

## Original Research Article

# Effect of combined Qilin pill and estradiol valerate tablets on irregular menstruation in patients, and their serum levels of estradiol, progesterone and luteinizing hormone

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### Abstract

**Purpose:** To determine the clinical effect of combined treatment with Qilin pill and estradiol valerate tablets on irregular menstruation patients, and its impact on serum levels of estradiol (E2), progesterone (P) and luteinizing hormone (LH).

**Methods:** A total of 120 irregular menstruation patients admitted to our hospital from January 2019 to January 2020 were randomly divided into group A (n=60) and group B (n = 60). Group B was treated with estradiol valerate tablets only, while group A was given Qilin pill, in addition to estradiol tablets. Treatment effectiveness, time taken to achieve normal menstruation, ovulation rate, hormonal levels, endometrial thickness, and clinical symptom scores were compared between the two groups of patients.

**Results:** There was higher treatment effectiveness in group A than in group B ( $p < 0.05$ ). The time taken to return to normal menstruation was significantly shorter in group A than in group B ( $p < 0.001$ ). Group A patients had markedly higher ovulation rate, higher endometrial thickness, and more favorable hormonal levels than patients in group B ( $p < 0.05$ ). Moreover, post-treatment clinical symptom score of group A was superior to that of group B ( $p < 0.001$ ).

**Conclusion:** The combined use of Qilin pills and estradiol valerate tablets mitigates clinical symptoms in patients with irregular menstruation, increases their ovulation rate and hormonal levels, and enhances return to normal menstruation. Therefore, the combination treatment appears to be suitable for the management of menstrual issues.

**Keywords:** Qilin pills, Estradiol valerate tablets, Irregular menstruation

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## INTRODUCTION

Irregular menstruation, frequently seen in women of childbearing age, refers to a condition that manifests as abnormal changes in the menstrual cycle or abnormal changes in menstrual volume.

It may be triggered by drugs as well as environmental and mental conditions, and it may lead to endometrial cancer, infertility and other diseases, if not promptly treated [1]. At present, Western medicine is the mainstay treatment for irregular menstruation. Estradiol valerate tablets

are the estrogens which are employed in the clinical treatment of irregular menstruation. These drugs regulate hormonal levels and maintain them within normal ranges in patients, thereby restoring normal menstrual cycle and relieving clinical symptoms. However, the use of estradiol valerate tablets does not result in timely normalization of the menstrual cycle, indicating that the drug yields an unsatisfying therapeutic effect, and does not provide a radical cure for irregular menstruation [2,3].

Traditional Chinese medicine (TCM) has continued to receive increasing recognition in the treatment of human diseases. In TCM, it is believed that irregular menstruation is caused by factors such as *sexual strain*, and that its treatment should be carried out by regulating *qi* and blood. For this purpose, acupuncture, massage, and decoction of Chinese medicine are the common methods applied [4]. The *Qilin pill* used in this study is a Chinese patent medicine containing multi-flavored prescriptions. It exerts a positive effect by replenishing *qi* and blood. The present study was carried out to investigate the clinical effects of the use of *Qilin pills* in combination with estradiol valerate tablets, on treatment of irregular menstruation patients in our hospital.

## METHODS

### General information on patients

A total of 120 irregular menstruation patients who were admitted in our hospital from January 2019 to January 2020 were selected and randomly divided into two groups: group A and group B, with 60 patients in each group ( $n = 60$ ). As shown in Table 1, there were no significant differences in baseline information between the two groups ( $p > 0.05$ ). The protocol was approved by the Medical Science Research Ethics Committee of *Shandong Provincial*

*Hospital affiliated to Shandong First Medical University* (approved no. 2018-13-243 and followed international guidelines for human studies [5].

### Inclusion criteria

The following categories of patients were included in this study: (1) patients who, with full understanding of the processes involved in the research, signed consent form with permission of family members; (2) patients diagnosed with irregular menstruation after examination done with reference to *Diagnostic Criteria for Gynecological Diseases* [6], and (3) those who had no reproductive system diseases [7].

### Exclusion criteria

The following patients were excluded from the study: (1) patients with mental problems, or those with communication impairments; (2) those with other organic diseases; (3) patients with irregular menstruation due to organic diseases [8]; (4) pregnant patients, and (5) those who had received relevant treatments for irregular menstruation [9].

### Treatments

Group B patients were treated with estradiol valerate tablets. Each patient received 2 tablets of estradiol valerate (Bayer Healthcare Co. Ltd. Guangzhou Branch, SFDA approval number J20130009) with warm water after a meal, once daily. Patients in group A was given *Qilin pill*, in addition to the treatment in group B. Each patient in group A received 6 g of *Qilin Pill* (Guangdong Tai'antang Pharmaceutical Co. Ltd., SFDA approval number Z10930034) 3 times daily. The course of treatment for both groups was 3 months.

**Table 1:** Comparison of general patient profile between the 2 groups

Group	A (n=60)	B (n=60)	X <sup>2</sup> /t	P-value
Age (years)			0.314	0.754
Range	18-48	18-47		
Mean age	27.65±5.98	27.98±5.54		
BMI (kg/m <sup>2</sup> )			0.998	0.320
Range	18-29	18-28		
Mean BMI	23.12±2.15	23.54±2.45		
Course of disease (years)			1.356	0.178
Range	1-7	1-7		
Mean disease course	3.11±0.54	3.24±0.51		
Menstrual period (days)	2.98±0.65	2.84±0.69	1.144	0.255
Menstrual volume (ml)	32.15±6.98	32.65±6.57	0.404	0.687
Complication with dysmenorrhea (n)	22	24	0.141	0.707

**Assessment of outcome indices**

**Treatment effectiveness**

This was categorized into *markedly effective*, *effective* and *ineffective*, depending on the effect observed. If the patient's menstrual volume returned to normal, with significantly shortened cycle, and the outcome was sustained for over 3 months, the treatment was markedly effective. If the patient's menstrual volume increased, with shortened cycle and reduced incidence of dysmenorrhea, but the outcome was not sustained for up to 3 months, the treatment was categorized as effective. However, if there were no changes in menstrual volume and cycle, the treatment outcome was deemed ineffective. Total treatment effectiveness was calculated as the sum of markedly effective and effective cases.

**Time lapse before return to normal menstruation**

The time taken to return to normal menstruation was compared between the two groups of patients.

**Ovulation rate, endometrial thickness and serum levels of P, E2 and LH**

Ovulation rates, endometrial thickness and serum levels of P, E2 and LH were determined and compared between the two groups of patients.

**Clinical symptom scores**

Lumbosacral pain score, breast pain score and lower abdominal pain score in the two groups of patients were determined and compared.

**Statistical analysis**

All statistical analyses were performed with SPSS, version 20, software, while graphics were plotted using GraphPad Prism 7 (GraphPad Software, San Diego, USA). Counting data and measurement data were analyzed with  $\chi^2$  test and *t*-test, respectively. A  $p \leq 0.05$  was taken as indicative of statistically significant difference.

**Table 2:** Comparison of treatment effectiveness [n (%)]

Group	Markedly effective	Effective	Ineffective	Total effectiveness
A	30 (50.0)	28 (46.7)	2 (3.3)	58 (96.7)
B	18 (30.0)	30 (50.0)	12 (20.0)	48 (80.0)
$\chi^2$	5.000	0.134	8.086	8.086
P-value	0.025	0.715	0.004	0.004

**RESULTS**

**Treatment effectiveness**

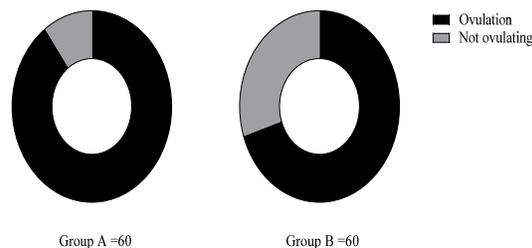
There was higher effectiveness in group A patients than in group B patients ( $p < 0.05$ ), as shown in Table 2.

**Time taken to return to normal menstruation**

The time lapse before return to normal menstruation was significantly shorter in group A than in group B ( $3.65 \pm 0.81$  months vs  $4.41 \pm 0.95$  months,  $p < 0.001$ ).

**Ovulation rate**

Group A patients had markedly higher ovulation rate than patients in group B ( $p < 0.05$ ), as shown in Figure 1.



**Figure 1:** Comparison of ovulation rate between the two groups. The black region represents ovulation, while the gray area represents non-ovulation.

There were 54 cases of ovulation in group A, and 6 cases of non-ovulation. In group B, there were 42 cases of ovulation, and 18 cases of non-ovulation ( $\chi^2 = 7.500$ ,  $p = 0.006$ ).

**Hormonal levels**

Table 3 shows that group A patients had more favorable hormone levels than group B patients ( $p < 0.05$ ).

**Endometrial thickness**

Prior to treatment, the endometrial thickness was similar in the two groups ( $0.70 \pm 0.23$  cm vs  $0.71$

**Table 3:** Comparison of hormonal levels (mean  $\pm$  SD)

Group	P (mmol/L)		E <sub>2</sub> (pmol/L)		LH (mIU/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
A	1.23 $\pm$ 0.21	3.68 $\pm$ 0.68	60.98 $\pm$ 14.32	108.98 $\pm$ 25.11	4.22 $\pm$ 1.21	11.10 $\pm$ 2.15
B	1.25 $\pm$ 0.23	3.10 $\pm$ 0.54	61.10 $\pm$ 14.52	94.54 $\pm$ 23.36	4.32 $\pm$ 1.20	8.21 $\pm$ 2.54
<i>t</i>	0.497	5.174	0.046	3.261	0.455	6.727

**Table 4:** Comparison of clinical symptom scores (mean  $\pm$  SD)

Group	Lumbosacral pain score		Breast tenderness score		Abdominal distension and pain score	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
A	2.31 $\pm$ 0.65	0.78 $\pm$ 0.31	2.34 $\pm$ 0.36	0.65 $\pm$ 0.15	2.87 $\pm$ 0.54	0.65 $\pm$ 0.22
B	2.35 $\pm$ 0.54	1.64 $\pm$ 0.58	2.36 $\pm$ 0.34	1.67 $\pm$ 0.57	2.89 $\pm$ 0.58	1.35 $\pm$ 0.35
<i>t</i>	0.367	10.129	0.313	13.405	0.195	13.116

$\pm$  0.21 cm); Post-treatment endometrial thickness was significantly higher in group A than in group B (1.06  $\pm$  0.25 cm) vs (0.92  $\pm$  0.24 cm,  $p < 0.05$ ).

### Clinical symptom scores

The post-treatment clinical symptom scores in group A patients were superior to the corresponding scores in group B patients, as presented in Table 4 ( $p < 0.001$ ).

## DISCUSSION

Irregular menstruation is a disease that arises from various factors such as diet, sleep, and emotional disturbance. Currently, approximately 10 % of young Chinese women suffer from the disease. With the current changes in lifestyles, the prevalence of irregular menstruation worldwide has been increasing annually. Apart from disorders in menstrual cycle, irregular menstruation may also result in endometrial cancer and other diseases which constitute serious threats to the lives of women. Unfortunately, the use of estradiol valerate (a western medicine) for the treatment of irregular menstruation does not result in long-term efficacy [10,11].

In TCM, it is believed that irregular menstruation is caused by *sexual strain*. Irregular menstruation patients often experience abnormalities in the functioning of the internal organs. Thus, the treatment of irregular menstruation should be focused on regulating the *qi* and blood so as to mitigate *qi* stagnation and *blood stasis*.

The *Qilin pill* used in this study is a Chinese patent medicine which replenishes *qi* and *nourishes the blood*, thereby helping patients to establish stable menstrual cycles [12]. From pharmacological perspectives, *Qilin pill* enhances

pituitary secretions, increases hormonal levels, and optimizes reproductive function, thereby playing a positive role in endocrine regulation. It is of interest that the results of the study showed that treatment effectiveness in group A was significantly better than that in group B, and the time lapse before return to normal menstruation in group A was significantly shorter than that in group B. This indicates that treatment of irregular menstruation with combination of TCM and western medicine yielded a superior outcome, when compared with treatment using estradiol valerate alone.

To the best of knowledge of the investigators, P accelerates maturation of the endometrium and promotes its transit to the secretory phase. Moreover, E<sub>2</sub> stems from the ovarian follicles, and it increases the rate of transition of the endometrium to the proliferative phase. Luteinizing hormone (LH) stabilizes ovulation and the frequency of progesterone secretion. These three hormones which symbolize endocrine status serve as indicators for evaluating the menstrual cycle [13,14].

In this study, it was found that the hormonal levels and endothelial thickness in group A were significantly higher than those in group B. It is known that P, E<sub>2</sub>, and LH are important in the development of the endometrium. Indeed, increased levels of P, E<sub>2</sub>, and LH enhance the thickness of the endometrium. These results indicate that the hormonal levels of the patients were significantly improved post-treatment. Moreover, the endocrine disorders were reduced, and the return of menstruation to normal was enhanced.

With increased awareness of irregular menstruation, research has revealed that abnormal follicles are implicated in the

pathogenesis of the disease. Developmental imbalance in follicles give rise to low levels of sex hormones, leading to reduced menstrual flow. Fortunately, it was observed in this study that the ovulation rate of group A was significantly higher than that of group B, probably due to the normalization of sex hormone levels and the increase in endometrial thickness. These results are in agreement with those obtained by Thufailah *et al* who reported higher ovulation rates in irregular menstruation patients treated with combination of *Qilin pills* and estradiol valerate tablets, than in controls given estradiol valerate tablets only [15]. These findings indicate that the combination of the two drugs can effectively improve endometrial development, increase ovulation rate, and stabilize the menstrual cycle of irregular menstruation patients.

## CONCLUSION

This study has demonstrated that the combination of *Qilin pills* and estradiol valerate tablets might be a preferred option for treating patients with irregular menstruation, since it increases ovulation rate and sex hormonal levels, and helps patients to return to normal menstruation. Thus, the combination treatment presents as an option for the management of irregular menstruation.

## DECLARATIONS

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### 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.

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