

## Original Article

# Effect of Bushen Yangluan decoction combined with clomiphene citrate on ovulation and ovarian function in patients with infertility due to polycystic ovary syndrome

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**Abstract:** Objective: We aimed to investigate the effect of Bushen Yangluan (BSYL) decoction combined with clomiphene citrate (CC) on ovulation and ovarian function in patients with infertility due to polycystic ovary syndrome (PCOS). Methods: Ninety-six patients who were treated in our hospital for infertility due to PCOS were enrolled in this prospective study. The patients were randomly divided into two groups with 48 cases in each. The patients in the control group received CC, whereas the patients in the study group received BSYL decoction combined with CC. The clinical efficacy, ovulation rate, dominant follicle diameter, pregnancy rate, serum sex hormone levels, ovarian volume, endometrial thickness, and incidence of adverse reactions were examined and compared between the two groups. Results: The total effective rate, ovulation rate, dominant follicle diameter, and pregnancy rate in the study group were higher than those in the control group (all  $P < 0.05$ ). After treatment, the serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), testosterone (t), and prolactin (PRL) and the ovarian volume all decreased, whereas the endometrial thickness increased in both groups, and the study group had a greater magnitude of changes in the levels of these markers than the control group (all  $P < 0.05$ ). No intergroup differences were observed in the incidence of adverse reactions ( $P > 0.05$ ). Conclusion: BSYL decoction combined with CC can achieve a good outcome in the treatment of PCOS-induced infertility. The combined therapy can significantly and safely improve the ovulation, pregnancy rate, levels of sex hormones, and the ovarian function of the patients, which is therefore recommended for clinical application.

**Keywords:** Bushen Yangluan decoction, polycystic ovary syndrome, infertility due to ovulatory disturbance, ovarian function, ovulation, sex hormone

## Introduction

Polycystic ovary syndrome (PCOS) is a common reproductive endocrine disorder in women of childbearing age. The disease is characterized by hyperandrogenism and polycystic ovarian changes. The clinical manifestations of PCOS include irregular menstrual cycle, amenorrhea, obesity, and infertility [1]. In recent years, the incidence of infertility due to PCOS has been increasing in China. The ovulatory disturbance in PCOS is the main cause of infertility, and it can bring a heavy burden to the patients and their family [2].

At present, the use of ovulation induction medication on the basis of balancing the endocrine system and metabolism is a common clinical method for treating patients with infertility due to PCOS [3, 4]. Clomiphene citrate (CC) is a steroidal antiestrogen and the most common ovulation induction drug. It can antagonize the estrogen receptor in the hypothalamus to inhibit the negative feedback of endogenous estrogen, improve the levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) released from pituitary gland, it also stimulates follicular growth, and increases the release of estrogen. When the estrogen reaches a certain

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level, the positive feedback of estrogen can induce gonadotropin release and complete ovulation [5, 6]. However, the use of CC alone in the treatment of PCOS-induced infertility cannot achieve excellent results in some patients. This may be due to the fact that CC can reduce the concentration of estrogen receptors and affect luteal function, leading to the thickening of cervical mucus that blocks sperm entry. Moreover, long-term use of CC can cause toxic side effects. Therefore, it is necessary to combine CC with other medicines for the treatment of this disease [7].

In recent years, a growing number of studies have demonstrated traditional Chinese medicine (TCM) has good efficacy in the clinical treatment of PCOS-induced infertility without causing toxic side effects [8-10]. According to TCM, PCOS-induced infertility is due to kidney deficiency and blood stasis, and the treatment needs to focus on tonifying the kidney and promoting blood circulation [11, 12]. Bushen Yangluan (BSYL) decoction is an empirical prescription in Zibo Hospital of Traditional Chinese Medicine for the treatment of infertility due to PCOS, which can tonify the kidney and promote blood circulation. In this present study, we combined BSYL decoction with the conventional western medicine, for the first time, in order to analyze its effect on ovulation and ovarian function in women with infertility due to PCOS.

### Materials and methods

#### Baseline data

A total of 96 patients who were treated in Zibo Hospital of Traditional Chinese Medicine for infertility due to PCOS between September 2018 and December 2019 were enrolled in this study. The patients were randomly divided into two groups, with 48 cases in each. This study was approved by Ethics Committee of Zibo Hospital of Traditional Chinese Medicine.

The patients met the diagnostic criteria according to western medicine defined in *Obstetrics and Gynecology* as follows: (1) Patients have a normal sexual life without contraception but cannot conceive for one year; (2) patients have oligomenorrhea, amenorrhea, or metrorrhagia; (3) patients have hyperandrogenemia and/or show clinical manifestations of hyperandrogen-

emia; (4) presence of polycystic ovary as detected by ultrasonography [13].

Meanwhile, the patients also met the diagnostic criteria for TCM as defined in *Criteria of diagnosis and therapeutic effect of diseases and syndromes in traditional Chinese medicine* as follows: (1) patients have kidney deficiency and blood stasis; (2) main symptom is long-term infertility; (3) minor symptoms are soreness and weakness of waist and knees, amenorrhea, scant menstrual flow, clear and profuse urine, decreased sexual desire, fatigue, dizziness and tinnitus, dysmenorrhea, purple period blood and presence of menstrual clot, light purple tongues or petechia on tongues, and fine rough pulse [14].

Inclusion criteria were as follows: (1) patients who met the diagnostic criteria as mentioned above; (2) patients who signed an informed consent; (3) patients who had normal sexual life and the spouse had no reproductive dysfunction; (4) patients who had good treatment compliance.

Exclusion criteria were: (1) patients who had infertility due to obstruction of fallopian tube, uterine fibroids, uterine hypoplasia, or endometriosis; (2) patients who had infertility caused by congenital physiological defects or malformations; (3) patients who were allergic to the medicines used in this study; (4) patients whose spouses had reproductive dysfunction; (5) patients who had severe heart, liver, or kidney dysfunctions.

#### Treatment methods

The patients in both groups received oral administration of CC tablets (Zhongxin Pharma, Beijing, China) once a day (50 mg) from the fifth day of the menstrual cycle. One treatment course lasted 5 consecutive days, and the patients underwent three treatment courses.

Meanwhile, the patients in the study group also received BSYL decoction. The formula of the BSYL decoction was as follows: cortex moutan 12 g, forsythia 12 g, fried malt 30 g, scutellaria 9 g, oriental wormwood 9 g, ligusticum wallichii 12 g, salvia miltiorrhiza Bge. 30 g, angelica sinensis 12 g, raw radix rehmanniae 30 g, prepared rehmannia 30 g, wolfberry 15 g, fructus corni 15 g, cuscuta chinensis Lam. 30 g,

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**Table 1.** Baseline data ( $\bar{x} \pm sd, \%$ )

	Age (year)	Duration of infertility (year)	Infertility type	
			Primary infertility	Secondary infertility
Control group (n=48)	28.1±2.3	3.25±1.39	29 (60.42)	19 (39.58)
Study group (n=48)	27.8±2.1	3.04±1.47	31 (64.58)	17 (35.42)
t/ $\chi^2$	t=0.667	t=0.719	$\chi^2=0.178$	
P	0.506	0.474	0.673	

**Table 2.** Clinical efficacy (n, %)

	Markedly effective	Effective	Ineffective	Total effective rate
Control group (n=48)	18 (37.50)	20 (41.67)	10 (20.83)	38 (79.17)
Study group (n=48)	26 (54.17)	19 (39.58)	3 (6.25)	45 (93.75)
$\chi^2$				4.360
P				0.037

**Table 3.** Ovulation rate, dominant follicle diameter, pregnancy rate ( $\bar{x} \pm sd, \%$ )

	Ovulation rate	Dominant follicle diameter (mm)	Pregnancy rate
Control group (n=48)	38 (79.17)	20.36±1.59	28 (62.50)
Study group (n=48)	46 (95.83)	25.03±1.63	38 (79.17)
t/ $\chi^2$	$\chi^2=4.521$	t=14.209	$\chi^2=4.849$
P	0.034	0.000	0.028

schisandra chinensis 6 g, raspberry 12 g, plantain seed 10 g, teasel root 30 g, radix cyathulae 15 g, fructus amomi 6 g, poria cocos 12 g, fried white atractylodes rhizome 18 g, dried Chinese yam 30 g, safflower 9 g, fried rhizoma cyperi 9 g, fluoritum 30 g, deer-horn gelatin 12 g, donkey-hide gelatin 6 g, tangerine peel 9 g, seed of job's tears 30 g, leech 3 g, rhizoma sparganii 12 g, curcuma zedoary 12 g, chicken's gizzard-membrane 30 g, rhizoma anemarrhenae 9 g, phellodendron chinense schneid 9 g, motherwort 9 g, radix paeoniae rubra 9 g, radix paeoniae alba 9 g, ginseng 9 g, astragalus mongholicus 9 g, and radix glycyrrhizae 9 g (supplier of the herbs: Tianho Herbal Source, Anhui, China). The herbs were added with 600 mL of water for decoction until the volume reached 400 mL. The patients took the decoction orally twice a day (200 mL each time) from the 5th day of the menstrual cycle. One treatment course lasted 5 consecutive days, and the patients underwent three treatment courses.

### Outcome measures

The clinical efficacy, ovulation rate, dominant follicle diameter, pregnancy rate, levels of serum sex hormones (FSH, LH, estradiol (E2), testosterone (t), and prolactin (PRL)), ovarian volume, endometrial thickness, and the incidence of adverse reactions were compared between the two groups.

### Main outcome measures

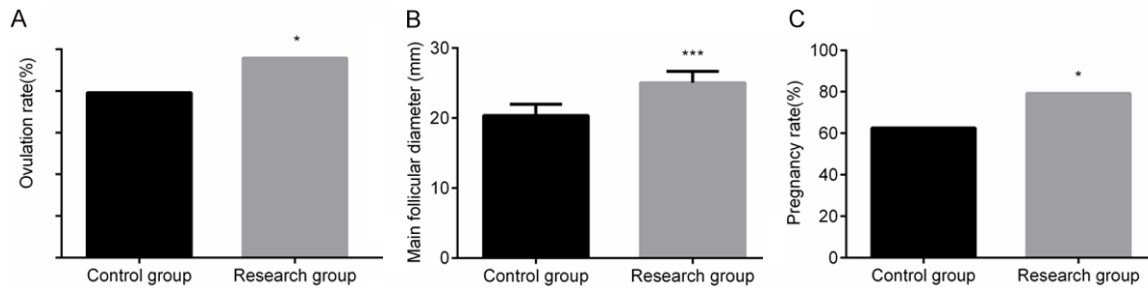
**Clinical efficacy:** If the clinical symptoms disappeared or improved markedly, the menstrual cycle and menstrual blood loss volume became normal, and there was recovery of ovulation or the patient became pregnant, the treatment was considered as markedly effective. If the clinical symptoms were alleviated, the menstrual cycle and menstrual blood loss volume were improved, and there was recovery of ovulation or patient became

pregnant, the treatment was considered as effective. If the clinical symptoms were not improved or even aggravated, the menstrual cycle and menstrual blood loss volume were not improved, and the ovulation was not restored or patients were not pregnant, the treatment was considered as ineffective. The total effective rate was the sum of effective rate and markedly effective rate.

**Sex hormone levels:** Before and after treatment, 3 mL of venous blood was collected from each patient while on an empty stomach in the morning. The blood samples were centrifuged at 3,000 rpm to collect the supernatant. The levels of FSH, LH, E2, t, and PRL were determined by radioimmunoassay according to the manufacturer's instructions of the test kits (Tongwei Biotechnology, Shanghai, China).

**Ovarian function:** The ovarian volume and the endometrial thickness of the patients were

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**Figure 1.** Ovulation rate, dominant follicle diameter, and pregnancy rate. A: Ovulation rate; B: Dominant follicle diameter; C: Pregnancy rate. \* $P < 0.05$ , \*\*\* $P < 0.001$  vs. the control group.

**Table 4.** Serum levels of FSH, LH,  $E_2$ , T, and PRL ( $\bar{x} \pm sd$ )

	Control group (n=48)	Study group (n=48)	t	P
<b>FSH (mIU/mL)</b>				
Before treatment	7.95±1.38	8.06±1.34	0.396	0.693
After treatment	7.13±1.24***	6.53±0.86***	2.755	0.007
<b>LH (mIU/mL)</b>				
Before treatment	7.69±1.32	7.74±1.29	0.188	0.852
After treatment	6.95±1.14***	6.13±0.79***	4.096	0.000
<b><math>E_2</math> (ng/dL)</b>				
Before treatment	56.96±5.74	56.62±5.63	0.293	0.770
After treatment	50.49±4.82***	43.58±4.52***	7.245	0.000
<b>T (ng/dL)</b>				
Before treatment	55.21±6.21	54.81±6.14	0.317	0.752
After treatment	48.36±4.92***	39.84±5.03***	8.389	0.000
<b>PRL (ng/mL)</b>				
Before treatment	17.75±1.65	17.93±1.57	0.548	0.585
After treatment	15.27±1.09***	12.03±1.24***	13.597	0.000

Note: \*\*\* $P < 0.001$  vs. pre-treatment within the same group. FSH: follicle-stimulating hormone; LH: luteinizing hormone;  $E_2$ : estradiol; T: testosterone; PRL: prolactin.

measured by transvaginal color Doppler imaging before and after treatment.

### Secondary outcome measures

The ovulation rate, dominant follicle diameter, and pregnancy rate of the patients were monitored using transvaginal color Doppler imaging. The incidences of adverse reactions in the two groups were also analyzed.

### Statistical analysis

SPSS 20.0 software was applied for data analysis. Measurement data are expressed as mean  $\pm$  standard deviation. Independent sam-

ple t-test was used for inter-group comparison, and paired samples t-test was used for intra-group comparison. Count data are expressed as number or percentage and were examined by Chi-square test or corrected Chi-square test.  $P < 0.05$  indicated a statistically significant difference.

## Results

### Baseline data

There were no intergroup differences in age, duration of infertility, and type of infertility (all  $P > 0.05$ ), and our study results were comparable. See **Table 1**.

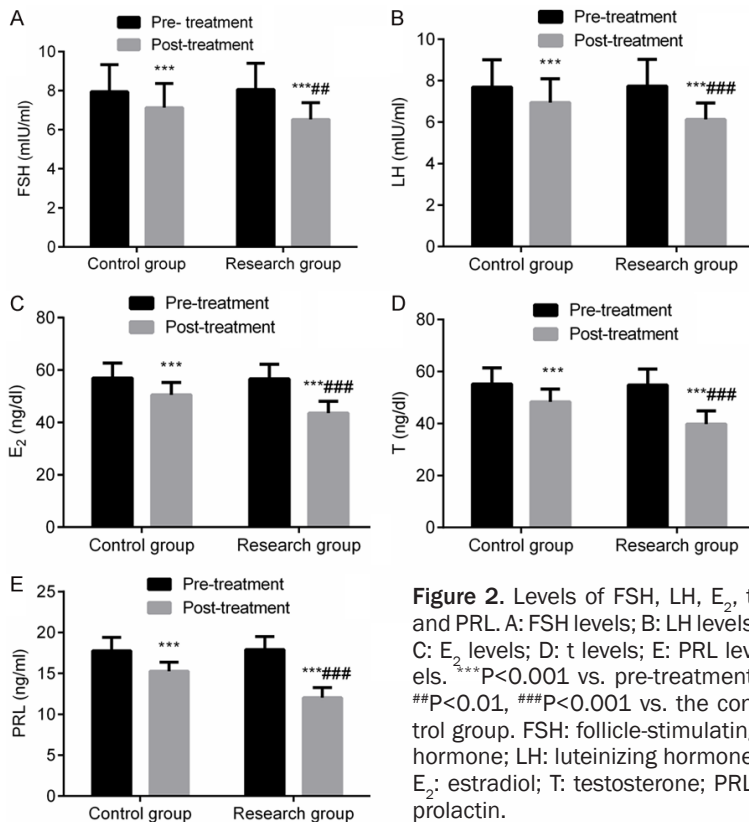
### Clinical efficacy

The study group had higher total effective rate than the control group ( $P < 0.05$ ), indicating that BSYL decoction can effectively improve the clinical efficacy in the treatment of patients with infertility due to PCOS. See **Table 2**.

### Ovulation rate, dominant follicle diameter, and pregnancy rate

The ovulation rate, dominant follicle diameter, and pregnancy rate in the study group were higher than those in the control group (all  $P < 0.05$ ), indicating that BSYL decoction can effectively improve the ovulation rate, dominant follicle diameter, and pregnancy rate in patients with infertility due to PCOS. See **Table 3** and **Figure 1**.

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**Figure 2.** Levels of FSH, LH, E<sub>2</sub>, t, and PRL. A: FSH levels; B: LH levels; C: E<sub>2</sub> levels; D: t levels; E: PRL levels. \*\*\*P<0.001 vs. pre-treatment. ##P<0.01, ###P<0.001 vs. the control group. FSH: follicle-stimulating hormone; LH: luteinizing hormone; E<sub>2</sub>: estradiol; T: testosterone; PRL: prolactin.

### Sex hormone levels

Before treatment, there were no differences in the serum levels of FSH, LH, E<sub>2</sub>, t, and PRL between the two groups (all P>0.05). After treatment, both groups had decreased levels of FSH, LH, E<sub>2</sub>, t, and PRL (all P<0.05), and the magnitude of reduction in the levels of these markers was greater in the study group compared with the control group (all P<0.05). The results indicate that BSYL decoction can effectively improve the sex hormone levels in patients with infertility due to PCOS. See **Table 4** and **Figure 2**.

### Ovarian function

Before treatment, there were no differences in the ovarian volume and endometrial thickness between the two groups (both P>0.05). After treatment, both groups had decreased ovarian volume and increased endometrial thickness (both P<0.05), and the magnitude of changes in these markers was greater in the study group than in the control group (both P<0.05), indicating that BSYL decoction can effectively improve the ovarian function in patients with infertility

due to PCOS. See **Table 5** and **Figure 3**.

### Adverse reactions

There was no intergroup difference in the incidence of adverse reactions (P>0.05), suggesting that PCOS decoction has good safety and does not increase the incidence of adverse reactions in the treatment of PCOS. See **Table 6**.

### Discussion

In TCM, there is no defined disease name for PCOS. Based on patients' clinical manifestations, PCOS is usually categorized into infertility, amenorrhoea, and uterine bleeding, and kidney deficiency and blood stasis is regarded as the common TCM syndrome of PCOS [15-17]. TCM theory reveals that PCOS is caused by kidney deficiency, disharmony

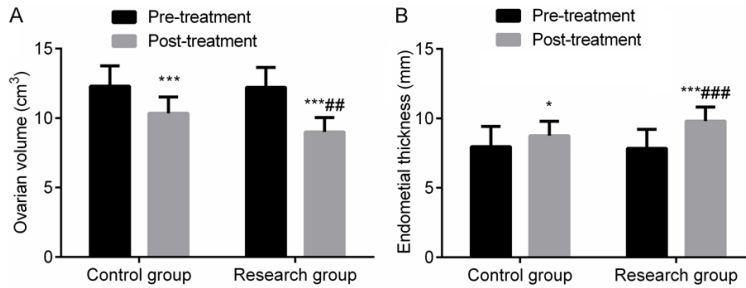
of thoroughfare and conception channels, and blood stasis obstructing the uterus, resulting in ovulation disorders [18-20]. Kidney deficiency is closely related to blood stasis and is considered as the root cause of PCOS, while blood stasis is the pathological product throughout the progression of this disease. Long-term kidney deficiency can cause blood stasis, and blood stasis can block thoroughfare and conception channels to aggravate kidney deficiency. Therefore, the treatment of infertility due to PCOS needs to focus on tonifying the kidney and promoting blood circulation. Since BSYL decoction has the effect of tonifying the kidney and promoting blood circulation, we combined the BSYL decoction with conventional western medicine for the treatment of infertility due to PCOS and found that combined therapy achieved greater improvement in the ovulation rate, pregnancy rate, and clinical efficacy than the use of CC alone. The improved clinical efficacy achieved by the combined medications may be due to a greater capacity to reduce the serum levels of FSH, LH, E<sub>2</sub>, t, and PRL, decrease the ovarian volume, and increase the endometrial thickness more significantly that

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**Table 5.** Ovarian volume and endometrial thickness ( $\bar{x} \pm sd$ )

	Ovarian volume (cm <sup>3</sup> )		Endometrial thickness (mm)	
	Before treatment	After treatment	Before treatment	After treatment
Control group (n=48)	12.31±1.46	10.35±1.18***	7.97±1.45	8.75±1.04*
Study group (n=48)	12.22±1.43	9.01±1.03***	7.85±1.37	9.81±1.01***
t	0.305	5.927	0.417	5.066
P	0.761	0.007	0.678	0.000

Note: \*P<0.05, \*\*\*P<0.001 vs. pre-treatment within the same group.



**Figure 3.** Ovarian volume and endometrial thickness. A: Ovarian volume; B: Endometrial thickness. \*P<0.05, \*\*\*P<0.001 vs. pre-treatment. ##P<0.01, ###P<0.001 vs. the control group.

**Table 6.** Adverse reactions (n, %)

	Abdominal pain	Abnormal leucorrhea	Breast tenderness	Total
Control group (n=48)	1 (2.08)	0 (0.00)	1 (2.08)	2 (4.17)
Study group (n=48)	1 (2.08)	1 (2.08)	1 (2.08)	3 (6.25)
$\chi^2$				0.000
P				1.000

CC alone. Moreover, there was no difference in the incidence rate of the adverse reactions between the two groups, suggesting that the combined therapy does not increase the incidence of adverse reactions in patients. These findings are consistent with the study by Zeng et al. [21].

BSYL decoction is an empirical prescription in our hospital for the treatment of infertility due to PCOS. In this prescription, cortex moutan, forsythia, scutellaria, oriental wormwood, ligusticum wallichii, salvia miltiorrhiza Bge, angelica sinensis, raw radix rehmanniae, plantain seed, radix cyathulae, safflower, leech, rhizoma sparganii, curcuma zedoary, rhizoma anemarrhenae, phellodendron chinense schneid, motherwort, radix paeoniae rubra, and radix paeoniae alba can clear away heat and toxic materials, promote blood circulation, and remove

blood stasis; fried malt, fructus amomi, poria cocos, and chicken's gizzard-membrane can promote Qi circulation and digestion, invigorate spleen, and increase appetite; prepared rehmannia, wolfberry, fructus corni, cuscuta chinensis Lam., schisandra chinensis, raspberry, teasel root, dried Chinese yam, deer-horn gelatin, ginseng, and astragalus mongholicus can nourish liver and kidney, replenish essence, and fill marrow; fried white atractylodes rhizome, tangerine peel, and seed of job's tears can strengthen the spleen and replenish Qi; fried rhizoma cyperi can regulate Qi to relieve stagnation, relieve pain, and regulate menstrual function; fluoritum can relieve

palpitation, tranquilize the mind and warm the lung and uterus; donkey-hide gelatin can nourish Yin and blood and prevent miscarriage; radix glycyrrhizae can tonify spleen and replenish Qi, clear away heat and toxic material, and moderate the property of herbs. The whole prescription can achieve the effect of tonifying kidney and promote blood circulation. Some pharmacological studies have revealed that the flavonoid extracts of cuscuta chinensis Lam. can promote follicular development by affecting the mRNA expression of luteinizing hormone receptor in ovary; lycium barbarum polysaccharide has protective effect on the ovarian tissue; total saponins of paeonia can reduce the blood viscosity and achieve antithrombotic, anticoagulant, and immunomodulatory effects; motherwort can bidirectionally regulate the uterus; and tanshinone can improve the expression levels of FSHR in the ovary and alleviate

E<sub>2</sub>-induced PCOS [22-24]. Therefore, BSYL decoction has synergistic effect with CC to improve the clinical efficacy in the treatment of infertility due to PCOS [25].

However, due to small sample size and limited time in this study, the mechanism of BSYL decoction combined with CC in the treatment of infertility due to PCOS was not investigated deeply. Therefore, more studies with a large sample size need to be carried out in the future for verification.

In conclusion, BSYL decoction combined with CC can achieve good clinical outcome in the treatment of infertility due to PCOS. This therapy can safely and markedly improve the ovulation, pregnancy rate, levels of sex hormones, and the ovarian function of patients, which can be recommended for clinical application.

#### Disclosure of conflict of interest

None.

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