

Clinical Efficacy and Adverse Reactions of Lianggu Decoction Combined with Clomiphene in the Treatment of Obese PCOS Patients with Infertility (Postprint)

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Abstract

Background: Polycystic ovary syndrome (PCOS) is an extremely prevalent endocrine disorder among women of reproductive age. Obese PCOS patients often present with insulin resistance, leading to disturbances in glucose and lipid metabolism, abnormal pancreatic islet function, which subsequently causes ovulation disorders and results in infertility. Clomiphene can improve ovulatory function in PCOS patients, but long-term administration is associated with numerous adverse reactions and the development of clomiphene resistance. Currently, the clinical efficacy and adverse reactions of Lianggu Decoction in the treatment of obese PCOS-related infertility remain unclear.

Objective: To investigate the effects of Lianggu Decoction combined with clomiphene on insulin resistance, ovarian hemodynamics, and pregnancy outcomes in obese PCOS patients with infertility.

Methods: A total of 127 obese PCOS infertility patients who presented to the Reproductive Medicine Department of Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine between February 2022 and December 2023 were enrolled as study subjects. Using a randomized grouping method, patients were allocated to an experimental group ($n=63$) and a control group ($n=64$). The control group received clomiphene treatment initiated on day 5 of menstruation at a dosage of 40 mg per dose, twice daily, for 5 consecutive days. The experimental group received Lianggu Decoction in addition to the control regimen. The herbal components of Lianggu Decoction were decocted to yield 150 mL of medicinal solution, administered twice daily, morning and evening, for 14 consecutive days. One month constituted one treatment cycle, and both groups received continuous treatment for 3 cycles. Inter-group differences were

compared for various laboratory parameters before and after treatment, including fasting insulin (FINS), homeostasis model assessment of insulin resistance (HOMA-IR), homeostasis model assessment of β -cell function (HOMA- β), fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), body mass index (BMI), ovarian peak systolic velocity (PVS), resistance index (RI), pulsatility index (PI), serum estrogen (E2), luteinizing hormone (LH), testosterone (T), and follicle-stimulating hormone (FSH). Outcome measures included ovulation rate, pregnancy rate, and miscarriage rate, with clinical efficacy and adverse reaction incidence recorded and compared between groups.

Results: Following 3 treatment cycles, the experimental group exhibited significantly lower levels of BMI, FPG, TG, TC, FINS, HOMA-IR, RI, serum E2, T, LH, and FSH, and significantly higher levels of HOMA- β , PVS, and PI compared with the control group ($P<0.05$). The ovulation rate and clinical pregnancy rate were significantly higher in the experimental group, while the miscarriage rate was significantly lower, compared with the control group ($P<0.05$). The total effective rate in the experimental group was significantly higher than that in the control group ($2=6.698$, $P<0.05$). No statistically significant difference was observed in the incidence of adverse reactions between the experimental and control groups ($2=0.192$, $P>0.05$).

Conclusion: Lianggu Decoction combined with clomiphene demonstrates favorable efficacy in treating obese PCOS-related infertility, effectively improving patients' insulin resistance, glucose and lipid metabolism, sex hormone levels, and ovarian hemodynamics, thereby increasing pregnancy rates.

Full Text

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Abstract

Background: Polycystic ovary syndrome (PCOS) is an extremely common endocrine disorder among women of reproductive age. Patients with obese PCOS often experience insulin resistance, leading to dysregulation of glucose

and lipid metabolism, abnormal pancreatic function, and subsequent ovulatory disorders that result in infertility. Clomiphene can improve ovulatory function in PCOS patients, but long-term use is associated with various adverse effects, and clomiphene resistance can easily develop. Currently, the clinical efficacy and adverse reactions of Lianggu Decoction in the treatment of obese PCOS-related infertility remain unclear.

Objective: To investigate the effects of Lianggu Decoction combined with clomiphene on insulin resistance, ovarian hemodynamics, and pregnancy outcomes in obese PCOS patients with infertility.

Methods: A total of 127 obese PCOS patients with infertility who presented to the Department of Reproductive Medicine at Cangzhou Integrated Traditional Chinese and Western Medicine Hospital between February 2022 and December 2023 were enrolled. According to random grouping principles, patients were divided into a trial group (n=63) and a control group (n=64). The control group received clomiphene starting on day 5 of menstruation (40 mg twice daily for 5 days). The trial group received Lianggu Decoction in addition to the clomiphene regimen. The decoction (150 mL, prepared from traditional Chinese medicinal herbs) was administered twice daily (morning and evening) for 14 consecutive days. One month constituted one treatment cycle, and both groups received continuous treatment for 3 cycles. Laboratory indicators including fasting insulin (FINS), homeostasis model assessment of insulin resistance (HOMA-IR), homeostasis model assessment of β -cell function (HOMA- β), fasting plasma glucose (FPG), triglycerides (TG), total cholesterol (TC), body mass index (BMI), peak systolic velocity (PVS), resistance index (RI), pulsatility index (PI), estrogen (E2), luteinizing hormone (LH), testosterone (T), and follicle-stimulating hormone (FSH) were compared between groups before and after treatment. Ovulation rate, pregnancy rate, and abortion rate were used as outcome measures, and clinical efficacy and adverse reaction rates were recorded and compared between groups.

Results: After 3 treatment cycles, the trial group showed significantly lower levels of BMI, FPG, TG, TC, FINS, HOMA-IR, RI, serum E2, T, LH, and FSH compared with the control group ($P<0.05$), while HOMA- β , PVS, and PI were significantly higher ($P<0.05$). The trial group also demonstrated higher ovulation and clinical pregnancy rates and a lower miscarriage rate than the control group, with all differences reaching statistical significance ($P<0.05$). The total effective rate in the trial group [92.1% (58/63)] was significantly higher than in the control group [75.0% (48/64)] ($\chi^2=6.698$, $P<0.05$). No significant difference in adverse reaction incidence was observed between the trial group [3.2% (2/63)] and control group [4.7% (3/64)] ($\chi^2=0.192$, $P>0.05$).

Conclusion: The combination of Lianggu Decoction and clomiphene is effective for treating obese PCOS-related infertility, improving insulin resistance, glucose and lipid metabolism, hormone levels, and ovarian hemodynamics while increasing pregnancy rates.

Keywords: Polycystic ovary syndrome; Lianggu Decoction; Clomiphene; Insulin resistance; Pregnancy

Introduction

Polycystic ovary syndrome (PCOS) is a highly prevalent endocrine disorder among women of reproductive age, characterized by complex pathogenesis and multiple influencing factors. Its clinical manifestations primarily include obesity, hirsutism, menstrual irregularities, and acne [1]. Research indicates that obesity increases the risk of insulin resistance, leading to excessive insulin secretion and abnormal lipid metabolism, which further exacerbates obesity [2]. Obese PCOS patients frequently present with insulin resistance, causing disorders of glucose and lipid metabolism and pancreatic dysfunction, ultimately resulting in ovulatory dysfunction and infertility [3]. Clomiphene, a commonly used ovulation-inducing agent, exerts potent anti-estrogenic effects and mild estrogenic activity that can improve ovulatory function in PCOS patients, but it cannot correct the endocrine disturbances associated with PCOS [4].

In traditional Chinese medicine, PCOS falls under the categories of “amenorrhea,” “infertility,” “masses,” and “metrorrhagia.” PCOS patients exhibit kidney yin deficiency with imbalance of yin and yang as the root cause, and phlegm-dampness, blood stasis, and qi stagnation as the branch manifestations, leading to ovulatory dysfunction [5]. Lianggu Decoction, composed of Rehmannia glutinosa, Cornus officinalis, Dioscorea opposita, Rubus chingii, Cuscuta chinensis, Lycium barbarum, Epimedium, and other ingredients, is clinically used to nourish yin and kidney, replenish blood and essence, eliminate dampness, and resolve stasis, thereby promoting blood circulation in the uterus and facilitating the transformation of yin and yang. This helps follicles mature and be discharged smoothly. However, the duration of treatment with Lianggu Decoction alone is relatively long, and its therapeutic effects may not be achieved quickly, limiting its application for women with urgent reproductive needs. This study employed a combination of Lianggu Decoction and clomiphene, comparing insulin resistance indices, blood glucose, blood lipids, ovarian hemodynamic parameters, serum sex hormones, ovulation rates, pregnancy outcomes, and adverse reactions between groups to provide a reference for treating obese PCOS-related infertility.

Methods

1.1 Study Participants A total of 127 obese PCOS patients with infertility who presented to the Department of Reproductive Medicine at Cangzhou Integrated Traditional Chinese and Western Medicine Hospital between February 2022 and December 2023 were enrolled. According to randomized controlled trial principles, participants were divided into a trial group (n=63) and a control group (n=64). This study was approved by the Medical Ethics Committee

of Cangzhou Integrated Traditional Chinese and Western Medicine Hospital (approval number: czzx-19052), and all patients and their families provided informed consent and voluntarily participated.

Inclusion criteria: (1) Met the diagnostic criteria for PCOS in the “Chinese Guidelines for Diagnosis and Treatment of Polycystic Ovary Syndrome” [1]: body mass index (BMI) $>28 \text{ kg/m}^2$; oligomenorrhea or irregular menstruation; hyperandrogenemia or clinical manifestations of hyperandrogenism; polycystic ovarian morphology. (2) Met the traditional Chinese medicine diagnostic criteria referencing the “Guiding Principles for Clinical Research of New Chinese Medicines” [6] and “Gynecology of Traditional Chinese Medicine” [7], with the syndrome type identified as kidney deficiency with phlegm-dampness and blood stasis. Main symptoms: soreness and weakness of the waist and knees, obesity, dark purple menstrual blood with clots, dark purple tongue with white greasy coating. Secondary symptoms: dull complexion, listlessness, increased nocturia. (3) Normal semen parameters in the male partner. (4) BMI $>28 \text{ kg/m}^2$; waist circumference $\geq 80 \text{ cm}$ or waist-to-hip ratio >0.8 .

Exclusion criteria: (1) Infertility due to other causes; (2) Comorbid endocrine disorders; (3) Severe cardiac, hepatic, or renal dysfunction; (4) Use of hormones, immunosuppressants, or drugs affecting glucose and lipid metabolism within one month; (5) Allergy to study medications; (6) Hematological disorders, immune system diseases, malignant tumors, or psychiatric disorders.

1.2 General Data Collection Patient age, height, weight, and disease duration were recorded. BMI was calculated using the formula: $\text{BMI} = \text{weight} (\text{kg}) / \text{height} (\text{m})^2$.

1.3 Treatment Methods The control group received clomiphene (Cyprus High-Tech Pharmaceutical Co., Ltd., approval number: H20140688, tablet formulation, batch numbers: K1215, M0706, Q1001). Patients with normal menstrual cycles started treatment on day 5 of menstruation (40 mg twice daily for 5 days). Patients with amenorrhea or irregular cycles started treatment on day 5 of withdrawal bleeding induced by progesterone (50 mg once daily for 5 days).

The trial group received Lianggu Decoction in addition to the clomiphene regimen. The decoction formula consisted of: Rehmannia glutinosa 15 g, Angelica sinensis 12 g, Cuscuta chinensis 15 g, Lycium barbarum 15 g, Dioscorea opposita 15 g, Rubus chingii 12 g, Epimedium 12 g, Cynomorium songaricum 12 g, Achyranthes bidentata 12 g, Dipsacus asper 15 g, Morinda officinalis 10 g, Poria cocos 15 g, Atractylodes macrocephala 10 g, and Atractylodes lancea 10 g. For severe liver stagnation, 10 g of Rosa chinensis and 15 g of Albizia julibrissin bark were added; for severe blood stasis, 15 g of soft-shelled turtle shell and 5 g of Eupolyphaga sinensis were added. Herbs were soaked for 30 minutes, boiled for 30 minutes over low heat after initial boiling, and decocted twice to obtain 150 mL of decoction, administered twice daily (morning and evening) for 14

consecutive days. One month constituted one treatment cycle, and both groups received continuous treatment for 3 cycles.

1.4 Outcome Measures

1.4.1 Blood Glucose and Lipid Detection On the day before treatment initiation and day 2 after treatment completion, 4 mL of fasting venous blood was collected and centrifuged at 2,000 r/min (r=10 cm) for 10 minutes. The supernatant was collected and stored at 4°C for testing. Fasting plasma glucose (FPG), triglycerides (TG), and total cholesterol (TC) were measured using a Roche C701 automatic biochemical analyzer and 配套 reagent kits (batch numbers: 22898731, 74703401, 2536293).

1.4.2 Insulin Resistance Indices Serum samples were collected as described in section 1.4.1. Fasting insulin (FINS) was measured using a Roche enzyme-linked immunosorbent assay kit (batch number: 37855919). HOMA-IR and HOMA- β were calculated using the following formulas:

$$\text{HOMA-IR} = [\text{FPG (mmol/L)} \times \text{FINS (mIU/L)}] / 22.5$$

$$\text{HOMA-}\beta = 20 \times [\text{FINS (mIU/L)} / (\text{FPG (mmol/L)} - 3.5)]$$

1.4.3 Ovarian Hemodynamic Parameters A GE Voluson 730 color Doppler ultrasound diagnostic instrument was used for transvaginal ultrasound examination to measure peak systolic velocity (PVS), resistance index (RI), and pulsatility index (PI) of ovarian blood flow.

1.4.4 Sex Hormone Levels Serum samples were collected as described in section 1.4.1. Estrogen (E2, batch number: 57633916), luteinizing hormone (LH, batch number: 58662149), testosterone (T, batch number: 64558756), and follicle-stimulating hormone (FSH, batch number: 67424391) were measured using a Roche Cobas 8000 e602 electrochemiluminescence immunoassay analyzer and 配套 reagent kits.

1.5 Follow-up and Outcome Indicators All patients were followed for 6 months. Ovulation, clinical pregnancy, and miscarriage were recorded, and ovulation rate, pregnancy rate, and miscarriage rate were calculated. A GE Voluson 730 color Doppler ultrasound diagnostic instrument was used to assess ovulation, clinical pregnancy, and miscarriage. Clinical pregnancy was defined as the presence of a gestational sac and primitive cardiac activity on ultrasound examination.

1.6 Clinical Efficacy According to the “Clinical Disease Diagnosis and Efficacy Criteria” [8], efficacy was classified as markedly effective, effective, or ineffective. Markedly effective: significant improvement in clinical symptoms

(menstrual abnormalities, hirsutism, acne), normalized menstrual cycles, normalized biochemical indicators (sex hormones, lipids, insulin), and normal ovulation or dominant follicles on ultrasound. Effective: improvement in clinical symptoms, basically normal menstrual cycles, improved biochemical indicators, and occasional ovulation on ultrasound. Ineffective: no change or worsening in clinical symptoms, laboratory indicators, or ultrasound findings. Clinical efficacy was recorded, and total effective rate was calculated as the sum of markedly effective and effective cases.

1.7 Adverse Reaction Rate Adverse reactions including abdominal pain, ovarian enlargement, and pelvic pain were observed, and the adverse reaction rate was calculated.

1.8 Statistical Analysis SPSS 26.0 statistical software was used for data analysis. Normally distributed continuous data were expressed as mean \pm standard deviation and compared between groups using t-tests. Categorical data were expressed as percentages and compared using χ^2 tests. $P < 0.05$ was considered statistically significant.

Results

2.1 Comparison of General Data Between Groups A total of 127 patients were enrolled, including 64 in the control group and 63 in the trial group. No statistically significant differences were observed between groups in age, disease duration, or BMI ($P > 0.05$).

2.2 Comparison of Clinical Indicators Before and After Treatment Before treatment, no statistically significant differences were observed between groups in BMI, FPG, TG, TC, insulin resistance indices, ovarian hemodynamic parameters, or serum sex hormone levels ($P > 0.05$). After treatment, the trial group showed significantly lower BMI, FPG, TG, TC, FINS, HOMA-IR, RI, serum E2, T, LH, and FSH levels compared with the control group, while HOMA- β , PVS, and PI were significantly higher ($P < 0.05$).

2.3 Comparison of Outcome Indicators Between Groups The trial group demonstrated significantly higher ovulation and clinical pregnancy rates and a significantly lower miscarriage rate compared with the control group ($P < 0.05$).

2.4 Comparison of Clinical Efficacy Between Groups In the control group, 12 cases (18.8%) were markedly effective, 36 cases (56.2%) were effective, and 16 cases (25.0%) were ineffective. In the trial group, 17 cases (27.0%) were markedly effective, 41 cases (65.1%) were effective, and 5 cases (7.9%) were ineffective. The total effective rate in the trial group [92.1% (58/63)]

was significantly higher than in the control group [75.0% (48/64)] ($\chi^2=6.698$, $P<0.05$).

2.5 Comparison of Adverse Reactions Between Groups In the control group, 1 case of abdominal pain, 1 case of ovarian enlargement, and 1 case of pelvic pain were observed. In the trial group, 1 case of abdominal pain and 1 case of pelvic pain were observed. No statistically significant difference in adverse reaction rate was found between the trial group [3.2% (2/63)] and control group [4.7% (3/64)] ($\chi^2=0.192$, $P>0.05$).

Discussion

The primary characteristics of PCOS include hyperandrogenism, chronic anovulation, and polycystic ovarian morphology, with approximately 40-60% of PCOS patients presenting with obesity. Obese PCOS is typically accompanied by insulin resistance, which stimulates excessive insulin secretion, leading to abnormal glucose and lipid metabolism. Obese PCOS patients undergoing assisted reproductive treatment have low pregnancy rates and high miscarriage rates. While Western medications offer short-term efficacy, they are associated with adverse reactions and cannot effectively improve insulin resistance and glucose metabolism abnormalities in obese PCOS patients, with high recurrence rates after discontinuation that reduce patient compliance [10-11]. Adjuvant treatment with traditional Chinese medicine can enhance clinical efficacy and reduce adverse reaction rates.

Obesity can induce insulin resistance and hyperinsulinemia, leading to abnormal glucose and lipid metabolism and elevated BMI. Research indicates that insulin resistance in PCOS is related to androgen levels, as insulin resistance can stimulate the ovaries to produce excessive androgens [12], and hyperandrogenism can cause follicular developmental disorders and ovulatory abnormalities while increasing the risk of ovarian hyperstimulation syndrome [13]. This study demonstrated that after treatment, the trial group had significantly lower FPG, TC, TG, BMI, FINS, and HOMA-IR, and significantly higher HOMA- β compared with the control group ($P<0.05$), suggesting that combination therapy can reduce androgen levels, effectively decrease insulin resistance, and improve pancreatic function. Crataegus pinnatifida in Lianggu Decoction contains triterpenoids and flavonoids that improve insulin resistance, promote insulin secretion, improve lipid metabolism in obese patients, inhibit hepatic TC synthesis, and promote hepatic TC uptake, thereby regulating lipid profiles. Liu et al. [14] reviewed that Crataegus pinnatifida can prevent metabolic syndrome through multiple pharmacological actions including lipid regulation, glucose reduction, insulin resistance improvement, anti-inflammatory, antioxidant, anti-coagulant, and anti-atherosclerotic effects, suggesting that Lianggu Decoction has favorable regulatory effects on insulin resistance and lipid profiles in obese PCOS.

This study found that after treatment, the trial group had significantly higher PVS and PI and significantly lower RI compared with the control group

($P<0.05$). Lianggu Decoction can tonify kidney qi, activate blood circulation, and resolve stasis, thereby improving ovarian hemodynamics, reducing ovarian volume, and increasing endometrial thickness. *Angelica sinensis* and *Achyranthes bidentata* in the formula nourish liver and kidney, replenish blood, and activate blood circulation. Combination therapy can reduce ovarian blood flow resistance and accelerate blood flow velocity in PCOS patients, restoring ovarian blood supply, improving endometrial receptivity and ovarian reserve function, and facilitating follicular development and pregnancy rates. Zhang et al. demonstrated [15] that clomiphene combined with *Cangfu Daotan* Decoction can better improve ovarian function and endometrial blood flow parameters, effectively increasing pregnancy rates. This study also found that clomiphene combined with Lianggu Decoction significantly improved ovarian hemodynamics, suggesting that Lianggu Decoction is effective for obese PCOS.

After treatment, the trial group showed significantly lower serum E2, T, LH, and FSH levels compared with the control group ($P<0.05$), along with higher ovulation and clinical pregnancy rates and lower miscarriage rates ($P<0.05$). These findings suggest that combination therapy promotes normalization of sex hormones, effectively improves endocrine disturbances, promotes development of female reproductive organs including the uterus and ovaries, and facilitates conception. Zhao et al. [16] reported that total flavonoids from *Cuscuta chinensis* can improve sex hormone levels, reduce insulin resistance, and promote ovulation in PCOS rats. The present results are consistent with these findings, as Lianggu Decoction contains *Cuscuta chinensis* and demonstrates favorable effects on sex hormone regulation and ovulation induction in obese PCOS patients. Pharmacological analysis reveals that *Cuscuta chinensis* can regulate the hypothalamic-pituitary-ovarian axis, enhance pituitary responsiveness to gonadotropin-releasing hormone, exert sex hormone-like effects, and improve reproductive endocrine function. Epimedium contains icariin and other components that can improve endocrine system function, exert hormone-like effects, regulate cellular metabolism, and enhance immune function.

The treatment of obese PCOS-related infertility should focus on strengthening the spleen, eliminating dampness, and tonifying kidney and activating blood [17]. Lianggu Decoction is a classical basic formula for treating infertility, derived from *Liuwei Dihuang Wan* and *Wuzi Yanzong Wan*. *Rehmannia glutinosa* tonifies kidney yin and nourishes essence; *Angelica sinensis* and other ingredients nourish liver and kidney, replenish blood, activate blood circulation, and regulate menstruation; *Cuscuta chinensis* and other ingredients tonify kidney yang and nourish essence and blood; *Crataegus pinnatifida* strengthens the spleen, eliminates food stagnation, and regulates blood lipids and pressure. The entire formula provides syndrome differentiation-based treatment with modifications according to specific symptoms, collectively achieving the effects of strengthening the spleen and resolving dampness, warming and tonifying kidney yang, and activating blood to resolve stasis. This study demonstrated that the trial group had a significantly higher total effective rate after treatment compared with the control group ($P<0.05$), indicating that Lianggu Decoction combined with

clomiphene has significant therapeutic effects on obese PCOS-related infertility.

Clomiphene, as a synthetic non-steroidal agent, has strong anti-estrogenic effects that can intervene in the hypothalamic-pituitary system. By competitively binding to estrogen receptors, it disrupts estrogen's negative feedback on the hypothalamus, stimulates pituitary gonadotropin secretion, and promotes follicular growth and development. However, long-term application is associated with numerous adverse reactions, and approximately 20% of patients develop clomiphene resistance [18]. Lianggu Decoction can effectively improve serum sex hormone levels and glucose-lipid metabolism, creating a positive synergistic effect with clomiphene by improving the endocrine environment while stimulating ovarian ovulation, effectively reducing BMI, improving abnormal glucose-lipid metabolism and insulin resistance, regulating reproductive endocrine disturbances, improving follicular quality, promoting ovulation, and increasing pregnancy rates. Chen et al. [19] demonstrated that Bushen Huoxue Decoction combined with clomiphene for obese PCOS-related infertility is significantly effective, improving endometrial receptivity, insulin resistance, ovulation rates, and pregnancy rates while reducing miscarriage rates. These findings suggest that clomiphene combined with Chinese herbal decoctions has significant effects on obese PCOS, and this study confirms that clomiphene combined with Lianggu Decoction also produces excellent therapeutic outcomes.

Furthermore, this study found no statistically significant difference in adverse reaction rates between the trial and control groups ($P>0.05$). Li et al. [20] similarly confirmed that clomiphene combined with modified Shugan Jianpi Formula can effectively regulate sex hormone levels, promote ovulation, and demonstrate significant clinical effects with high safety in treating PCOS-related infertility. These results indicate that combination therapy is safe and reliable for broader clinical application.

This study has several limitations: (1) No age-stratified analysis was performed. This study used uniform drug dosages for all patients, but different age groups may require different dosages to achieve the same therapeutic effect. Future studies should investigate dosage requirements across age groups. (2) The sample size was relatively small. Multi-center, large-sample prospective clinical studies are needed to obtain more objective and reliable clinical data to validate these findings. (3) The follow-up period was relatively short, limited to pregnancy outcomes without continued collection of data on pregnancy prognosis. Future studies should extend follow-up duration to further explore whether this treatment regimen can improve pregnancy outcomes in obese PCOS-related infertility.

Conclusion

In summary, Lianggu Decoction combined with clomiphene for obese PCOS-related infertility can effectively improve insulin resistance, glucose and lipid metabolism, sex hormone levels, and ovarian hemodynamics while increasing

pregnancy rates, warranting broader clinical application.

Author Contributions

WANG Yan proposed the main research objectives, conceptualized and designed the study, and supervised implementation. HU Xin and MU Xianli collected and organized data, performed statistical analysis, created figures and tables, and drafted the manuscript. PENG Peng revised the manuscript, provided quality control and review, and assumed overall responsibility for the article.

Conflict of Interest

The authors declare no conflicts of interest.

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