ORIGINAL RESEARCH ARTICLE

Efficacy of concurrent utilization of estradiol valerate and Chinese herbal capsule in managing premature ovarian failure

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Abstract

The objective of this study was to examine the efficacy of the concurrent utilization of estradiol valerate and kuntai capsule (a Chinese herbal preparation) in addressing premature ovarian failure (POF) and its ramifications for ovarian hemodynamics and sex hormone levels. A retrospective study of 104 patients with POF was conducted, dividing them into control (n=50) and observation groups (n=54). The control group received estradiol valerate, while the observation group received estradiol valerate and KunTai capsules over 12 weeks. Clinical effectiveness, ovarian pulsatility index (PI), resistance index (RI), hormone levels, ovarian function, and adverse reactions were analyzed. The observation group showed significantly improved PI, RI, LH, FSH, E2 levels, and ovarian function in relative to the control group (P<0.05). We conclude that the concurrent use of estradiol valerate and KunTai capsules improves ovarian hemodynamics and hormone levels, offering significant clinical benefits. *(Afr J Reprod Health 2024; 28 [11]: 135-140).*

Keywords: Sex hormone levels, Estradiol valerate, KunTai Capsule, Hemodynamics, Premature ovarian failure

Résumé

L'objectif de cette étude était d'examiner l'efficacité de l'utilisation simultanée du valérate d'estradiol et de la capsule kuntai (une préparation à base de plantes chinoise) pour traiter l'insuffisance ovarienne prématurée (POF) et ses ramifications sur l'hémodynamique ovarienne et les niveaux d'hormones sexuelles. Une étude rétrospective de 104 patients atteints de POF a été menée, les divisant en groupes de contrôle (n = 50) et d'observation (n = 54). Le groupe témoin a reçu du valérate d'estradiol, tandis que le groupe d'observation a reçu du valérate d'estradiol et des capsules KunTai pendant 12 semaines. L'efficacité clinique, l'indice de pulsatilité ovarienne (IP), l'indice de résistance (IR), les niveaux d'hormones, la fonction ovarienne et les effets indésirables ont été analysés. Le groupe d'observation a montré une amélioration significative des niveaux de PI, RI, LH, FSH, E2 et de la fonction ovarienne par rapport au groupe témoin (P <0,05). Nous concluons que l'utilisation concomitante de valérate d'estradiol et de capsules KunTai améliore l'hémodynamique ovarienne et les niveaux d'hormones, offrant ainsi des avantages cliniques significatifs. *(Afr J Reprod Health 2024; 28 [11]: 135-140).*

Mots-clés: Taux d'hormones sexuelles, valérate d'estradiol, capsule KunTai, hémodynamique, insuffisance ovarienne prématurée

Introduction

Premature ovarian failure (POF) is a frequently encountered gynecological situation where the ovarian function declines prematurely, leading to manifestations such as menstrual disruptions, infertility, and atypical hormone levels[1-3]. The origins of POF are intricate, potentially involving genetic factors, autoimmune factors, environmental factors, and other elements[4-6]. Conventional treatment methods in clinical practice encompass hormone replacement therapy, stem cell therapy, nutritional support, and psychological counseling[7-9]. Kuntai Capsule, an ancient Chinese herbal remedy, is renowned for its impact on enhancing blood circulation, alleviating blood stasis, and nurturing and invigorating the female reproductive system. It has extensive applications in addressing disorders of the female reproductive system [10-11]. In situations where ovarian dysfunction leads to hormonal deficiencies, estradiol valerate, a man-made estrogen, is utilised for hormone replacement

therapy[12-13]. At present, the comprehensive exploration of the effectiveness of Kuntai Capsule along with estradiol valerate for managing POF, along with its influence on ovarian hemodynamics and hormone levels in patients, remains incomplete. The objective of this study is to investigate the effectiveness of combining Kuntai capsule with estradiol valerate for managing POF, as well as to analyze its influence on ovarian hemodynamics and hormone levels among patients. The outcomes of the study will offer a more substantial scientific foundation for clinical interventions, thereby fostering the recuperation and enhancement of the quality of life for individuals affected by POF.

Methods

The study retroactively incorporated 104 POF patients diagnosed by the Department of Obstetrics and Gynecology from January 2019 to December 2023. Patients were divided into control group (50 cases) and observation group (54 cases) according to different treatments they received. The mean age of the control group fell within the 30-39 years range (36.76±2.24), with an amenorrhea duration of 1-3 years (1.84±0.37). The average age in the observation group was within the range of 30 to 38 years (36.52±2.34), and the time of amenorrhea was from 1 to 4 years (1.93±0.33). No substantial distinctions in general characteristics between groups were identified (P>0.05).

Inclusion criteria: POF diagnosed according to Western medicine criteria, featured by premature amenorrhea prior to 40 years of age, perimenopausal syndrome, or menopausal symptoms, with two consecutive blood tests (with an interval of at least one month) showing FSH levels higher than 40 IU/L[14]; TCM diagnosis characterized by a red tongue with little coating and a thin and rapid pulse, with main complaints of decreased menstrual flow or amenorrhea, insomnia with frequent dreams, fatigue, hot flushes with sweating, poor appetite; amenorrhea for more than 3 months and not in a pregnant state; tolerance to corresponding treatment; good compliance.

Exclusion criteria: Abnormal liver or kidney function, breast-related diseases, other diseases that may cause related symptoms (such as hyperprolactinemia, polycystic ovary syndrome, reproductive tract abnormalities); severe organ diseases; cognitive function impairment; severe systemic infection.

Treatment administered

The control group received oral treatment with estradiol valerate (DELPHARM Lille S.A.S., 1 mg/tablet, Approval No. H20160679), 1 mg per dose, once daily. The observation group received Kuntai Capsule (0.5 g, Guiyang Xintian Pharmaceutical Co., Ltd., National Drug Approval No. Z20000083) in addition to the estradiol valerate treatment, 2 g per dose, three times a day. Both groups underwent a 4-week treatment course, and a total of 3 consecutive treatment courses. For non-hysterectomized patients in the observation and control groups, progesterone capsules (100 mg per dose, twice daily) were given during the 3rd and 4th week of each treatment course.

Observed Indicators

Quantitative evaluation was conducted using the TCM symptom scoring system [Main symptoms (amenorrhea) scored from 0 to 9, specific definitions as follows: 0 points: indicating mild amenorrhea, which may be temporary due to emotional fluctuations or life stress and generally does not require special treatment, can be restored by adjusting lifestyle and emotions. 3 points: indicating moderate amenorrhea, which may be caused by hormonal imbalance or physical weakness and requires appropriate TCM treatment and regulation to restore menstruation. 6 points: indicating severe amenorrhea, which may be caused by chronic diseases or disorders in physical functions and requires a longer period of TCM treatment and regulation to restore menstruation. 9 points: indicating extremely severe amenorrhea, which may be caused by severe hormonal imbalance or organ dysfunction and requires comprehensive treatment and long-term regulation to restore menstruation. Sub-symptoms (irritability, chest and hypochondrium distension pain, stuffiness in the chest, dizziness and tinnitus, flushing and sweating, mental depression, waist and knee weakness and soreness) scored from 0 to 3. The total score amounts to 30]. The quantitative index of effectiveness assessment includes: (1) Markedly effectiveness: improvement of TCM symptom score ≥70%; (2) efficacy: improvement range of TCM symptom score 40%-69%; (3) ineffectiveness: improvement of TCM symptom score <40%. The treatment effective rate was calculated as (markedly effective plus effective) divided by the total case count,

multiplied by 100%[15]. Color Doppler ultrasound was used to measure the ovarian PI and RI as follows: PI = (peak systolic velocity (S) of the ovarian artery - end diastolic velocity (D))/(mean maximum blood flow velocity); RI = (S-D)/S. Fasting venous blood samples were collected in the non-ovulatory period and analyzed for LH, E2, and FSH using electrochemiluminescence immunoassay. Evaluation of the uterine endometrium thickness and ovarian volume before and after the treatment was conducted, and any adverse reactions that occurred during the treatment were carefully noted and documented.

Statistical analysis

Utilizing SPSS 25.0 software, all the data were processed. Intergroup comparison of measurement data was achieved by employing independent sample t-tests, whereas count data was analyzed utilizing the chi-square test. Statistical significance was determined by setting $P<0.05$ as the criterion.

Ethical considerations

This study followed the Declaration of Helsinki guidelines and received ethical approval from the Ethics Committee of Tianjin Medical University General Hospital. The study and its details were presented to the patients and their family members, who then proceeded to endorse the informed consent documents.

Results

Clinical efficacy

Statistical findings unveiled a substantial contrast in the treatment effectiveness rate, signifying that the observation group outperformed the control group notably ($P<0.05$) (Table 1).

Ovarian hemodynamic indexes

Initially, there were no substantial variations in the PI and RI levels between groups before treatment ($P>0.05$). Subsequently, both groups witnessed a decline in the PI and RI levels, with the observation group displaying lesser changes than the control group, leading to noteworthy discrepancies ($P<0.05$) (Table 2).

Hormone levels

Prior to the initiation of medication, the hormonal levels did not show remarkable distinctions between groups ($P>0.05$). Subsequent to medication, the observation group demonstrated decreased levels of LH and FSH when compared to the control group, and elevated levels of E2 in contrast to the control group, resulting in statistically notable variations ($P<0.05$) (Figure 1).

Ovarian function

Preceding the administration of medication, no notable distinctions in ovarian function were identified between groups ($P>0.05$). Following treatment, the uterine endometrium of the observation group was substantially thicker and the ovarian volume was larger in relative to the control group ($P<0.05$) (Table 3).

Adverse reactions

The cumulative frequency of adverse reactions during the treatment duration was 16.67% in the observation group and 16.00% in the control group, exhibiting no remarkable statistical distinctions ($P>0.05$) (Table 4).

Discussion

In deciding the treatment of POF, it is crucial to contemplate its origin and development. POF is a multifaceted condition, potentially originating from genetic components, immune issues, environmental influences, and other factors. Impaired ovarian function and alterations in hormone levels are pivotal factors in the progression of POF. As a result, the primary objectives of POF treatment entail reinstating ovarian function and regulating hormone levels. The evidence indicates that the merger of Western medicine and traditional Chinese medicine can lead to beneficial therapeutic outcomes[16,17]. As a result, this study aligns with the principles of evidence-based medicine and utilizes a treatment strategy that combines Kuntai Capsule with estradiol valerate. As part of this study, the observation group was administered oral Kuntai capsule along with the estradiol valerate treatment. It is believed that the constituents of Kuntai Capsule may have an influence on the regulation of hormone levels.

Table 1: Curative effect (%)

Group (n)	Markedly effective	Effective	Ineffective	Total effective rate
Observation (54)	28 (51.85)	22 (40.74)	4 (7.41)	50 (92.59)
Control (50)	19 (38.00)	20 (40.00)	11 (22.00)	39 (78.00)
χ^2				4.479
P				0.034

Table 2: Ovarian hemodynamic index (x±s)

Group (n)	PI		RI	
	Before	After	Before	After
Observation (54)	2.17±0.80	1.42±0.45*	0.97±0.22	0.69±0.18*
Control (50)	2.29±0.89	1.95±0.70*	0.91±0.24	0.80±0.22*
t	0.754	4.701	-1.247	2.617
P	0.453	0.000	0.215	0.010

* Signifies remarkable change following treatment in contrast to before the treatment.

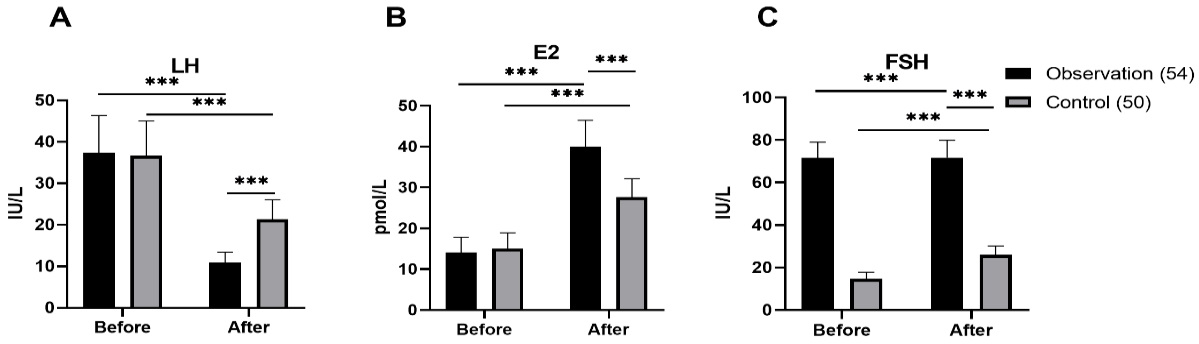

Figure 1: Sex hormone levels (A: luteinizing hormone (LH), B: estradiol (E2), C: follicle-stimulating hormone (FSH)) ***p <0.001.

Table 3: Ovarian function (x±s)

Group (n)	Endometrial thickness (mm)		Ovarian volume (cm^3)	
	Before	After	Before	After
Observation (54)	5.13±1.36	8.44±1.41*	15.78±2.72	25.11±3.46*
Control (50)	5.24±1.30	7.12±1.26*	15.62±2.75	21.35±3.01*
t	0.422	-5.232	-0.294	8.283
P	0.674	0.000	0.769	0.000

Note: * Signifies remarkable change following treatment in contrast to before the treatment.

Table 4: Adverse reactions n (%)

Group (n)	Water and sodium retention	Breast distension and pain	Irregular vaginal bleeding	Overall incidence
Observation (54)	3 (5.56)	4 (7.41)	2 (3.70)	9 (16.67)
Control (50)	2 (4.00)	3 (6.00)	3 (6.00)	8 (16.00)
χ^2				0.008
P				0.927

The study results revealed that, in conjunction with Kuntai Capsule, the observation group had decreased magnitudes of LH and FSH and an increased magnitude of E2 in contrast to the control group. This implies that Kuntai Capsule may enhance the condition of POF patients by regulating hormone levels.

Hormone replacement therapy has evolved into a fundamental treatment approach for addressing POF. Estradiol valerate, a prolonged-release form of estradiol, is present in long-acting contraceptives and is viable for managing menstrual irregularities and hormone replacement therapy[18]. It showcases estrogenic pharmacological characteristics, fostering and overseeing the regular development of female reproductive organs and secondary sexual features, and contributing to the control of the ovarian axis. It is presently widely utilized in the management of POF[19]. The formulation of Kuntai Capsule is based on the formula Huanglian Ejiao Tang, with the ingredients of Rehmannia rehmannia and donkey-hide gelatin to nourish the kidney, nourish the yin and supplement the essence; Mongolian Milkvetch Root and Coptis Root to clear heat and remove fire inside the body; White Peony Root to regulate menstruation and nourish blood; Poria to benefit the heart and spleen. The collective impact of these herbal elements contributes to nurturing yin, alleviating internal heat, soothing the mind, nourishing the liver, and invigorating the kidneys. The integration of Chinese and Western medicine engenders a harmonizing effect that bolsters the observed clinical treatment impact[20].

Moreover, with the support of Kuntai Capsule, the observation group experienced an augmentation in uterine endometrial thickness and ovarian volume in contrast to the control group. This effect may be ascribed to the constituents of Kuntai Capsule, which potentially facilitate the proliferation of the endometrium and the development of the ovaries, subsequently enhancing the reproductive capability of POF patients.

Nevertheless, this study possesses certain constraints. Firstly, being a retrospective study, it may impart selection bias and information bias. Secondly, the relatively modest sample size could potentially influence the accuracy and broad applicability of the findings. Moreover, the brief treatment period may not permit an appraisal of the long-term impacts and safety.

The advantage of this study is the use of integrated traditional Chinese and Western medicine treatment strategy, Kuntai capsules and valerate estradiol combined for the treatment of premature ovarian failure, the results showed that the combination group was better than the control group using valerate alone in a number of indicators, with certain clinical application prospects; at the same time, the study conducted a detailed evaluation of multiple indicators, including TCM symptom scores, ovarian hemodynamic indicators, hormone levels, ovarian function and adverse reactions, etc., providing rich data support for evaluating the treatment effect. The limitations of this paper include: it is a retrospective study, so there may be selection and information biases; the sample size is relatively small, affecting the accuracy and applicability of the results; the treatment period is short, so it is impossible to evaluate the long-term impact and safety.In conclusion, the study results suggest that the oral administration of Kuntai Capsule may present prospective clinical value for treating POF patients. Nonetheless, the study limitations warrant further research to substantiate its effectiveness and safety, and to delve deeper into its mechanisms of action. The primary objective is to introduce more effective and safe treatment approaches for POF patients, with the aim of enhancing their quality of life and reproductive health.

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Authors' contributions

Lu Sun designed the protocol of the study and made a major contribution to writing the manuscript. Xiaodong Fan and Qian Chen analyzed the data of participants. Guoyan Liu thoroughly amended the manuscript. All authors perused and ratified the final draft of the manuscript.

Conflicting interests

No conflict of interest exits in this manuscript.

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