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Application of Bushen Zhuyun Decoction Combined with Clomiphene Citrate Capsule in Patients with Polycystic Ovary Syndrome

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Keywords

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Abstract

Objective: This study investigates the efficacy of Bushen Zhuyun Decoction combined with clomiphene citrate capsule in patients with polycystic ovary syndrome (PCOS). **Methods:** Forty PCOS patients who received Bushen Zhuyun Decoction combined with clomiphene citrate capsule in our hospital from March 2021 to March 2022 were allocated into observation group, and another 40 PCOS patients who received clomiphene citrate capsule were assigned into control group. The treatment course was limited to 3 menstrual cycles. The clinical efficacy in the two groups of patients was compared, the ovulation and serum sex hormone levels of the patients with different treatment methods were evaluated, and the safety and 1-year efficacy were analyzed. **Results:** The clinical total effective rate, ovulation rate, and pregnancy rate after 1 year in observation group were higher than those in control group ($p < 0.05$). After treatment, endometrial thickness and levels of estradiol (E_2) and serum follicle stimulating hormone (FSH) were elevated, but luteinizing hormone (LH) and testosterone (T) levels were reduced in both groups, where the change of these indicators in observation group was greater than that in control group ($p < 0.05$). There was no significant difference in the occurrence of adverse reactions such as nausea, vomiting, and breast tenderness between the two groups ($p > 0.05$). **Conclusion:** Bushen Zhuyun Decoction combined with clomiphene citrate capsule may have a better effect on PCOS patients, which can improve ovulation and sex hormone secretion, with high safety and better 1-year efficacy.

1 Introduction

Polycystic ovary syndrome (PCOS), a common endocrine and metabolic disorder, is most frequently seen in women of childbearing age with an incidence rate of 12-18% [1,2]. PCOS patients mainly present with symptoms such as ovulation disorder, excessive androgen levels, and abnormal blood lipids. Ovulation disorder or abnormal secretion of sex hormones may lead to infertility and abnormal blood lipids may cause cardiovascular diseases such as diabetes, significantly impacting the quality of patients' life [3]. At present, the clinical treatment modalities in western medicine include lifestyle intervention, ovulation induction therapy, laparoscopic ovarian drilling, etc., of which drug therapy is the main mean of ovulation induction therapy [4].

Clomiphene citrate is a commonly used medication for promoting ovulation, but its effectiveness is limited when used alone [5]. Additionally, it may have adverse effects on endometrial receptivity and thickness, leading to a relatively low clinical pregnancy rate [6]. Therefore, it is necessary to find a safer and more effective treatment method. In traditional Chinese medicine, PCOS belongs to the categories of "infertility" and "menstrual irregularities" Traditional Chinese medicine can improve ovulation rates and hormone levels by regulating the qi, blood, yin, and yang in all phases of the menstrual cycle [7]. Previous studies showed that traditional Chinese medicine such as Jinfeng pill, Bu-Shen-Tian-Jing Formula, Dingkun pill and Qi Gong Wan has the functions of improving hormone disorder and insulin sensitivity, and increasing pregnancy rate, protect adipose tissue [8-11]. Bushen Zhuyun Decoction is a traditional Chinese medicine decoction based on nourishing the kidneys and boosting yang energy. Research has confirmed that Bushen Zhuyun Decoction can increase the receptivity of endometrium, improve the ovarian microenvironment, regulate ovarian function, and promote ovarian development and maturation, thereby achieving the effect of promoting fertility [12-14].

In light of these, this study compared the clinical efficacy of clomiphene citrate capsule alone or together with Bushen Zhuyun Decoction in PCOS patients, and explored the latter's application results on PCOS patients, so as to provide reference and guidance for improving the efficacy of PCO.

2 Materials and methods

2.1 General data

Forty PCOS patients who received Bushen Zhuyun Decoction combined with clomiphene citrate capsule in our hospital from March 2021 to March 2022 were allocated into observation group, and another 40 PCOS patients who received clomiphene citrate capsule were assigned into control group.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria

(1) Patients met the diagnostic criteria for PCOS in *Chinese Guidelines for the Diagnosis and Treatment of Polycystic Ovary Syndrome* [15]. (2) Patients who did not use contraception in the last 1 year. (3) Patients were not pregnant and had no history of pregnancy. (4) Patients did not receive any other treatments, such as ovulation promotion or hormone therapy, in the past 3 months.

2.2.2 Exclusion criteria

(1) Patients who were allergic to the drugs in this study. (2) Patients with previous history of pelvic surgery. (3) Patients with ovulation disorder due to premature ovarian failure, and pituitary or hypothalamic amenorrhoea. (4) Patients with endocrine disorders such as thyroid and parathyroid. (5) Patients with malignancy. (6) Patients with coagulation dysfunction. (7) Patients with insufficiency

of heart, liver, and kidneys. (8) Patients with mental disorder and poor adherence to treatment. (9) Patients with incomplete clinical data.

2.3 Methods

In the control group, 5 days after menstruation, patients were orally given 50 mg of clomiphene citrate capsule (Shanghai Hengshan Pharmaceutical Co., Ltd, National Medical Products Administration (NMPA) Approval No.: H31021107, specification: 50 mg) every day for a total of 5 days. Amenorrhoeic patients were first orally administered with progesterone capsule (Zhejiang Xianju Pharmaceutical Co., Ltd, NMPA Approval No.: H20041902, specification: 100 mg) twice a day, with 100 mg each time, and then orally given clomiphene citrate capsule 5 days after withdrawal bleeding in the same way as above.

Based on the treatment in control group, patients in observation group were given Bushen Zhuyun Decoction 5 days after menstruation. The formula of Bushen Zhuyun Decoction was detailed below: 30 g of *fluoritum*, *Cuscuta chinensis Lam*, *Salvia miltiorrhiza Bunge*, and *Astragalus*; 20 g of *Lycii Fructus* and *Rehmannia glutinosa*; 15 g of *Epimedium brevicornu Maxim*, *Angelica sinensis*, *Cyperus rotundus L*, and *Cyathula officinalis Kuan*; and 6 g of *Amomum villosum Lour*. The decoction was provided by the pharmacy department of our hospital, and it was decocted with water to the final volume of 300 mL. Patients were given this decoction twice a day, with 150 mL per time. The treatment duration for both groups was 3 menstrual cycles, and the normal menstrual cycle was defined as 21-35 days. In case of abnormal menstruation, 30 days would be considered as one menstrual cycle. After the treatment was completed, follow-up was conducted for one year.

2.4 Observational indicators

2.4.1 Clinical efficacy

The clinical efficacy in the two groups of patients was compared. Efficacy assessment criteria were listed below. Significantly effective: the results of human chorionic gonadotropin (HCG) detection and ultrasound indicated pregnancy, with the clinical symptoms basically disappearing and ovulation and hormone levels returning to normal; effective: clinical symptoms were improved, with ovulation and hormone levels returning to normal; ineffective: no significant change or even worsening of clinical symptoms. The total effective rate = (number of significantly effective cases + number of effective cases)/total number of cases × 100%.

2.4.2 Ovulation

Ovulation in two groups of patients was evaluated and compared before and after 3 menstrual cycles of treatment. The color Doppler ultrasound diagnostic system (Neusoft Medical Systems Co., Ltd.) was used to measure endometrial thickness, and Clearblue ovulation test kits were applied for the detection of luteinizing hormone (LH) level in urine, followed by the calculation of ovulation rate. The examination was conducted 9 days after the menstrual cycle.

2.4.3 Serum sex hormone levels

Serum sex hormone levels were quantified and compared between the two groups of patients before and after 3 menstrual cycles of treatment. 2-3 days after the menstrual cycle, 5 mL of fasting peripheral venous blood was drawn from both groups of patients in the morning. The blood was left to stand at room temperature for 30-60 min, and then centrifuged at 3000 r/min for 10 min. After separation of the serum, it was stored at -20 ℃ for testing.

The levels of luteinizing hormone (LH), testosterone (T), estradiol (E_2), and serum follicle stimulating hormone (FSH) in both groups of patients were measured using fully automatic chemiluminescence immunoassay analyzer (Suzhou Lihe Biomedical Engineering Co., Ltd.).

2.4.4 Adverse reaction

The incidence of adverse reactions between the two groups of patients during the treatment period was recorded and compared.

2.4.5 1-year efficacy

The 1-year efficacy in the two groups of patients was assessed and compared. The pregnancy of patients in both groups during the follow-up period was recorded and the pregnancy rate was calculated. Pregnancy rate = number of pregnancies/total number of cases × 100%.

2.5 Statistical analysis

Statistical analysis was performed using SPSS 20.0. Count data were expressed as cases (%), comparisons between the two groups were carried out using x^2 test, and measurement data were expressed as mean ± standard deviation. Independent samples t-test was used for comparison between the two groups, and paired samples t-test was performed for the comparison before and after treatment in the same group. Difference was considered to be statistically significant at $p < 0.05$.

3 Results

3.1 Comparison of general data between the two groups

There was no statistically significant difference between the two groups in terms of age, duration of disease, body mass index (BMI), and menstruation ($p > 0.05$), but these data were comparable, as shown in Table 1.

3.2 Comparison of clinical efficacy between the two groups

The clinical total effective rate in observation group was higher than that in control group ($p < 0.05$), as seen in Table 2.

Table 1 Comparison of general data in two groups.

Groups	Cases	Age (years old)	Duration of disease (years)	BMI (kg/m^2)	Menstruation (cases)	
					Oligomenorrhea	Amenorrhea
Observation group	40	28.95 ± 2.41	2.14 ± 0.32	22.98 ± 1.28	30	10
Control group	40	28.64 ± 2.38	2.20 ± 0.28	23.01 ± 1.34	28	12
x^2/t		0.579	0.892	0.102	0.251	
p		0.564	0.375	0.919	0.617	

Table 2 Comparison of clinical efficacy between the two groups of patients [case (%)].

Groups	Cases	Significantly effective	Effective	Ineffective	Total effective rate
Observation group	40	16 (40.00)	22 (55.00)	2 (5.00)	38 (95.00)
Control group	40	14 (35.00)	18 (45.00)	8 (20.00)	32 (80.00)
x^2					4.114
p					0.043

3.3 Comparison of ovulation between the two groups

The ovulation rate in the observation group was higher than that in the control group ($p < 0.05$). Before treatment, there was no statistically significant difference between the endometrial thickness in the two groups ($p > 0.05$). After treatment, the endometrial thickness in the two groups was increased ($p < 0.05$), and the thickness in the observation group was raised compared with that in control group ($p < 0.05$), as seen in Table 3.

Table 3 Comparison of ovulation in the two groups before and after treatment.

Groups	Cases	Ovulation rate [cases (%)]	Endometrial thickness (mean ± standard deviation, mm)	
			Before treatment	After treatment
Observation group	40	29 (72.50)	6.08 ± 1.54	9.45 ± 1.87 *
Control group	40	17 (42.50)	6.04 ± 1.66	7.06 ± 1.26 *
x^2/t		7.336	0.112	6.704
p		0.007	0.911	<0.001

Note: Comparison with before treatment: * $p < 0.05$.

3.4 Comparison of serum sex hormones between the two groups

Before treatment, the difference between the LH, T, E_2 and FSH levels in the two groups was of no statistical significance ($p > 0.05$). After treatment, LH and T levels were reduced, but levels of E_2 and FSH were elevated in both groups, where the change of these indicators in observation group was greater than that in control group ($p < 0.05$), as exhibited in Table 4.

3.5 Comparison of adverse reactions between the two groups

There was no significant difference in the occurrence of adverse reactions such as nausea, vomiting, and breast tenderness between the two groups ($p > 0.05$), as described in Table 5.

3.6 Comparison of pregnancy rate between the two groups

The pregnancy rate was higher in the observation group than that in the control group ($p < 0.05$), as displayed in Table 6.

Table 4 Comparison of serum sex hormones in the two groups before and after treatment (mean ± standard deviation).

Groups	Cases	LH (mIU/mL)		T (pmol/L)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	40	17.45 ± 1.87	10.03 ± 1.21 *	2.95 ± 0.76	1.35 ± 0.57 *
Control group	40	17.55 ± 1.91	12.42 ± 1.37 *	2.99 ± 0.84	1.72 ± 0.46 *
t		0.237	8.270	0.223	3.195
p		0.814	<0.001	0.824	0.002
Groups	**Cases**	**E_2 (pg/mL)**		**FSH (min/mL)**	
		Before treatment	**After treatment**	**Before treatment**	**After treatment**
Observation group	40	140.56 ± 9.31	190.33 ± 11.36 *	5.83 ± 0.67	9.64 ± 1.11 *
Control group	40	141.67 ± 9.05	174.62 ± 10.52 *	5.92 ± 0.74	8.89 ± 1.07 *
t		0.541	6.417	0.570	3.077
p		0.590	<0.001	0.570	0.003

Table 5 Comparison of adverse reactions between the two groups [cases (%)].

Groups	Cases	Nausea and vomiting	Breast tenderness	Dizziness	Total
Observation group	40	1 (2.50)	1 (2.50)	0 (0.00)	2 (5.00)
Control group	40	2 (5.00)	0 (0.00)	1 (2.50)	3 (7.50)
χ^2		0.346	1.013	1.013	0.213
p		0.556	0.314	0.314	0.644

Table 6 Comparison of pregnancy rate between the two groups [cases (%)].

Groups	Cases	Pregnancy rate
Observation group	40	19 (47.50)
Control group	40	8 (20.00)
χ^2		8.205
p		0.004

4 Discussion

To improve the clinical efficacy of PCOS, this study discussed the application results of Bushen Zhuyun Decoction combined with clomiphene citrate capsule in PCOS patients. Our findings uncovered that Bushen Zhuyun Decoction combined with clomiphene citrate capsule may have a better efficacy for PCOS patients.

PCOS patients often have impaired luteal function, which can lead to ovulation disorders and infertility [16]. This study highlighted that compared to the treatment with clomiphene citrate capsules alone, Bushen Zhuyun Decoction combined with clomiphene citrate capsule showed a better clinical efficacy for PCOS patients, with more noticeable effects of improving ovulation. With regard to the possible reason, clomiphene citrate capsule, a commonly used drug to promote ovulation, can exert an anti-estrogen effect by binding to the hypothalamic estrogen receptors, thereby stimulating follicle development and maturation, improving ovulation, increasing the number of dominant follicles, raising the success rate of fertilization, and helping patients to successfully conceive [17,18]. The formulas used in Bushen Zhuyun Decoction have the effects of tonifying the kidneys, benefiting the liver as well as regulating qi and blood, which can improve the patients' reproductive endocrine environment as a whole, promote the recovery of ovarian function, and increase the rate of ovulation [19]. Combined treatment of Bushen Zhuyun Decoction and clomiphene citrate capsule can not only promote the recovery of ovarian function and enhance ovulation induction, but also regulate the tolerance of the uterus, boost endometrial growth, and increase the success rate of fertilization, which is conducive to conception [19,20]. Hence, Bushen Zhuyun Decoction combined with clomiphene citrate capsule may have a better efficacy for PCOS patients, which can promote ovulation.

The abnormal secretion of sex hormones in PCOS patients, such as increased levels of LH and T in the follicles as well as decreased synthesis of FSH and E_2, indicates a worsening condition, which is accompanied by the inhibited development of the endometrium and follicles, and an increase of androgen levels [21,22]. This study demonstrated that serum sex hormone levels were more significantly regulated in patients treated with Bushen Zhuyun Decoction combined with clomiphene citrate capsule when compared with that in patients treated with clomiphene citrate capsule alone. The reason may be that clomiphene citrate capsule can induce the secretion of gonadotropins from the anterior pituitary gland, stimulate the secretion of follicle-producing hormones, and elevate the levels of sex hormones [17]. Liver and kidney Yin deficiency syndrome, blood stasis syndrome, kidney Yang deficiency, phlegm-dampness were the pathogenesis of PCOS [23]. In the formula of Bushen Zhuyun Decoction, *fluoritum*, *Cuscuta chinensis*, and *Lycii Fructus* have the efficacy of tonifying the liver and benefiting the kidneys. *Cuscuta chinensis* had estrogen-like effect and had the efficacy of tonifying the kidney and regulating menstruation [24]. *Angelica sinensis* and *Cyathula officinalis Kuan* can activate blood circulation, remove blood stasis, and regulate qi and blood circulation. *Cyperus rotundus L* and *Amomum villosum Lour* have the efficacy of calming

the mind, regulating qi, dredging the liver, and warming up the spleen. Previous study also showed that PCOS has a long course of disease, and most patients have varying degrees of emotional disorders. Therefore, *Cyperus rotundus L* is added throughout the menstrual cycle to ease liver depression and regulate menstrual flow [25]. *Epimedium brevicornu Maxim* could reduce luteinizing hormone/follicle-stimulating hormone levels and testosterone levels [26]. Further, the joint action of these herbs can regulate the function of hypothalamus-pituitary-gonadal axis, increase the levels of E_2 and FSH, and modulate the micro-environment of the ovary site in multi-targets and multi-systems to improve the levels of sex hormones [19]. Combination of Bushen Zhuyun Decoction and clomiphene citrate capsule can enhance the secretion of sex hormones and reduce the inhibitory effect of clomiphene citrate capsule on follicular development. Therefore, Bushen Zhuyun Decoction combined with clomiphene citrate capsule may help to improve the secretion of sex hormones.

In addition, compared with clomiphene citrate capsule treatment alone, Bushen Zhuyun Decoction combined with clomiphene citrate capsule did not increase the risk of adverse reactions such as nausea, vomiting, and breast tenderness. The pregnancy rate was higher after 1 year, hinting that Bushen Zhuyun Decoction combined with clomiphene citrate capsule had a better safety and improved the long-term efficacy. However, due to the limited number of samples in this study, the results are not representative of all patients, so we need to include more samples for future studies.

5 Conclusion

In summary, Bushen Zhuyun Decoction combined with clomiphene citrate capsule may have a better efficacy for PCOS patients, which can improve ovulation and sex hormone secretion, with high safety and better 1-year efficacy.

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Not applicable.

Conflict of Interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization, X.H.; Data curation, Y.L.; Formal analysis, X.H.; Methodology, Y.L.; Writing-Original draft, X.H.; Writing-review and editing, Y.L.; All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee, and the patients were informed and consented.

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Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Supplementary Material

Not applicable.

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