Am J Transl Res 2025;17(7):5081-5089
www.ajtr.org /ISSN:1943-8141/AJTR0166232

Original Article

Clinical effectiveness of ethinylestradiol-cyproterone acetate and raloxifene combination therapy in polycystic ovary syndrome-associated infertility

Pengyu Huang[1*], Suhua Jiang[2,3*], Beihong Zheng[4*], Yun Fu[1], Wenqiang You[5], Haiyan Li[4]

[1]Fujian Provincial Human Sperm Bank, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics and Gynecology and Pediatrics, Fujian Medical University, Fuzhou 350001, Fujian, China; [2]Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics and Gynecology and Pediatrics, Fujian Medical University, Fuzhou 350001, Fujian, China; [3]School of Life Sciences, Xiamen University, Xiamen 361000, Fujian, China; [4]Center of Reproductive Medicine, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics and Gynecology and Pediatrics, Fujian Medical University, Fuzhou 350001, Fujian, China; [5]Department of Obstetrics and Gynecology, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics and Gynecology and Pediatrics, Fujian Medical University, Fuzhou 350001, Fujian, China. [*]Equal contributors and co-first authors.

Received May 21, 2025; Accepted June 26, 2025; Epub July 15, 2025; Published July 30, 2025

Abstract: Objective: To evaluate the therapeutic outcomes of combining ethinylestradiol-cyproterone acetate (EE-CPA) with raloxifene in the management of polycystic ovary syndrome (PCOS)-associated infertility. Methods: The study included 115 women diagnosed with PCOS-associated infertility, admitted between January 2021 and January 2025. The participants were divided into two groups: 55 women receiving raloxifene monotherapy (control group) and 60 treated with EE-CPA plus raloxifene (observation group). The following were assessed: therapeutic effectiveness, adverse drug reactions (abdominal/pelvic pain, nausea/vomiting, body weight fluctuations, and breast tenderness), metabolic markers (fasting plasma glucose [FPG], fasting serum insulin [FINS], and homeostasis model assessment of insulin resistance [HOMA-IR]), sex hormones (estradiol [E2], follicle-stimulating hormone [FSH], and luteinizing hormone [LH]), ovarian function (ovarian volume and endometrial thickness), endometrial receptivity (resistance index [RI] and pulsatility index [PI]), and pregnancy outcomes (ovulation, miscarriage, and clinical pregnancy). Results: The combination therapy showed superior outcomes, including enhanced overall effectiveness, increased ovulation and pregnancy rates, and a reduced miscarriage rate (all P>0.05). No significant differences in adverse drug reactions were found between the two groups (P>0.05). After treatment, the observation group showed greater improvements in metabolic markers, FSH, LH, ovarian volume, RI, and PI (all P>0.05). Additionally, E2 levels and endometrial thickness were more significantly enhanced in the observation group compared to the control group (all P>0.05). Conclusions: The combination of EE-CPA and raloxifene is highly effective in managing PCOS-associated infertility, improving therapeutic outcomes without significantly increasing adverse effects. It also leads to notable improvements in metabolism, sex hormones, ovarian function, and endometrial receptivity, ultimately enhancing pregnancy outcomes.

Keywords: Polycystic ovary syndrome-associated infertility, ethinylestradiol-cyproterone acetate, raloxifene, therapeutic outcomes

Introduction

Polycystic ovary syndrome (PCOS) is a disorder that impacts female reproduction, metabolism, and psychological health, affecting 5.0-18.0% of women during their lifespan [1]. Pathologically, PCOS is characterized by infertility, obesity, anovulation, polycystic ovarian morphology, and insulin resistance, with contributing factors including genetic predisposition, dietary habits, lifestyle choices, gut microbiota dysbiosis, and neuroendocrine disturbances [2, 3]. The etiology of PCOS involves ovarian enlargement and dysfunction, coupled with elevated androgen levels that disrupt the ovarian microenvironment. This frequently leads to symp-

https://doi.org/10.62347/ZUHL5679

toms such as acne, hirsutism, and androgenetic alopecia [4, 5]. Infertility prevalence in PCOS patients has risen globally, with the age-standardized prevalence rate of PCOS-related infertility increasing from 223.50 to 308.25 per 100,000 between 1990 and 2019 [6]. Despite this, there is no ideal treatment for PCOS-related infertility, and current strategies are primarily tailored based on predominant clinical features [7]. This study aims to optimize treatment approaches for PCOS-related infertility by identifying more clinically effective options to enhance patient outcomes.

Raloxifene, a benzothiophene-derived selective estrogen receptor modulator, has both prophylactic and therapeutic effects on osteoporosis [8]. It is indicated for early postmenopausal women, where it positively impacts bone mineral density and vertebral fracture prevention [9]. An in vitro study found that raloxifene, when combined with estrogen and methotrexate, enhances cytotoxicity and apoptosis in human endometrial stromal cells, potentially explaining its therapeutic role in endometrial hyperplasia-associated infertility [10]. Ethinylestradiol-cyproterone acetate (EE-CPA) also demonstrates therapeutic potential for PCOS, exerting anti-gonadotropic effects by antagonizing androgen receptors. This mechanism blocks the action of androgens on target organs, improving ovulation disorders [11]. Previous studies have shown that EE-CPA effectively improves serum sex hormones and lipid metabolism in PCOS patients [12]. Furthermore, EE-CPA's therapeutic effects on PCOS appear to be related to its improvement in obesity, glucose metabolism, and lipid metabolism, with minimal adverse events [13].

This study primarily compares the effectiveness of raloxifene alone versus a combination of EE-CPA and raloxifene in treating infertility in PCOS patients, aiming to identify an optimal therapeutic strategy. The study presents several innovations. First, it introduces a novel therapeutic regimen combining EE-CPA and raloxifene for managing infertility in PCOS patients. Preliminary findings suggest promising therapeutic potential, though further clinical validation is needed. Second, the study evaluates multiple parameters - clinical outcomes, adverse drug reactions (ADRs), metabolic parameters, sex hormone profiles, ovarian function metrics, endometrial receptivity indices, and pregnancy outcomes - offering a comprehensive evaluation that provides robust evidence supporting the clinical advantages of combined therapy. These findings offer valuable insights for the potential application of this approach in clinical practice.

Materials and methods

Participant selection

This study employed a retrospective design. Inclusion criteria: Diagnosis of PCOS based on established criteria [14]; presence of symptoms such as irregular menstruation, hirsutism, acne, and infertility; ovarian enlargement with polycystic changes on ultrasound; normal sexual activity and hysterosalpingography findings; laboratory results indicating a luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio ≥2.5 and serum testosterone levels >2.5 nmol/L; normal hepatic and renal function; treatment-naive patients; normal semen analysis from the partner. Exclusion criteria: Infertility due to uterine anomalies, immune disorders, salpingemphraxis, inflammation, etc.; hormonal medication use within the past three months; known hypersensitivity to the study medication; diabetes or other endocrine disorders; organic lesions of the reproductive system; Cushing's syndrome, neoplastic diseases, or psychiatric conditions.

Following institutional ethics committee approval, 115 PCOS patients with infertility were recruited from Fujian Maternity and Child Health Hospital between January 2021 and January 2025. Participants were randomly assigned to two treatment groups: the control group (n=55), receiving raloxifene monotherapy, and the observation group (n=60), receiving combination therapy with EE-CPA and raloxifene.

Intervention methods

Control group: Patients in the control group received raloxifene therapy, initiated on day 5 of the menstrual cycle with an oral dose of 120 mg raloxifene (Shanghai Aladdin Bio-Chem Technology Co., Ltd., R426198), administered once daily for 5 consecutive days (days 5-9). Follicular development was monitored via transvaginal ultrasound, with the first assess-

ment on day 12 to evaluate endometrial thickness, morphology, and follicular growth. Ovulation was triggered by intramuscular injection of 10,000 U human chorionic gonadotropin (hCG; AmyJet Scientific Inc., HOR-250) once the dominant follicle reached ≥18 mm in diameter. Timed intercourse was recommended 24-36 hours post-injection, with ovulation confirmed by follow-up ultrasound 48 hours after hCG administration. If no dominant follicle (≥18 mm) was observed by day 16 or ovulation did not occur within 3 days of hCG injection, the cycle was deemed ineffective, and the patient proceeded to the next treatment cycle. All participants underwent three consecutive treatment cycles.

Observation group: In addition to the raloxifene regimen described above, patients in the observation group received EE-CPA therapy. On day 5 of the menstrual cycle, one tablet of EE-CPA (containing 35 μg EE and 2 mg CPA; Bayer HealthCare Pharmaceuticals Guangzhou Branch, J20140114) was taken orally each night before bedtime for 21 consecutive days, followed by a withdrawal period until breakthrough bleeding occurred. Raloxifene administration, follicular monitoring, ovulation triggering, and follow-up procedures were identical to those in the control group. Both groups followed the same treatment duration (3 cycles), monitoring schedule, and outcome assessment criteria.

Data collection and outcome assessment

Clinical outcomes: Therapeutic effectiveness was assessed based on established PCOS-related infertility criteria [15]. Outcomes were classified as: (i) Markedly effective - achievement of pregnancy; (ii) Effective - restoration of regular menstrual cycles and follicular development normalization, confirmed by ultrasonography, without conception; (iii) Ineffective - failure to meet the above criteria. The overall response rate was defined as the proportion of cases with markedly effective or effective outcomes relative to the total cohort.

ADRs [16]: Documented ADRs included abdominal/pelvic pain, nausea/vomiting, body weight fluctuations, and breast tenderness. Incidence rates were compared between groups.

Metabolic parameters [17]: Fasting plasma glucose (FPG), fasting serum insulin (FINS), and the homeostasis model assessment of insulin resistance (HOMA-IR) index were measured pre- and post-treatment. FPG was quantified using glucose oxidase methodology, and FINS was measured by chemiluminescent immunoassay. HOMA-IR was calculated as: HOMA-IR = [FINS (μU/mL) × FPG (mmol/L)]/22.5.

Sex hormone profiling [18]: Morning fasting venous blood samples were collected pre- and post-treatment. After centrifugation, serum concentrations of estradiol (E2), FSH, and LH were determined by radioimmunoassay.

Ovarian function metrics [19, 20]: Transvaginal ultrasound was used to evaluate ovarian volume, endometrial thickness, uterine artery resistance index (RI), and endometrial spiral artery pulsatility index (PI) before and after treatment.

Pregnancy outcomes [21]: The ovulation, miscarriage, and clinical pregnancy rates were compared between groups.

Statistical analysis

Data were analyzed using IBM SPSS Statistics (Version 20.0), with statistical significance set at $P<0.05$. Quantitative data were expressed as means ± standard deviation ($\bar{x}\pm sd$), with between-group differences assessed using independent t-tests and within-group changes evaluated using paired t-tests. For categorical variables, frequency distributions [n (%)] were compared using χ^2 analysis.

Results

Comparison of participant characteristics

Both study groups had comparable baseline characteristics, with no significant differences in age, body mass index (BMI), PCOS duration, infertility period, marital status, or reproductive status, as detailed in **Table 1** (all $P>0.05$).

Comparison of clinical outcomes

The observation group demonstrated a significantly higher overall effectiveness rate (95.00%) compared to the control group (78.18%) ($P<0.01$). See **Table 2**.

Table 1. Comparison of baseline demographics

Factor	Control group (n=55)	Observation group (n=60)	t/χ^2 value	*P* value
Age (years)	31.71±4.81	30.30±4.91	1.553	0.123
Body mass index (kg/m^2)	24.49±2.97	23.67±3.07	1.453	0.149
PCOS duration (years)	5.25±2.16	5.15±2.31	0.239	0.811
Infertility duration (years)	1.58±0.81	1.85±1.01	1.572	0.119
Marital status			0.515	0.473
Married	50 (90.91)	52 (86.67)		
Unmarried	5 (9.09)	8 (13.33)		
Reproductive status			1.509	0.219
Parous	11 (20.00)	7 (11.67)		
Nulliparous	44 (80.00)	53 (88.33)		

Note: PCOS, polycystic ovary syndrome.

Table 2. Comparison of therapeutic effectiveness

Factor	Control group (n=55)	Observation group (n=60)	χ^2 value	*P* value
Markedly effective	17 (30.91)	35 (58.33)		
Effective	26 (47.27)	22 (36.67)		
Ineffective	12 (21.82)	3 (5.00)		
Overall effectiveness	43 (78.18)	57 (95.00)	7.156	0.008

Table 3. Comparison of adverse drug reactions

Adverse drug reaction	Control group (n=55)	Observation group (n=60)	χ^2 value	*P* value
Abdominal/pelvic pain	2 (3.64)	1 (1.67)		
Nausea/vomiting	2 (3.64)	2 (3.33)		
Body weight fluctuations	0 (0.00)	2 (3.33)		
Breast tenderness	1 (1.82)	2 (3.33)		
Total	5 (9.09)	7 (11.67)	0.204	0.652

Comparison of ADRs

The frequency of reported ADRs - including abdominal/pelvic pain, nausea/vomiting, body weight fluctuations, and breast tenderness - was similar between both groups (P>0.05). See **Table 3**.

Comparison of metabolic parameter

Baseline metabolic characteristics were well-balanced between groups (all P>0.05). Post-intervention assessments revealed significant improvements in all metabolic indices for both cohorts. Notably, the observation group showed significantly better outcomes in FPG, FINS, and HOMA-IR compared to controls (all P<0.05). See **Figure 1**.

Comparison of sex hormonal profiles

Baseline assessments revealed no significant intergroup differences in sex hormone parameters (all P>0.05). Post-intervention, both cohorts showed significant increases in E_2 concentrations and reductions in FSH and LH levels (all P<0.05). The observation group achieved superior results, with significantly higher E2 concentrations and more pronounced suppression of FSH/LH levels compared to the control group (all P<0.05). See **Figure 2**.

Comparison of ovarian function

Pretreatment evaluations showed comparable ovarian volumes and endometrial thickness between groups (P>0.05). Post-treatment, both groups exhibited significant morphological changes, including reduced ovarian volumes and enhanced endometrial thickness. The observation group displayed more favorable outcomes, with significantly smaller ovarian volumes and greater endometrial thickening compared to the control group (all P<0.05). See **Figure 3**.

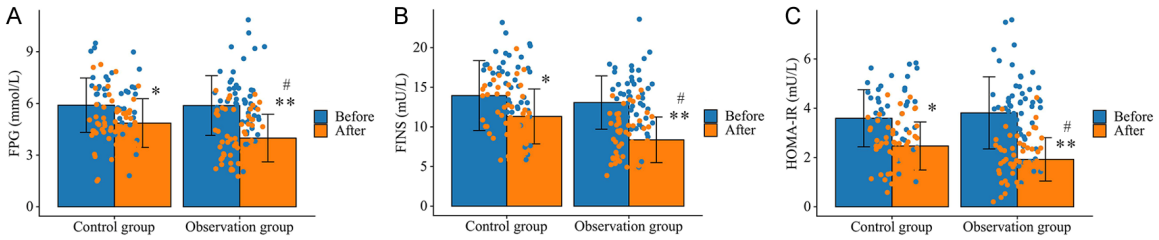

Figure 1. Longitudinal changes in metabolic parameters. A: Comparative FPG measurements pre- and post-treatment. B: FINS concentration variations during the study period. C: HOMA-IR dynamics before and following therapeutic intervention. Note: FPG, fasting plasma glucose; FINS, fasting serum insulin; HOMA-IR, homeostasis model assessment of insulin resistance. *P<0.05, **P<0.01 versus baseline; #P<0.05 versus control group.

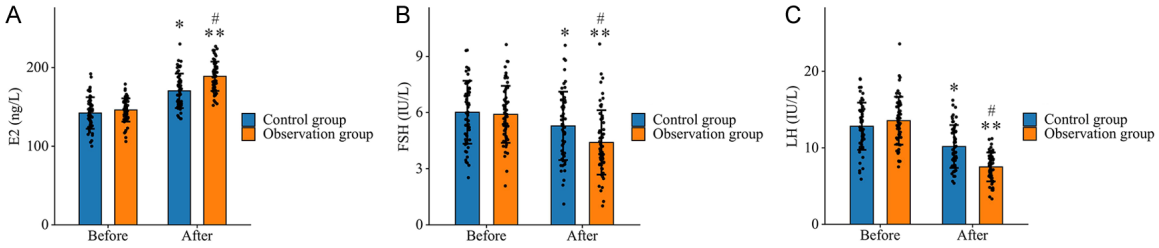

Figure 2. Comparison of sex hormone dynamics. A: E_2 concentration trajectories. B: FSH level variations. C: LH level fluctuations. Note: E_2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone. *P<0.05, **P<0.01 versus baseline; #P<0.05 versus control group.

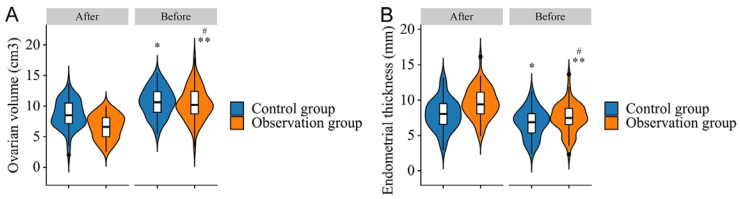

Figure 3. Per- and post-treatment ovarian function parameters. A: Ovarian volume changes. B: Endometrial thickness alterations. Note: *P<0.05, **P<0.01 versus baseline; #P<0.05 versus control group.

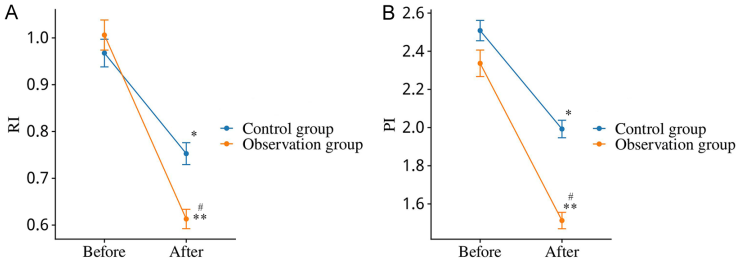

Figure 4. Pre- and post-interventional endometrial receptivity. A: RI temporal patterns. B: PI longitudinal changes. Note: RI, resistance index; PI, pulsatility index. *P<0.05, **P<0.01 versus baseline; #P<0.05 versus control group.

Comparison of endometrial receptivity

Doppler parameters (RI and PI) were equivalent at baseline (both P>0.05). Post-treatment, significant improvements in endometrial receptivity parameters were observed in both groups, with the observation group showing superior reductions in both RI and PI values compared to the control group (both P<0.05). See **Figure 4**.

Comparison of pregnancy outcomes

The observation group demonstrated significantly better reproductive performance, including higher ovulation rates, improved clinical pregnancy success, and lower miscarriage rates compared to the control group (all P<0.05). See **Table 4**.

Discussion

PCOS is the most common cause of infertility in women of reproductive age, leading to hyperandrogenism, metabolic disturbances, and ovulation failure. The optimal treatment strategy remains controversial [22]. As a highly heterogeneous syndrome, PCOS has a wide range of

Table 4. Comparison of pregnancy outcomes

Reproductive outcome	Control group (n=55)	Observation group (n=60)	χ^2 value	*P* value
Ovulation	28 (50.91)	50 (83.33)	13.825	<0.001
Miscarriage	18 (32.73)	3 (5.00)	14.780	<0.001
Clinical pregnancy	17 (30.91)	36 (60.00)	9.774	0.002

physical effects on female patients. For example, up to 75% of women with PCOS experience infertility, nearly 70% have hirsutism, more than 50% experience amenorrhea, and nearly 40% have obesity [23]. Effective treatment for PCOS-induced infertility remains a critical area of ongoing research.

This study found a significantly superior overall effectiveness rate in the observation group receiving EE-CPA plus raloxifene therapy, suggesting that this combination can optimize therapeutic outcomes in patients with PCOS-associated infertility. EE-CPA, a compound consisting of CPA and EE, exerts strong anti-androgenic and anti-gonadotropic activities. This helps suppress excessive endometrial hyperplasia in women with PCOS-induced infertility. By antagonizing estrogen receptors in the hypothalamus, EE-CPA removes the negative feedback of estrogen on gonadotropin-releasing hormone (GnRH) secretion, stimulating FSH release and promoting follicular development [24, 25]. Raloxifene, on the other hand, suppresses the negative feedback mechanism of the hypothalamic-pituitary-gonadal axis, thereby increasing serum FSH levels and accelerating follicular development and maturation, which ultimately enhances the probability of conception. The combination of EE-CPA and raloxifene has complementary effects, synergistically enhancing therapeutic outcomes [26]. In the study by Ruan et al. [27], EE-CPA was shown to effectively alleviate hyperandrogenic dermatitis, reduce the negative impact of clinical symptoms on quality of life and psychological well-being, and improve menstrual irregularities, helping to maintain fertility.

Our study also demonstrated no significant increase in total ADRs with EE-CPA plus raloxifene, indicating that this combination therapy has good safety and tolerability. Singhal et al. [28] found that EE-CPA did not affect periodontal or systemic inflammatory status in PCOS patients, which may partly explain the safety of this combined approach. Furthermore, the combination therapy significantly improved metabolic parameters, evidenced by decreases in FPG, FINS, and HOMA-IR levels. These metabolic improvements are likely due to EE-CPA's ability to reduce free testosterone levels through CPA, mitigating androgen-induced insulin resistance and enhancing peripheral tissue (muscle and adipose) insulin sensitivity. Additionally, EE-CPA suppresses hepatic glucose production, reducing FPG levels and alleviating compensatory hyperinsulinemia [29, 30].

This combination therapy also had favorable effects on sex hormone levels in infertile PCOS patients. It significantly elevated E2 while suppressing FSH and LH levels. This outcome is likely due to EE-CPA's provision of exogenous estrogen, which increases serum E2, rapidly addresses low estrogen levels, and promotes endometrial proliferation, creating favorable conditions for embryo implantation. Additionally, EE-CPA's action on the hypothalamus and pituitary gland helps exert negative feedback, reducing the synthesis and release of FSH and LH [12, 31].

In addition, this combined approach significantly enhanced ovarian function and endometrial receptivity. As observed in our clinical results, the observation group showed more pronounced reductions in ovarian volume, RI, and PI, as well as a greater increase in endometrial thickness compared to the control group. Enhanced endometrial blood flow improves endometrial receptivity, which is crucial for embryo implantation. RI and PI are closely related to endometrial blood flow, and reduced levels are associated with increased blood flow and better receptivity [32]. Research shows that EE-CPA can stimulate endometrial vascular development, enhance endometrial thickness, and prevent uterine artery blood flow obstruction, which helps mitigate the adverse effects of poor endometrial perfusion on receptivity [33].

Finally, the combination of EE-CPA and raloxifene achieved superior pregnancy outcomes in infertile PCOS patients, reflected in significantly higher ovulation and clinical pregnancy rates, as well as lower miscarriage rates. This suggests that the combined regimen significantly increases conception rates. EE-CPA restores regular menstrual cycles, improves ovarian ovulation function, and facilitates sperm passage through the cervical mucus, which may contribute to the increased pregnancy rate [34].

Several limitations of this study should be acknowledged. First, the representativeness of the findings may be limited by the relatively small sample size and single-center design, highlighting the need for multicenter studies to improve sample diversity and enhance the generalizability of the results. Second, this study lacks mechanistic investigations to elucidate the underlying biological pathways. Future research should incorporate cellular and animal models to explore the molecular mechanisms of EE-CPA combined with raloxifene in the treatment of PCOS. Lastly, the absence of long-term follow-up data restricts conclusions regarding the sustained efficacy and safety of the combination therapy. Prospective studies with extended observation periods are warranted to further validate the clinical superiority of this therapeutic approach. Future research will aim to address these critical gaps.

In conclusion, EE-CPA plus raloxifene therapy for PCOS-associated infertility optimizes clinical efficacy without substantially increasing ADRs. The treatment demonstrates marked efficacy in improving metabolism, sex hormones, ovarian function, endometrial receptivity, and pregnancy outcomes, showing considerable clinical potential for broader application in managing PCOS-associated infertility.

Acknowledgements

This research was funded by the following grants: 1. the Fujian Provincial Natural Science Foundation of China (Grant number: 2021-J05083); 2. the Joint Funds for the Innovation of Science and Technology, Fujian province (Grant number: 2023Y9384); 3. the Joint Funds for the Innovation of Science and Technology, Fujian province (Grant number: 2021Y9177); 4. the Fujian Provincial Natural Science Foundation of China (Grant number: 2023J0112-29); 5. the Fujian provincial health technology project (Grant number: 2025QNGGA010).

Disclosure of conflict of interest

None.

Address correspondence to: Haiyan Li, Center of Reproductive Medicine, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics and Gynecology and Pediatrics, Fujian Medical University, Fuzhou 350001, Fujian, China. Tel: +86-13960724539; E-mail: lihaiyan2011made@163.com; Wenqiang You, Department of Obstetrics and Gynecology, Fujian Maternity and Child Health Hospital, College of Clinical Medicine for Obstetrics and Gynecology and Pediatrics, Fujian Medical University, Fuzhou 350001, Fujian, China. Tel: +86-15859018261; E-mail: hlpywq@163.com

References

[1] Joham AE, Norman RJ, Stener-Victorin E, Legro RS, Franks S, Moran LJ, Boyle J and Teede HJ. Polycystic ovary syndrome. Lancet Diabetes Endocrinol 2022; 10: 668-680.

[2] Singh S, Pal N, Shubham S, Sarma DK, Verma V, Marotta F and Kumar M. Polycystic ovary syndrome: etiology, current management, and future therapeutics. J Clin Med 2023; 12: 1454.

[3] Zhao H, Zhang J, Cheng X, Nie X and He B. Insulin resistance in polycystic ovary syndrome across various tissues: an updated review of pathogenesis, evaluation, and treatment. J Ovarian Res 2023; 16: 9.

[4] Witchel SF, Oberfield SE and Pena AS. Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. J Endocr Soc 2019; 3: 1545-1573.

[5] Taieb A and Feryel A. Deciphering the role of androgen in the dermatologic manifestations of polycystic ovary syndrome patients: a state-of-the-art review. Diagnostics (Basel) 2024; 14: 2578.

[6] Liu X, Zhang J and Wang S. Global, regional, and national burden of infertility attributable to PCOS, 1990-2019. Hum Reprod 2024; 39: 108-118.

[7] Sadeghi HM, Adeli I, Calina D, Docea AO, Mousavi T, Daniali M, Nikfar S, Tsatsakis A and Abdollahi M. Polycystic ovary syndrome: a comprehensive review of pathogenesis, management, and drug repurposing. Int J Mol Sci 2022; 23: 583.

[8] Guo Z, Afza R, Moneeb Khan M, Khan SU, Khan MW, Ali Z, Batool S and Din FU. Investigation of the treatment potential of Raloxifene-loaded polymeric nanoparticles in osteoporosis: In-vitro and in-vivo analyses. Heliyon 2023; 9: e20107.

[9] Condi FLF, Fuchs LFP, Carvalho KC and Baracat EC. Treatment with raloxifene induces the expression of kisspeptin, insulin, and androgen receptors in bones of castrated adult female rats. Rev Bras Ortop (Sao Paulo) 2024; 59: e228-e234.
[10] Nikolic I, Andjelkovic M, Zaric M, Zelen I, Milosavljevic Z, Canovic P and Mitrovic M. Enhanced cytotoxicity and apoptosis by raloxifene in combination with estrogen and methotrexate in human endometrial stromal cells. Chem Biol Drug Des 2018; 91: 885-892.
[11] Chang KJ, Chen JH and Chen KH. The pathophysiological mechanism and clinical treatment of polycystic ovary syndrome: a molecular and cellular review of the literature. Int J Mol Sci 2024; 25: 9037.
[12] Lu K, Li N, Zhang M, Lin J and Chen J. Effects of letrozole combined with ethinylestradiol and cyproterone acetate tablets on serum sex hormones and lipid metabolism in patients with polycystic ovary syndrome. Am J Transl Res 2023; 15: 1271-1280.
[13] Fu Y, Xie P, Yang Q, Chen P and Yu J. Analysis on the therapeutic effect of Cangfu Daotan Decoction combined with drospirenone and ethinylestradiol tablets (II) on patients with polycystic ovary syndrome. Prostaglandins Other Lipid Mediat 2024; 170: 106801.
[14] Stener-Victorin E, Teede H, Norman RJ, Legro R, Goodarzi MO, Dokras A, Laven J, Hoeger K and Piltonen TT. Polycystic ovary syndrome. Nat Rev Dis Primers 2024; 10: 27.
[15] Xu Y, Han YM, Xu W, Shi C, Chen YE and Li N. Clinical efficacy and safety of the Jinfeng pill in the adjuvant treatment of infertility in patients with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trial. Ann Palliat Med 2022; 11: 352-362.
[16] Oliver A and Overton C. Detecting ovarian disorders in primary care. Practitioner 2014; 258: 15-19, 2.
[17] Chang H, Shi B, Ge H, Liu C, Wang L, Ma C, Liu L, Zhang W, Zhang D, Wang Y, Wang CC and Wu X. Acupuncture improves the emotion domain and lipid profiles in women with polycystic ovarian syndrome: a secondary analysis of a randomized clinical trial. Front Endocrinol (Lausanne) 2023; 14: 1237260.
[18] Peng Q, Chen X, Liang X, Ouyang J, Wang Q, Ren S, Xie H, Wang C, Sun Y, Wu X, Liu H, Hei C, Sun M, Chang Q, Liu X, Li G and He R. Metformin improves polycystic ovary syndrome in mice by inhibiting ovarian ferroptosis. Front Endocrinol (Lausanne) 2023; 14: 1070264.
[19] Jiang S, Tang T, Sheng Y, Li R and Xu H. The effects of letrozole and metformin combined with targeted nursing care on ovarian function, LH, and FSH in infertile patients with polycystic ovary syndrome. J Healthc Eng 2022; 2022: 3712166.
[20] Yang J, Lin QP, You XM, Zhang JX, Liu Y, Huang J, Dun JJ, Huang S, Xu JB and Ji F. Effect of combined treatment with acupuncture, moxibustion and medication on endometrial receptivity and expression of serum HOXA10 in polycystic ovary syndrome of kidney deficiency and blood stagnation. Zhongguo Zhen Jiu 2020; 40: 1154-1158.
[21] Yang M, Shen X, Lu D, Peng J, Zhou S, Xu L and Zhang J. Effects of vitamin D supplementation on ovulation and pregnancy in women with polycystic ovary syndrome: a systematic review and meta-analysis. Front Endocrinol (Lausanne) 2023; 14: 1148556.
[22] Peng G, Yan Z, Liu Y, Li J, Ma J, Tong N and Wang Y. The effects of first-line pharmacological treatments for reproductive outcomes in infertile women with PCOS: a systematic review and network meta-analysis. Reprod Biol Endocrinol 2023; 21: 24.
[23] Attia GM, Almouteri MM and Alnakhli FT. Role of metformin in polycystic ovary syndrome (PCOS)-related infertility. Cureus 2023; 15: e44493.
[24] Amiri M, Rahmati M, Hedayati M, Nahidi F and Ramezani Tehrani F. Effects of oral contraceptives on serum concentrations of adipokines and adiposity indices of women with polycystic ovary syndrome: a randomized controlled trial. J Endocrinol Invest 2021; 44: 567-580.
[25] Jin P and Xie Y. Treatment strategies for women with polycystic ovary syndrome. Gynecol Endocrinol 2018; 34: 272-277.
[26] de Paula Guedes Neto E, Savaris RF, von Eye Corleta H, de Moraes GS, do Amaral Cristovam R and Lessey BA. Prospective, randomized comparison between raloxifene and clomiphene citrate for ovulation induction in polycystic ovary syndrome. Fertil Steril 2011; 96: 769-773.
[27] Ruan X, Kubba A, Aguilar A and Mueck AO. Use of cyproterone acetate/ethinylestradiol in polycystic ovary syndrome: rationale and practical aspects. Eur J Contracept Reprod Health Care 2017; 22: 183-190.
[28] Singhal R, Tewari S, Sharma R, Singhal S, Tanwar N and Sangwan A. Effect of cyproterone acetate/ethinyl estradiol combination on periodontal status and high-sensitivity C-reactive protein levels in women with polycystic ovary syndrome: a cross-sectional study. Quintessence Int 2024; 55: 274-285.
[29] Mhao NS, Al-Hilli AS, Hadi NR, Jamil DA and Al-Aubaidy HA. A comparative study to illustrate

the benefits of using ethinyl estradiol-cyproterone acetate over metformin in patients with polycystic ovarian syndrome. Diabetes Metab Syndr 2016; 10 Suppl 1: S95-98.
[30] Lemay A, Dodin S, Turcot L, Dechene F and Forest JC. Rosiglitazone and ethinyl estradiol/cyproterone acetate as single and combined treatment of overweight women with polycystic ovary syndrome and insulin resistance. Hum Reprod 2006; 21: 121-128.
[31] Stanczyk FZ. Metabolism of endogenous and exogenous estrogens in women. J Steroid Biochem Mol Biol 2024; 242: 106539.
[32] Zhang CH, Chen C, Wang JR, Wang Y, Wen SX, Cao YP and Qian WP. An endometrial receptivity scoring system basing on the endometrial thickness, volume, echo, peristalsis, and blood flow evaluated by ultrasonography. Front Endocrinol (Lausanne) 2022; 13: 907874.
[33] Palomba S, Costanzi F, Caserta D and Vitagliano A. Pharmacological and non-pharmacological interventions for improving endometrial receptivity in infertile patients with polycystic ovary syndrome: a comprehensive review of the available evidence. Reprod Biomed Online 2024; 49: 104381.
[34] Bargiota A and Diamanti-Kandarakis E. The effects of old, new and emerging medicines on metabolic aberrations in PCOS. Ther Adv Endocrinol Metab 2012; 3: 27-47.