

## Dose-effect analysis of treatment by modified Zhibaidihuang decoction on polycystic ovary syndrome hyperandrogenism

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### Abstract

**OBJECTIVE:** To observe the efficacy and safety of different dosages of modified Zhibaidihuang decoction (MZBDD) on polycystic ovary syndrome (PCOS) hyperandrogenism (HA) patients.

**METHODS:** Ninety PCOS HA patients and 30 infertile patients due to tubal factor were selected. Ninety PCOS HA patients were randomly divided into three groups: low dosage group (LDG), medium dosage group (MDG) and high dosage group (HDG) and infertile patients were selected as normal control group (NCG). PCOS HA patients were treated with different dosage of MZBDD for 4 weeks. For HA patients, serum total testosterone

(T), estradiol ( $E_2$ ), follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), alanine aminotransferase (AST), aspartate amino transferase (AST) were determined before and after treatment, while acne scores (Rosenfield) were signed. Basal body temperatures (BBT) were asked to be measured every day. And for the else, T,  $E_2$ , FSH, LH, PRL, AST, and AST were determined before treatment.

**RESULTS:** Totally 111 patients completed the clinical research. There were no differences among the four groups on serum T before treatment ( $P = 0.221$ ). Serum T concentration of both MDG and HDG after treatment significantly were lower than that of before treatment ( $P = 0.039$ ,  $P = 0.000$ ), while there was no obvious difference in LDG ( $P = 0.829$ ). Serum T concentration of both MDG and HDG were significantly lower than that of LDG after treatment ( $P = 0.048$ ,  $P = 0.006$ ). To compared with before treatment, there were no differences in Serum FSH, LH,  $E_2$ , P and PRL among the three groups (LDG, MDG, HDG) (as for FSH,  $P = 0.136$ ,  $P = 0.503$ ,  $P = 0.062$ ; as for LH,  $P = 0.473$ ,  $P = 0.513$ ,  $P = 0.096$ ; as for  $E_2$ ,  $P = 0.206$ ,  $P = 0.927$ ,  $P = 0.076$ ; as for PRL,  $P = 0.120$ ,  $P = 0.903$ ,  $P = 0.407$ , as for P,  $P = 0.308$ ,  $P = 0.866$ ,  $P = 0.480$ ). Acne scores of all the three groups were obviously lower than that of before treatment ( $P = 0.031$ ;  $P = 0.033$ ;  $P = 0.002$ ). 39.5% of the patients had biphasic BBT, but there were no differences among the three groups ( $P = 0.510$ ). There were no differences with ALT and AST between after and before treatment among the three groups (LDG, MDG, HDG) (as for ALT,  $P = 0.742$ ,  $P = 0.383$ ,  $P = 0.053$ ; as for AST,  $P = 0.732$ ,  $P = 0.519$ ,  $P = 0.120$ ).

**CONCLUSION:** Different dosage of MZBDD has

dose-effect relationship in treating PCOS HA.

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**Keywords:** Zhibaidihuang decoction; Dose-response relationship, drug; Polycystic ovary syndrome; Hyperandrogenism

## INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in reproductive-age women with an estimated prevalence rate of 5%-10%,<sup>1,2</sup> and it is characterized by chronic oligo-anovulation, clinical and/ or biochemical hyperandrogenism and polycystic ovaries. Hyperandrogenism (HA) is found in 60%-80% of PCOS patients.<sup>3</sup> HA includes clinical and biochemical manifestations, and the main performance of the former is acne and hirsutism. PCOS women of our country are with more acne and less hirsutism.<sup>4</sup> Moreover, it will take a long period of time for hirsutism to be improved effectively.

Reducing androgen is the important component of the basic treatment of PCOS. Currently, the treatment methods of Traditional Chinese Medicine (TCM) in reducing androgen include smoothing liver and purging fire,<sup>5,6</sup> regulating kidney and clearing lung<sup>7</sup> and reinforcing kidney and dissolve phlegm,<sup>8</sup> etc., which all have varying extent of efficacy. Our previous clinical observation found that PCOS HA had relationship with kidney-*Yin* deficiency and hyperactivity of fire,<sup>9</sup> and modified Zhibaidihuang decoction (MZBDD) had efficacy on treatment of PCOS HA by reducing serum testosterone (T) and acne score. Of which, the dose of the main herbs Huangbai (*Cortex Phellodendri Amurensis*), Zhimu (*Rhizoma Anemarrhenae*) and Dihuang (*Radix Rehmanniae*) were all 30 g.<sup>10</sup> The dosage of herbs directly effects on the efficacy of TCM.<sup>11</sup> Is 30 g the optimum dose in reducing PCOS HA? Does lower dose have the ideal treatment outcome? The objective of this paper is to observe the therapeutic effect of different dosages of MZBDD on PCOS HA patients in order to provide the basis for its clinical application.

## MATERIALS AND METHODS

### Diagnostic criteria

PCOS was diagnosed according to the Rotterdam criteria provided by the American Society for Reproductive Medicine and the European Society for Human Reproduction and Embryology.<sup>12</sup> A diagnosis of PCOS was made if at least two of the following criteria were met: (a) oligo/anovulation, (b) signs of hyperandrogenism (i.e., hirsutism and acne) and/or biochemical measurements, (c) enhanced ovaries (at least 12 discrete folli-

cles of 2-9 mm in diameter in one ovary or the ovarian volume > 10 cm<sup>3</sup> observed by transvaginal ultrasonography). Women with other androgen-excess disorders or specific etiologies including congenital adrenal hyperplasia, Cushing's syndrome, thyroid hormone abnormalities, hyperprolactinemia, or ovarian/adrenal tumors were excluded.

### Inclusion criteria

Corresponding to the diagnosis criteria of PCOS; the level of serum T was higher than the criterions (> 0.569 ng/mL); within the age range of 18-35 years old; voluntarily joined the clinical observation and signed informed consent.

### Exclusion criteria

Complicated with endocrine diseases such as thyroid or adrenal disorders, diabetes; complicated with severe cardiac, pulmonary, hepatic, renal or neurological disease or mental illness; complicated with thrombotic diseases; Use of hormonal drugs (except for progesterone) or any other drugs which can affect reproductive endocrine in the past 12 weeks; body mass index (BMI) ≥ 24.

### Case sources

Ninty PCOS women, who asked for treatment at the department of gynecology of Guang'an men Hospital, China Academy of Chinese Medical Sciences from June 2014 to May 2015 and corresponding to inclusion criteria and exclusion criteria, were divided into high dosage group (HDG), medium dosage group (MDG) and low dosage group (LDG) by random number with 30 women in each group according to the random number table. And 30 infertile patients due to tubal factor were selected.

### Treatment method

The PCOS HA patients all used Zhibaidihuang decoction [Huangbai (*Cortex Phellodendri Amurensis*), Zhimu (*Rhizoma Anemarrhenae*), Dihuang (*Radix Rehmanniae*)] which were decocted by Guang'anmen Hospital as a basic treatment. The recipe in LDG consisted of Zhimu (*Rhizoma Anemarrhenae*) 10 g, Huangbai (*Cortex Phellodendri Amurensis*) 10 g, Dihuang (*Radix Rehmanniae*) 10 g. The recipe in MDG consisted of Zhimu (*Rhizoma Anemarrhenae*) 20 g, Huangbai (*Cortex Phellodendri Amurensis*) 20 g, Dihuang (*Radix Rehmanniae*) 20 g. The recipe in HDG consisted of Zhimu (*Rhizoma Anemarrhenae*) 30 g, Huangbai (*Cortex Phellodendri Amurensis*) 30 g, Dihuang (*Radix Rehmanniae*) 30 g. Yinyanghuo (*Herba Epimedii Brevicornus*) and Tusizi (*Semen Cuscutae*) were added for deficiency of kidney-*Yang*. Stir-frying Baizhu (*Rhizoma Atractylodis Macrocephalae*) was added for deficiency of spleen-*Qi*. Baishao (*Radix Paeoniae Alba*) and Muli (*Concha Ostreae*) were added for hyperactivity of liver-*Yang*. Stir-frying Suanzaoren (*Se-*

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