basal sinus follicles than the control group, suggesting that Kirin pill was effective in restoring ovary function since decrease in E2 and increase in FSH and LH levels are usually observed in compromised ovary functions [19]. In the Kirin pill, Semen Cuscutae, Lycii Fructus and Chinese yam aids the kidneys, fills the essence and tonifies the marrow; Epimedii Folium warms the kidneys and strengthens the yang; White Paeony Root with mulberry, Herba Ecliptae regulates menstruation and nourishes the blood; and Radix Polygoni Multiflori tonifies the kidney and aids the liver function [20].

Current research has demonstrated that Kirin pill exhibits phytoestrogen-like effects, which influence body estrogen levels and have a bidirectional impact on gonadal axis function as well as the expression of ovarian luteinizing hormone receptors. Epimedii Folium and Semen Cuscutae enhance ovarian function by modulating the hypothalamus-pituitary gland. Kirin pill also enhance endogenous estrogen levels and develops primary follicles towards dominant follicles [18]. It has been reported that the Kirin pill increased the mean number and quality of ova obtained, thereby achieving an increased pregnancy rate [19].

Coenzyme Q10 is a potent antioxidant that scavenges free radicals, stabilizes cell membranes, resists lipid peroxidation and enhance immunity. Studies have confirmed that coenzyme Q10 protects oocyte mitochondria and improves ovarian reserve function and ovarian responsiveness by restoring mitochondrial function against ovarian physiological aging [21]. Coenzyme Q10 has been shown to enhance fertility in both males and females by regulating intracellular redox status and altering gene expressions. A study by Jamal *et al* [22] showed that the use of coenzyme Q10 adjuvant in the treatment of *in vitro* fertilization-embryo transfer effectively improved the ovarian reserve function of patients, increased endometrial thickness, enhanced endometrial tolerance, and boost fertilization and pregnancy rates. Severe deficiencies of vitamins C and E in the middle of pregnancy may lead to miscarriage, premature rupture of membranes and stillbirth, and compromised micronutrient levels in the newborn. Therefore, a reasonable diet during pregnancy through the intake of vitamin EC and trace elements of animal and plant foods contributes to preventing adverse pregnancy outcomes such as premature rupture of membranes during pregnancy.

The CD3+, CD4+ and CD8+ T cells are important components of the body's immune system, and their balance is achieved through mutual antagonism, which allows for the maintenance of a normal immune state in an organism. It has been found that the immune system is directly or indirectly involved in the process of follicular development and atresia, thereby affecting the function of the ovary[23]. The results of the present study showed that the study group had higher serum levels of CD3+ and CD4+ T-cell and lower CD8+ T-cell levels than the control group after treatment, which means that Kirin pill combined with vitamin CE and coenzyme Q10 regulated the levels of CD3+, CD4+ and CD8+ T-cell.

Limitations of the study

The short study period and the small number of samples collected in this study may lead to bias in the study results. Also, the mechanism of action of the drugs using animal experiments were not investigated; The indicators of menstrual improvement in this study were subjectively described by the patients, which may be inconsistent with the facts, thus compromising the reliability of the results. The follow-up period of this experiment was short, and there was no assessment of its long-term effects on patients. Further studies with a larger sample size and longer-term follow-up needs to be conducted to provide more reliable data.

CONCLUSION

Co-administration of *Kirin* pill with vitamin CE and coenzyme Q10 treatment regimen enhances the ovarian reserve function of patients with DOR infertility by optimizing basal sex hormones, menstrual cycle and volume, AMH and ovarian basal sinus follicle count. However, further studies are required prior to application of this treatment strategy in clinical practice.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Ling Zheng and Kuo Liu contributed equally to the study.

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