Efficacy of Chinese patent medicine Tian Gui Capsule in patients with polycystic ovary syndrome: a randomized controlled trial

Susana Kuek, Wen-jun Wang, Sui-qi Gui
Department of Integrated Traditional Chinese and Western Medicine, Obstetrics and Gynecology Hospital, Fudan University, Shanghai 200011, China

Background: Polycystic ovary syndrome (PCOS) is a complex hormonal disorder and one of the most common reproductive endocrinology abnormalities in women. Recently, many studies have been conducted assessing Chinese herbal medicine as an alternative treatment for women with PCOS, it is, therefore, worthwhile to analyze and observe the curative effects of traditional Chinese medicine treatment in PCOS.

Objective: To evaluate the efficacy of the Chinese patent medicine Tian Gui Capsule, in women with PCOS and compare its effects with metformin and ethinyl estradiol plus cyproterone acetate (Diane-35).

Design, setting, participants and intervention: A total of 47 PCOS outpatients from the Obstetrics and Gynecology Hospital of Fudan University were randomly divided into 3 groups. Patients in group A (n = 19) were given Tian Gui Capsule, patients in group B (n = 17) were given metformin, and patients in group C (n = 11) were given Diane-35. The 3 groups of patients were treated for 3 months.

Main outcome measures: Serum testosterone (T), sex hormone binding globulin (SHBG) and dehydroepiandrosterone sulfate (DHEA-S) levels, free androgen index (FAI), fasting blood glucose (FPG), fasting insulin (FINS), homeostasis model assessment of insulin resistance (HOMA-IR), insulin sensitive index (ISI) and left and right ovary volumes of the 3 groups were evaluated before and after treatment.

Results: After 3 months of treatment, when compared with before treatment data, group A patients showed decreased serum T and SHBG levels, FAI, FINS, and left and right ovary volumes (P<0.05), and increased serum DHEA-S (P<0.05), while the FPG level showed no significant change. Although the level of serum T and FINS among the 3 groups after the treatment were similar, group A demonstrated better results than group B in reducing the FAI and increasing the serum SHBG, but less significant results than group C besides, group B was the only group showed improved insulin sensitivity. Although the level of FPG of the 3 groups after treatment
were similar, group C had the most increased FPG.

**Conclusion:** The effects of Tian Gui Capsule on hyperandrogenism are not as significant as Diane-35, but more effective than metformin. The effects of Tian Gui Capsule on hyperinsulinemia are not as significant as metformin but better than Diane-35. Tian Gui Capsule treats PCOS by regulating ovarian functions and reducing blood insulin level without inhibiting the function of the hypothalamic-pituitary-ovarian axis. Further studies with larger sample size are needed to confirm the above results.

**Keywords:** polycystic ovary syndrome; Chinese patent drugs; Tian Gui Capsule metformin; ethinyloestradiol and cyproterone acetate tablet; hyperandrogenism; insulin resistance; randomized controlled trials

Polycystic ovary syndrome (PCOS) is an extremely complex syndrome and one of the most common hormonal disorders, affecting 5% to 10% of women of reproductive age[11]. PCOS is characterized by chronic anovulation (ongoing failure or absence of ovulation), hyperandrogenism (excessive production of androgen in women) and dyslipidaemia (lipid metabolism disorder), and is associated with insulin resistance[11] (a reduced glucose response to a given amount of insulin) leading to hyperinsulinemia (compensatory serum insulin increase). Women with PCOS may present with an irregular menstrual cycle, infertility (failure to conceive), hirsutism (excessive hair growth), acne and obesity. The cause of PCOS remains unclear. It is proposed that a high level of androgen in serum is the primary cause. However, insulin resistance and obesity may also trigger the development of this hormonal defect. Insulin resistance causes PCOS by raising insulin level in the blood serum. An unhealthy lifestyle and genetic conditions can lead to over production of insulin by the pancreas. This excess insulin stimulates the ovaries to produce large amounts of the male hormone, testosterone (T), which may prevent ovulation each month, thus causing infertility. High level of insulin may also impact the conversion of androgens (male hormones) to estrogens (female hormones), thus upsetting a delicate balance between the two and having a direct effect on weight gain and the formation of cystic follicles or ovarian cysts[11].

Traditional Chinese medicine (TCM) pursues an independent theoretical and methodological pathway to review the cause of PCOS. Although there is no classification for PCOS in TCM, the symptoms and signs that women with PCOS present (Rotterdam 2003 criteria)[11] can be grouped into two disease categories in TCM, namely, amenorrhea (failure to menstruate) and infertility. Systematic research on PCOS in TCM has been carried out since 1980s.

The aetiology and clinical characteristics of PCOS remain controversial but are considered to be related to disorders of the kidneys, liver and spleen. From the perspective of TCM, reproductive function is governed by the kidneys, as well as the brain and emotions. It is believed that kidney deficiency may be the main causative factor in PCOS. TCM is used in treating PCOS by tonifying the kidneys to induce ovulation.

Treatment for PCOS is particularly complex. The Obstetrics and Gynecology Hospital of Fudan University has conducted a series of clinical and experimental studies of PCOS over the past 30 years. PCOS is a condition occurring due to hormonal imbalances in the body of a woman; the Chinese patent medicine Tian Gui Capsule, is developed to treat the condition by correcting these hormonal imbalances. By improving the action of hypothalamic-pituitary-ovarian (H-P-O) axis, Tian Gui Capsule effectively corrects the irregularities of menstrual cycle in women with PCOS[11].

This study collected 47 cases of PCOS outpatients from the Obstetrics and Gynecology Hospital of Fudan University from November 2008 to December 2009. The purpose of this study was to observe
the efficacy of Tian Gui Capsule versus metformin and ethinylestradiol and cyproterone acetate (CPA) tablet (Diane-35) and to explore whether Tian Gui Capsule can serve as one of the main medications for treating PCOS.

1 Materials and methods

1.1 Clinical data A total of 47 PCOS outpatients from the Department of Integrated Traditional Chinese and Western Medicine, Obstetrics and Gynecology Hospital of Fudan University were collected from November 2008 to December 2009.

1.2 Research methods

1.2.1 Diagnostic and inclusion criteria Based on the diagnostic criteria from the 2003 European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) conference in Rotterdam (2003 Rotterdam diagnosis standard of PCOS) \cite{1}, the diagnostic and inclusion criteria are as follows: (1) Irregular ovulation: oligomenorrhea, amenorrhea, or irregular menstrual cycle. (2) Obvious signs of hyperandrogen or increased androgen level or anomalies of circulation androgens. (3) Polycystic ovary: ultrasound showed more than 12 follicles of 2 to 9 mm in diameter per side or 10 cm² of ovarian volume in 3 to 5 d of menstruation. Patient with any 2 of the above mentioned signs or symptoms are then diagnosed with PCOS.

1.2.2 Exclusion criteria (1) Not meeting the above diagnostic criteria for PCOS. (2) Other reasons causing hyperandrogenism: late-onset congenital adrenal hyperplasia, Cushing's syndrome, androgen secretion of ovarian or adrenal tumors. (3) Hyperprolactinemia or hypothalamic amenorrhea. (4) Thyroid dysfunction.

1.2.3 Medication Tian Gui Capsule is composed of Shudihuang (Radix Rehmanniae), Zhiimu (Rhizoma Anemarrhenae), Yinyanghuo (Herba Epimedii Breviscorus), Huangjing (Rhizoma Polygonati Sibirici), Danggui (Radix Angelicae Sinensis), Taoren (Semen Persicae), Shichangpu (Rhizoma Acori Tatarinovii), Guijia (Carapax et Plastrum Testudinis), Buguzhi (Fructus Psoraleae), Huzhanggeng (Radix Polygoni Cuspidati) and Mabiancao (Herba Verbenae Officinalis). It is a hospital prescription which was approved by the Shanghai Food and Drug Administration and produced by Cai Tong De Shanghai Pharmaceutical Co., Ltd. The drug approval number of Tian Gui Capsule is YZ090087. Metformin hydrochloride enteric-coated tablets were produced by Bristol-Myers Squibb. The drug approval number is BX20000396. Ethinylestradiol and CPA tablets (trade name Diane-35) were produced by Bayer (China) Limited. The drug approval number is J20040104(2001)-70.

1.2.4 Grouping and treatment The 47 patients were randomly assigned to Group A (Tian Gui Capsule group), Group B (metformin group) and Group C (Diane-35 group) after they signed the informed consent. Group A (19 cases): 6 Tian Gui capsules 3 times daily for 3 months; group B (17 cases): one piece of 500 mg metformin tablet, 2 times daily for 3 months; group C (11 cases): 1 tablet of Diane-35 (containing 2 mg cyproterone acetate and 35 μg ethinylestradiol) per day on the 5th day of menstruation or withdrawal bleeding for a period of 21 d and 3 cycles of menstruation. Patients in group A and group B who faced amenorrhea within 60 d during treatment were given 10 mg daily of medroxyprogesterone acetate for a total of 5 d to induce menstruation.

1.2.5 Methods and efficacy evaluation index

1.2.5.1 Anthropometry Waist circumference, body weight and waist-hip ratio (WHR) were measured and body mass index (BMI) was calculated according to the World Health Organization measurement standard.

1.2.5.2 Hormone determination Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), T and dehydroepiandrosterone sulfate (DHEA-S) were determined by chemiluminescence immunoassay (CLIA) and the level of serum sex hormone binding globulin (SHBG) was determined by enzyme-linked immunosorbent assay (ELISA) on the progesterone withdrawal bleeding or 3 to 5 d of menstruation before treatment. The main efficacy evaluation indexes for the treatment were serum T and serum SHBG, and decrease of these two indexes can be considered as that hyperandrogen has been improved.

1.2.5.3 Blood biochemistry measurement Fasting plasma glucose (FPG) was tested by glucose oxidase method, fasting insulin (FINS) by CLIA, and the free androgen index (FAI, T (mmol/L)/SHBG (mmol/L)×100%) was calculated to assess the level of biological activity of androgens. The homeostasis model assessment of insulin resistance (HOMAIR, FINS (mIU/L)/XFPG (mmol/L)/22.5, value $\geq 1.66$ means insulin resistance) and insulin sensitivity index (ISI, $1/(FINS\times\text{FPG})$, value $< 0.021$ means reduced susceptibility) were calculated, as the assessment of hyperinsulinemia, insulin resistance and abnormal glucose metabolism status.

1.2.5.4 Ultrasound monitoring The number of follicles of each ovary were calculated and the follicle size and volume of each ovary were measured through the vaginal or rectum with the three-dimensional Doppler. A decrease in the ovary volume confirms the fact that the function and morphosis of the ovaries have been improved.

After 3 months of treatment, the aforementioned data were measured and retested (Figure 1).

1.3 Statistical analysis Data were analyzed with SPSS 11.5 software, and presented as mean ± standard deviation (SD). Before and after treatment comparison within each group were analyzed by paired t tests. Comparisons among the 3 groups were analyzed by analysis of variance.
2 Results

2.1 Baseline data A total of 47 outpatients aged from 15 to 40 years were included in this study: 4 cases unmarried; 43 cases married; 2 cases fertilized; 41 cases of infertility, accounting for 95.35% (41/43). The differences of body weight and WHR among the 3 groups before treatment were not significant and were comparable. Body weight, BMI and WHR of groups A and B were declined after treatment. Group C was the only group in which the body weight and BMI had an increase tendency after treatment (Table 1).

2.2 Efficacy evaluation index

2.2.1 Hormone level Comparison of before and after treatment within each group showed that serum T and SHBG levels of group A reduced ($P<0.05$); serum LH, T and SHBG levels of group B reduced ($P<0.05$); serum LH, T and DHEA-S levels of group C reduced ($P<0.05$) and serum SHBG and $E_2$ levels increased ($P<0.01, P<0.05$).

Before treatment, the levels of serum T, DHEA-S and SHBG did not show significant differences among the 3 groups and were comparable. After treatment, comparison on the reduction of the serum T level among the 3 groups had no difference, yet comparison on the reduction of the serum DHEA-S and the increment of serum SHBG showed differences (Table 2).

2.2.2 Glucose metabolism Comparison of before and after treatment within each group showed that FINS level of group A reduced ($P<0.05$); FINS and HOMA-IR levels of group B reduced ($P<0.01$) and FAI and ISI of group B increased ($P<0.01, P<0.05$); FINS level of group C reduced ($P<0.05$).

Before treatment, differences of FPG and ISI had no significance among the 3 groups and were comparable. After treatment, comparison of FPG level among the 3 groups showed no difference, yet each group demonstrated an increased tendency, while group C increased the most. Comparison of ISI among the 3 groups showed no difference (Table 3).

![Flow diagram of this clinical trial](image)

Table 1 Baseline data of each group (mean±SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
<th>BMI (kg/m²)</th>
<th>WHR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>A</td>
<td>19</td>
<td>1.59±0.03</td>
<td>59.47±8.76</td>
<td>58.57±8.37*</td>
<td>23.26±3.34</td>
</tr>
<tr>
<td>B</td>
<td>17</td>
<td>1.58±0.05</td>
<td>61.55±7.77</td>
<td>61.46±6.90*</td>
<td>25.70±2.96</td>
</tr>
<tr>
<td>C</td>
<td>11</td>
<td>1.58±0.02</td>
<td>58.86±10.66</td>
<td>59.04±10.18</td>
<td>19.27±10.46</td>
</tr>
</tbody>
</table>

* $P<0.05$, vs group A before treatment; △ $P<0.05$, vs group B before treatment; ▲ $P<0.05$, vs group C before treatment. A: Tian Gui Capsule group; B: Metformin group; C: Diane-35 group; SD: standard deviation; BMI: body mass index; WHR: waist:hip ratio.

Table 2 Serum hormone level of each group (mean±SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>FSH (IU/L)</th>
<th>LH (IU/L)</th>
<th>E₂ (pmol/L)</th>
<th>T (nmol/L)</th>
<th>DHEA-S (μmol/L)</th>
<th>SHBG (nmol/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>A</td>
<td>19</td>
<td>6.47±1.33</td>
<td>6.53±1.36</td>
<td>9.03±5.05</td>
<td>9.49±7.19</td>
<td>138.88±76.71</td>
<td>146.22±80.02*</td>
</tr>
<tr>
<td>B</td>
<td>17</td>
<td>7.54±1.98</td>
<td>7.14±1.59</td>
<td>9.79±4.88</td>
<td>8.48±5.22</td>
<td>157.16±65.02</td>
<td>172.26±130.10△</td>
</tr>
<tr>
<td>C</td>
<td>11</td>
<td>8.27±2.64</td>
<td>7.08±3.39</td>
<td>11.40±4.00</td>
<td>5.45±2.74*</td>
<td>164.48±52.77</td>
<td>175.62±69.09*</td>
</tr>
</tbody>
</table>

* $P<0.05$, vs group A before treatment; △ $P<0.05$, vs group B before treatment; ▲ $P<0.05$, ▲ $P<0.01$, vs group C before treatment; ▼ $P<0.05$, ▼ $P<0.01$, vs group C after treatment. A: Tian Gui Capsule group; B: Metformin group; C: Diane-35 group; SD: standard deviation; FSH: follicle-stimulating hormone; LH: luteinizing hormone; $E_2$: estradiol; T: testosterone; DHEA-S: dehydroepiandrosterone sulfate; SHBG: sex hormone binding globulin.
Before treatment, differences of FINS and HOMA-IR among the 3 groups were statistically significant ($P<0.05$). Therefore, the D-values (difference value of before and after treatment) of FINS and HOMA-IR of each group were calculated and they had no significant difference and were comparable. Comparison of the D-values of FINS and HOMA-IR among the 3 groups showed no difference (Table 4).

### Table 3  Glucose metabolism indexes of each group

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>FPG (mmol/L)</th>
<th>FINS (IU/L)</th>
<th>HOMA-IR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>A</td>
<td>19</td>
<td>4.25±0.39</td>
<td>4.36±0.40</td>
<td>11.36±7.37</td>
</tr>
<tr>
<td>B</td>
<td>17</td>
<td>4.47±0.45</td>
<td>4.57±0.45</td>
<td>14.60±4.35</td>
</tr>
<tr>
<td>C</td>
<td>11</td>
<td>4.28±0.36</td>
<td>4.65±0.26</td>
<td>12.01±8.81</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>ISI</th>
<th>FAI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>A</td>
<td>19</td>
<td>0.05±0.10</td>
<td>0.05±0.10</td>
</tr>
<tr>
<td>B</td>
<td>17</td>
<td>0.01±0.05</td>
<td>0.02±0.01△△</td>
</tr>
<tr>
<td>C</td>
<td>11</td>
<td>0.02±0.01</td>
<td>0.02±0.01</td>
</tr>
</tbody>
</table>

* $P<0.05$, vs group A before treatment; △△ $P<0.01$, vs group B before treatment; △△△ $P<0.05$, △△△ $P<0.01$, vs group C before treatment.

A: Tian Gui Capsule group; B: Metformin group; C: Diane-35 group; SD: standard deviation; FPG: fasting plasma glucose; FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance; ISI: insulin sensitivity index; FAI: free androgen index.

### Table 4  D-values of FINS and HOMA-IR of each group

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>FINS (IU/L)</th>
<th>HOMA-IR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>A</td>
<td>19</td>
<td>−0.62±5.76</td>
<td>0.03±0.52</td>
</tr>
<tr>
<td>B</td>
<td>17</td>
<td>−2.19±7.87</td>
<td>−0.29±0.61</td>
</tr>
<tr>
<td>C</td>
<td>11</td>
<td>−3.01±6.92</td>
<td>−0.02±0.33</td>
</tr>
</tbody>
</table>

D-values: difference value of before and after treatment; A: Tian Gui Capsule group; B: Metformin group; C: Diane-35 group; SD: standard deviation; FINS: fasting insulin; HOMA-IR: homeostasis model assessment of insulin resistance.

2.2.3 Ovarian volume Comparison of before and after treatment within each group showed that both left and right ovary volumes of group A reduced ($P<0.05$); left ovary volume of group B reduced ($P<0.05$) while right ovary volume had an increased tendency; both left and right ovary volumes of group C reduced ($P<0.01$).

Before treatment, the ovary volumes among the 3 groups showed no significant difference and were comparable. After treatment, comparison between groups A and B and group C showed statistically significant difference ($P<0.05$) (Table 5).

### Table 5  Ovary volume of each group

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Left ovary volume</th>
<th>Right ovary volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>A</td>
<td>19</td>
<td>11.42±4.24</td>
<td>9.02±4.00*</td>
</tr>
<tr>
<td>C</td>
<td>11</td>
<td>11.18±3.31</td>
<td>8.90±3.59△△△△</td>
</tr>
</tbody>
</table>

* $P<0.05$, vs group A before treatment; □ $P<0.05$, vs group B before treatment; △△△ $P<0.01$, vs group C before treatment; △△△△ $P<0.05$, vs group C after treatment. A: Tian Gui Capsule group; B: Metformin group; C: Diane-35 group; SD: standard deviation.

3 Discussion

The ancient TCM classic *Huangdi Neijing* stated that when a girl is 7 years old, the kidney qi becomes abundant, so her teeth begin to change and her hair grows longer; when she is 14 years old, the kidney essence which promotes the reproductive function is abundant and the thoroughfare vessel and the conception vessel begin to activate and become stronger, so she begins her menstruation and is able to conceive\[1\]. It indicates that once the physiological conditions are matured, a girl begins her menstruation which is generated and formatted under the balance of the kidney qi-kidney essence-thoroughfare vessel and conception vessel-uterus axis.

According to TCM theory, water of the human body is governed by kidney qi. Once kidney qi is insufficient, it may cause water retention which will transform into phlegm and result in metabolic disorders. Therefore, insufficiency of kidney qi can be considered as the main reason for phlegm formation. Besides, according to TCM theory, blood stagnation and phlegm will lead to disharmony of the thoroughfare vessel and the conception vessel and will transform into heat which may impair yin, if such conditions persist\[9\].

Based on the above theories, kidney qi and kidney yin deficiencies are directly related to PCOS. However, since the H-P-O axis in PCOS patients functions abnormally\[2, 3\] with metabolic disorders in which hyperandrogenism and insulin resistance
are manifested, the cause of hyperandrostenogenism and insulin resistance is possibly due to kidney deficiency.

It was reported that when rats with hyperandrostenogenism, hyperinsulinemia and anovulation were administered Tian Gui prescription, which is a prescription for tonifying kidney yin, conditions of hyperinsulinemia and hyperandrostenogenism improved significantly\(^{16, 9, 10}\). According to those studies, prescription of Tian Gui has been produced as a patent medicine and widely used as PCOS medication.

Although the safety and the mechanism of Tian Gui Capsule in treating PCOS is still unclear, in this study, 19 PCOS patients in group A treated with Tian Gui Capsule for 3 months showed improved hyperandrostenogenism with a lowered T level \((P<0.05)\) and a lowered FINS level \((P<0.05)\) compared with before treatment. Even though the HOMA-IR and ISI of group A patients had no difference compared with before treatment, some patients with different degrees of skin pigmentation or acanthisis which were caused by hypersecretion of insulin and androgen were improved and the elasticity of their skin was enhanced after treatment. These results showed that Tian Gui Capsule could treat hyperinsulinemia and insulin resistance effectively.

Moreover, both the left and right ovary volumes of group A patients decreased \((P<0.05)\) while the level of serum LH and FSH were not inhibited, and the FAI of group A patients reduced after treatment. These results confirmed that Tian Gui Capsule not only has the effect of reducing androgen and insulin levels without inhibiting the function of the H-P-O axis, but also can be used to change ovary morphology by ameliorating the micro-environment of the ovaries, and its effects in reducing androgen levels is better than metformin. Besides, during the post-treatment follow-up, most patients did not complain about any gastrointestinal upset, and patients with complications of constipation felt better. This feedback confirmed that the ingredients of Tian Gui Capsule are suitable and applicable in treating the PCOS patients with yin deficiency and internal heat. Perhaps the effect will be more obvious if the treatment could be prolonged. Due to the short-term medication and potentially inadequate sample size, the effect of reducing serum LH and DHEA-S was not noticeable.

Metformin is a biguanide used as an insulin sensitizter by inhibiting intestinal absorption of glucose, promoting gluconeogenesis from glycogen and promoting anaerobic glycolysis of sugar to increase the extrinsic muscle tissue glucose uptake and utilization. Metformin could also increase tissue sensitivity to insulin, reduce insulin resistance which is caused by hyperinsulinemia and hyperandrostenogenism, correct disorder of lipid metabolism, improve menstrual disorders and stimulate spontaneous ovulation induction\(^{16-11}\). In this study, 17 PCOS patients of group B treated with metformin for 3 months showed that hyperinsulinemia and hyperandrostenogenism were alleviated with a lowered serum T level \((P<0.05)\), a lowered FINS level \((P<0.01)\), a lowered HOMA-IR \((P<0.01)\) and an increased ISI \((P<0.05)\) compared with before treatment. Signs of acne and hirsutism were also improved and the right ovary volume and FAI were increased. These results showed that metformin could reduce androgen level by adjusting insulin metabolism. However, during the post-treatment follow-up, most patients complained gastrointestinal upset, diarrhea, and other side effects. This feedback showed that metformin is an unsuitable treatment method as a long-term medication for PCOS.

Diane-35 is a short-term oral contraceptive drug. Each tablet contains 2 mg CPA and 35 μg ethinylestradiol\(^{12}\). CPA has a strong and effective anti-androgen and progestin activity which can inhibit secretion of pituitary gonadotropin, especially the secretion of serum LH, T and dihydrotestosterone. It enables competitive inhibition of androgen receptors, thereby ovarian-source androgen secretion can be reduced\(^{13}\). CPA and ethinyl estradiol mixture can increase the serum SHBG synthesized in the liver, thus decreasing free T\(^{14}\) and improving hyperandrostenogenism signs such as acne and hirsutism. It can also regulate menstruation and inhibit endometriosis\(^{15, 16}\). In this study, 11 PCOS patients of group C treated with Diane-35 for 3 medical cycles showed improved signs of acne and hirsutism and other signs of hyperandrostenogen with lowered serum T and DHEA-S levels \((P<0.05)\), an increased serum SHBG level \((P<0.01)\), a lowered FINS level \((P<0.05)\), a reduced tendency of HOMA-IR and an increased tendency of ISI compared with before treatment. Besides, due to reduction of serum LH level and renal source androgens, both the left and right ovary volumes significantly reduced \((P<0.01)\). These results showed that the mechanism of Diane-35 in treating patients with PCOS is to restrain and inhibit the H-P-O axis function. However, during and after the course of treatment, patients’ body weight, BMI and FPG were increased and the increased rate of FPG was obvious. Moreover, during the post-treatment follow-up, most patients complained of breast pain, gastrointestinal upset, weight gain and other side effects. This indicated that Diane-35 is not effective in improving glucose metabolisms of PCOS. Whether long-term use of Diane-35 may lead to an increase of blood sugar level in patients with PCOS and cause other side effects still requires further investigation.

4 Conclusion

Therefore, with regard to PCOS treatment, the role of metformin focuses more in adjusting insulin metabolism, while Diane-35 in restraining the H-
P-O axis function. Tian Gui Capsule can improve the menstruation cycle, ovary function and metabolic abnormalities without inhibiting H-P-O axis. As the mechanism of this Chinese patent medicine is still unclear and incomplete, further studies are required to clarify the mechanism and to confirm whether other medications should be used together that may improve ovulation, lower down blood insulin level and increase serum SHBG level.

5 Competing interests

The authors declare that they have no competing interests.

REFERENCES


中药天癸胶囊治疗多囊卵巢综合征的随机对照疗效观察

郭素珊，王文君，周继琪
复旦大学妇产科医院中西医结合科，上海 200011

背景：多囊卵巢综合征（polycystic ovary syndrome，PCOS）是一组复杂的症候群。许多研究表明，中药药可作为治疗PCOS的替代疗法，故分析和观察中西传统医药对PCOS的疗效是必要和有价值的。

目的：观察中药天癸胶囊治疗PCOS的有效性，比较天癸胶囊与二甲双胍和达英-35治疗PCOS在调整卵巢功能、改善胰岛素抵抗和改变卵泡形态学等方面的效果。

设计、场所、对象和干预措施：收集复旦大学附属妇产科医院门诊符合PCOS诊断标准的PCOS患者共47例，随机分入A、B、C三个治疗组。A组（19例）给予天癸胶囊治疗，B组（17例）给予二甲双胍治疗，C组（11例）给予达英-35治疗，3组均治疗3个月。

主要结局指标：检测治疗前后雄激素（testosterone，T）、性激素结合球蛋白（sex hormone binding globulin，SHBG）、硫酸脱氢表雄酮（dehydroepiandrosterone sulfate，DHEA-S）水平以及游离雄激素指数（free androgen index，FAI）、空腹血糖（fasting blood glucose，FPG）、空腹胰岛素（fasting insulin，FINS）、胰岛素敏感指数（homeostasis model assessment-insulin resistance，HOMA-IR）、胰岛素敏感指数（insulin sensitive index，ISI）和双侧卵巢体积的变化。

结果：A组治疗后血清T 、SHBG水平及FAI、FINS下降（P<0.05），双侧卵巢缩小（P<0.05），血清DHEA-S水平增加（P<0.05），FPG有增加趋势但无统计学意义。治疗3个月后3组间血清T水平比较虽无差异，但在降低FAI及增加血SHBG作用方面A组比B组强，B组与C组无显著差异，B组治疗后胰岛素敏感性增加（P<0.05），但C组FPG水平增加幅度最大。

结论：中药天癸胶囊改善雄激素血症作用优于达英-35，优于二甲双胍，改善高胰岛素血症作用比二甲双胍弱，优于达英-35。天癸胶囊在不抑制下丘脑-垂体-卵巢轴功能的基础上，通过调整卵巢功能，改善胰岛素水平及改变卵泡形态等多方面治疗PCOS。以上结果值得进一步扩大样本量予以证实。

关键词：多囊卵巢综合征；中药药；天癸胶囊；二甲双胍；炔雌醇环丙孕酮片；高胰岛素血症；胰岛素抵抗；随机对照试验