

Guishen Yugong Decoction Combined with Sequential Hormone Replacement Therapy in the Treatment of Premature Ovarian Failure and Its Effect on Serum Sex Hormones

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Abstract: *Objective:* To analyze the therapeutic effect of Guishen Yugong Decoction + sequential hormone (estrogen and progesterone) replacement therapy and its effect on serum sex hormones in patients with premature ovarian failure. *Methods:* From July 2020 to July 2022, 100 patients with premature ovarian failure were included in the study. Random number table method was used to divide the patients into groups: the control group received sequential hormone replacement therapy, whereas the treatment group received Guishen Yugong Decoction + sequential hormone replacement therapy. The curative effect, traditional Chinese medicine (TCM) syndrome scores, serum sex hormone levels, and incidence of adverse reactions of both groups of patients were compared. *Results:* The total effective rate in the treatment group was higher than that in the control group, $P < 0.05$; the TCM syndrome scores in the treatment group were lower than those in the control group, $P < 0.05$; the serum sex hormone indices in the treatment group were better than those in the control group ($P < 0.05$); the treatment group had lower incidence of adverse reactions, as compared to the control group ($P < 0.05$). *Conclusion:* Guishen Yugong Decoction + sequential hormone replacement therapy can regulate serum sex hormone levels and relieve symptoms of premature ovarian failure. This treatment is not only effective, but also safe for clinical use.

Keywords: Premature ovarian failure; Estrogen and progesterone; Guishen Yugong Decoction; Serum sex hormones; Curative effect

Online publication: March 28, 2023

1. Introduction

Premature ovarian failure (POF) is typically characterized by amenorrhea, but some patients may present with other symptoms, such as loss of libido, flushing, and infertility. POF is defined as primary ovarian defect occurring before the age of 40 in women with normal menarche. The incidence of POF is high [1]. POF can affect the endocrine system, resulting in decreased estrogen and increased gonadotropin; in long term, disorders of the endocrine system can induce cardiovascular disease, osteoporosis, and threaten the patient's physical and mental health. At present, hormone replacement therapy is widely used in western medicine to treat POF. It can effectively relieve POF symptoms, but the risk of adverse reactions after long-term medication is high; moreover, relapse may occur after stopping medication [2]. TCM treatment of patients with premature ovarian failure is based on the holistic concept of dialectical treatment. It makes up

for the shortcomings of simple western medicine, is conducive to the recovery of ovarian function, and prevents adverse drug reactions. In this study, 100 POF patients admitted from July 2020 to July 2020 were enrolled to explore the therapeutic effect of Guishen Yugong Decoction + sequential hormone replacement therapy.

2. Materials and methods

2.1. Baseline data

From July 2020 to July 2022, 100 patients with POF were included in this study. They were grouped by random number table. Baseline data of the control group: age 25–39 (mean 34.19 ± 2.43) and course of disease 3 months to 3 years (mean 1.44 ± 0.41 years). Baseline data of the treatment group: age 25–39 (mean 34.21 ± 2.39) and course of disease 4 months to 3 years (mean 1.38 ± 0.39 years). There was no difference in baseline data between both groups of patients ($P > 0.05$).

2.2. Diagnostic, inclusion, and exclusion criteria

Diagnostic criteria: western medicine “Gynecology and Obstetrics of Traditional Chinese Medicine” [3] standard (amenorrhea for more than 6 months, and serum follicle stimulating hormone [FSH] > 40 mIU/mL two consecutive times); TCM “Guiding Principles for Clinical Research of New Drugs of Traditional Chinese Medicine” [4] standard (kidney deficiency and blood stasis syndrome, pale tongue with thin fur, deep and thready pulse, amenorrhea, insomnia, backache, soft knees, and abdominal pain).

Inclusion criteria: (i) patients under 40 years old; (ii) informed consent given; (iii) approved by the research ethics committee.

Exclusion criteria: (i) patients with pituitary tumors or polycystic ovaries; (ii) patients with organ dysfunction; (iii) patients who self-medicated before enrollment.

2.3. Treatment methods

Sequential treatment with estrogen and progesterone in the control group: estradiol valerate tablets (Bayer Healthcare Co., Ltd.) taken for 5 days of menstruation, 1 mg orally before dinner, once a day, and continued for 21 days; progesterone capsules (Zhejiang Pharmaceutical Co., Ltd. Xinchang Pharmaceutical Factory) taken for 20 days at a single dose of 100 mg, twice a day continuously for 5 days. The patients underwent three courses of treatment, each of which lasted for one menstrual cycle.

Shenyugong Decoction + sequential treatment with estrogen and progesterone in the treatment group: same regimen of estrogen and progesterone as that of the control group; Shenyugong Decoction prescription (*Cuscuta* 20 g, *Poria cocos* 15 g, Chinese yam 15 g, *Spatholobus* 15 g, *Radix Polygoni Multiflori Preparata* 15 g, charred hawthorn 15 g, himalayan teasel root 12 g, *Lycium barbarum* 12g, *Eucommia* 10 g, *Cornu Cervi Degelatinatum* 10 g, *Cornus*, *Rehmannia* 10 g, *Placenta Hominis* 10 g, and prepared licorice 6 g), 1 dose (400 mL decoction) in the morning and evening for 3 months.

2.4. Evaluation indicators

- (i) Efficacy: markedly effective (menses resumed, normalized FSH, estradiol [E_2], and luteinizing hormone [LH], and TCM syndrome scores decreased by $\geq 95\%$); effective (increased menstrual flow, improvement in sex hormones, and TCM syndrome scores decreased by 30%–94%); or ineffective (amenorrhea, no improvement in sex hormones, and TCM syndrome scores remained unchanged).
- (ii) TCM syndrome scores: 4 domains (lower abdominal pain, dizziness and tinnitus, insomnia, and soreness over the waist and knees); each domain scored based on the degree of symptoms (0 = none, 1 = mild, 2 = moderate, and 3 = severe).

- (iii) Serum sex hormones: FSH, E₂, and LH detected by a fully automatic chemiluminescent instrument.
- (iv) Incidence of adverse reactions: Nausea and vomiting, skin itching, and breast tenderness were recorded.

2.5. Statistical analysis

The data of the patients were processed by SPSS 21.0. Count data were recorded as percentage (%), and χ^2 test was performed. Measurement data were recorded as mean \pm standard deviation, and *t*-test was performed. *P* < 0.05 indicates statistically significant test result.

3. Results

3.1. Curative effect

The total effective rate in the treatment group was higher than that in the control group, *P* < 0.05, as shown in **Table 1**.

Table 1. Curative effect analysis

Group	Markedly effective	Effective	Ineffective	Total effective rate
Treatment group (n = 50)	41 (82.0)	8 (16.0)	1 (2.0)	98.0
Control group (n = 50)	35 (70.0)	8 (16.0)	7 (14.0)	86.0
χ^2	–	–	–	4.8913
<i>P</i>	–	–	–	0.0270

Data are given as n (%).

3.2. TCM syndrome score

After treatment, the syndrome scores of the treatment group were lower than those of the control group, *P* < 0.05, although the differences in scores were not significant before treatment, *P* > 0.05. See **Table 2** for details.

Table 2. TCM syndrome analysis

Group	Abdominal pain		Dizziness and tinnitus	
	Before treatment	After treatment	Before treatment	After treatment
Treatment group (n = 50)	2.62 \pm 0.81	0.73 \pm 0.36	2.71 \pm 0.83	0.69 \pm 0.38
Control group (n = 50)	2.59 \pm 0.76	1.34 \pm 0.49	2.74 \pm 0.85	1.31 \pm 0.44
<i>t</i>	0.1910	7.0940	0.1786	7.5408
<i>P</i>	0.8489	0.0000	0.8587	0.0000
Group	Insomnia		Soreness over the waist and knees	
	Before treatment	After treatment	Before treatment	After treatment
Treatment group (n = 50)	2.51 \pm 0.72	0.74 \pm 0.42	2.66 \pm 0.74	0.78 \pm 0.39
Control group (n = 50)	2.49 \pm 0.69	1.41 \pm 0.79	2.61 \pm 0.76	1.43 \pm 0.61
<i>t</i>	0.1418	5.2952	0.3333	6.3482
<i>P</i>	0.8875	0.0000	0.7396	0.0000

Data are given as mean \pm standard deviation.

3.3. Serum sex hormones

Although the difference in FSH, E₂, and LH levels of patients in the treatment group and the control group was insignificant before treatment (*P* > 0.05), the difference was significant after treatment, whereby the

sex hormones of patients in the treatment group were better than those in the control group ($P < 0.05$). See **Table 3** for details.

Table 3. Serum sex hormone level analysis

Group	FSH (mIU/mL)		E ₂ (pg/mL)		LH (mIU/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Treatment group (n = 50)	53.87 ± 2.41	30.61 ± 1.69	31.24 ± 1.87	52.87 ± 2.08	31.27 ± 1.87	20.39 ± 1.51
Control group (n = 50)	53.91 ± 2.39	38.11 ± 1.84	31.22 ± 1.85	45.69 ± 1.96	31.29 ± 1.84	25.11 ± 1.69
<i>t</i>	0.0833	21.2273	0.0538	17.7644	0.0539	14.7267
<i>P</i>	0.9338	0.0000	0.9572	0.0000	0.9571	0.0000

Data are given as mean ± standard deviation.

3.4. Incidence of adverse reactions

The incidence of adverse reactions in the treatment group was significantly lower than that in the control group ($P < 0.05$), as shown in **Table 4**.

Table 4. Analysis of incidence of adverse reactions

Group	Feel unwell and vomiting	Itchy skin	Breast tenderness	Incidence rate
Treatment group (n = 50)	1 (2.0)	0 (0.0)	0 (0.0)	2.0
Common group (n = 50)	3 (6.0)	2 (4.0)	1 (2.0)	12.0
χ^2	–	–	–	
<i>P</i>	–	–	–	

Data are given as n (%).

4. Discussion

POF is related to long-term estrogen deficiency-induced genital atrophy. If not treated early, it can lead to bone loss, affect blood lipid metabolism, and increase the risk of osteoporosis and cardiovascular disease, thus affecting women's physical and mental health. At present, the specific cause of POF is not known. It is believed that the disease is related to multiple factors, such as immunity, genetics, history of ovarian surgery, infection, and lack of synthetic enzymes [5]. According to relevant literature reports, once POF occurs, the growth of interstitial fibers in the patient's body increases, the estrogen level decreases, and the vascular lumen becomes thinner, which in turn reduces the compliance of the vessel wall, increases blood flow and vascular resistance, causes a reduction in ovarian volume, and induces amenorrhea [6]. Another literature has reported that the pathophysiology of POF involves a decrease in ovarian reserve function, manifested as a decrease in FSH levels [7]. In the treatment of POF with western medicine, medications are used to relieve symptoms. For example, estrogen and progesterone replacement therapy can effectively improve POF symptoms, but their long-term administration can increase the risk of endometrial cancer and breast cancer; in addition, relapse may occur once the treatment stops [8]. In TCM theory, POF belongs to the category of "infertility" and "amenorrhea" and is related to the deficiency of essence and blood, kidney essence deficiency, *etc.* Amenorrhea is believed to occur when the blood sea cannot be filled [9]. In this paper, Guishen Yugong Decoction is used for treatment. In the prescription, *Cuscuta* can consolidate essence and strengthen yang, as well as nourish the liver and the kidney; Chinese yam can nourish the kidney and essence; Poria can calm the heart and strengthen the spleen; charred hawthorn can remove blood

stasis and promote blood circulation; *Eucommia ulmoides*, himalayan teasel root, *Lycium barbarum*, and *Cornus* can also nourish the liver and the kidney; *Rehmannia glutinosa* can nourish the blood and yin; while Cornu Cervi Degelatinatum can aid yang and warm the kidney. Guishen Yugong Decoction combined with various prescriptions plays a role in nourishing the blood and yin, replenishing essence, tonifying the kidney, soothing the liver, regulating menstruation, removing blood stasis, and promoting blood circulation [10-12].

According to our analysis, the total effective rate in the treatment group was significantly higher than that in the control group; the syndrome scores of POF patients in the treatment group were significantly lower than those of patients in the control group; the FSH, E₂, LH levels of patients in the treatment group were significantly better, as compared to those in the control group. Hence, it is suggested that Guishen Yugong Decoction + sequential hormone replacement therapy has a better effect in treating POF in terms of regulating the levels of sex hormones and improving symptoms. Analyzing the reasons, western medicine sequential therapy can solve the problem from the source with the addition of Guishen Yugong Decoction, as the synergistic effect of various TCMs includes tonifying the kidney and strengthening the spleen, as well as regulating the body's immune function and endocrine function. This effect is conducive to the recovery of the patient's ovarian function [13]. Combined with modern pharmacological analysis, in Guishen Yugong Decoction, *Cuscuta* is rich in total flavonoids, which can stimulate follicle development, regulate estrogen levels, and thus promote the recovery of ovarian function; *Rehmannia glutinosa* can stimulate hematopoiesis; Chinese yam can induce endometrial thickening, regulate sex hormone levels, correct hormone secretion disorders, delay ovarian function decline, and shorten the recovery time; *Lycium barbarum* is rich in polysaccharides, trace elements, amino acids, and other substances, which can regulate the secretion of hormones and enhance the body's immune function [14]. Our data also showed that the incidence of adverse reactions in the treatment group was significantly lower than that in the control group, suggesting that Guishen Yugong Decoction + sequential hormone replacement therapy is safer in treating POF. Analyzing the reason, western medicine sequential therapy can stimulate the development of female genitalia, reduce bone loss, and reduce the risk of osteoporosis. However, long-term use of estrogen-progesterone therapy can damage kidney function and increase the risk of ovarian cancer. The safety of hormonal therapy is dubious. However, when combined with Guishen Yugong Decoction, it works synergistically to effectively regulate qi and blood, thereby optimizing sex hormone levels and improving ovarian function. This is beneficial to the prognosis of patients [15].

In conclusion, Guishen Yugong Decoction + sequential hormone replacement therapy with estrogen and progesterone in the treatment of POF can effectively regulate the levels of sex hormones, improve the symptoms of POF, and promote the recovery of ovarian function. Therefore, it has clinical value in the treatment of POF.

Disclosure statement

The authors declare no conflict of interest.

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