ORIGINAL ARTICLE: REPRODUCTIVE ENDOCRINOLOGY

Comparing the individual effects of metformin and rosiglitazone and their combination in obese women with polycystic ovary syndrome: a randomized controlled trial

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Objective: To compare the effects of metformin, rosiglitazone, and their combination in obese polycystic ovary syndrome (PCOS) patients with insulin resistance.
Design: Prospective randomized controlled trail.
Setting: Tertiary teaching hospital.
Patient(s): Obese Chinese women (body mass index [BMI] ≥ 25 kg/m^2) with insulin resistance who fulfilled the Rotterdam criteria of PCOS.
Intervention(s): In group 1, 68 patients administered metformin (1,500 mg/day); in group 2, 67 patients administered rosiglitazone (4 mg/day); in group 3, 69 patients administered metformin (1,000 mg/day) and rosiglitazone (4 mg/day) for 6 months, all with the same diet and regular exercise lifestyle recommendation.
Main Outcome Measure(s): Average menstrual interval, anthropometric measurements, androgen-related parameters, and metabolic features of insulin, carbohydrates, and lipids, with intention-to-treat analysis.
Result(s): The baseline parameters showed no statistically significant differences. After the 6-month treatment, most participants showed an improved menstrual pattern. There were statistically significant decreases in acne scores, weight, BMI, waist circumference, waist-to-hip ratio, and serum testosterone. The metabolic indexes of insulin, carbohydrates, and lipids were improved obviously compared with the baseline in each group. Among the three groups, the patients administered 1,500 mg/day metformin experienced greater reductions in weight. However, the rosiglitazone users (alone or combined with metformin) showed a more notable decline in total cholesterol and triglyceride levels.
Conclusion(s): Considering the benefits of metformin on weight loss, high-dose metformin (1,500 mg/day) along with lifestyle modification should be recommended for obese, insulin-resistant women with PCOS. Rosiglitazone alone or combined with low-dosage metformin plus lifestyle modification should be considered for the women with abnormal lipid profiles.
Clinical Trial Registration Number: ChiCTR-TRC-13003642 (Chinese Clinical Trial Registry). (Fertil Steril® 2019;■:■–■. ©2019 by American Society for Reproductive Medicine.)
Key Words: Insulin resistance, metformin, obesity, polycystic ovary syndrome, rosiglitazone

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Y.L. and J.T. should be considered similar in author order.
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As one of the most common endocrine-gynecologic disorders, polycystic ovary syndrome (PCOS) affects approximately 5.6% of Chinese women aged 19–45 years (1). Patients with PCOS often suffer from diverse symptoms, including endocrine-related conditions such as irregular menstrual cycles, ovulatory disorders, infertility, androgen-related acne and hirsutism, metabolic-related obesity, insulin resistance, type 2 diabetes, the metabolic syndrome, and psychological problems (2).

Overweightness, obesity, and central obesity are prevalent in PCOS and affect approximately 30% to 70% of patients (3–5). Furthermore, insulin resistance has been documented to affect 75% of lean women and 95% of overweight women (6). The magnitude of insulin resistance and secondary hyperinsulinemia is exacerbated in obese women compared with nonobese individuals (7). Abdominal obesity is closely correlated with insulin resistance because of the deposit of visceral adiposity (8). The impact of obesity on the metabolic and reproductive outcomes of PCOS—including glucose and lipid metabolism, hyperandrogenism, menstrual disturbances, infertility, and PCOS-associated comorbidities such as associated type 2 diabetes, hyperlipidemia, and arterial hypertension—may be worsened (9).

The recommended first-line therapy for PCOS is lifestyle management (10). Even a reduction of as little as 5% body weight could result in benefits. However, the efficacy of lifestyle management often remains unsatisfactory and unsustainable in clinical practice, so pharmacologic treatment is needed. At present, evidence-based guidelines recommend metformin in addition to lifestyle adjustments for obese, insulin-resistant women with PCOS, with the aim of managing weight and endocrine-metabolic disturbances (2). As the most extensively used insulin sensitizer in PCOS, metformin can reduce hepatic glucose production, inhibit gluconeogenesis and lipogenesis, and elevate peripheral tissue sensitivity to insulin (11). Moreover, considerable studies have suggested that metformin not only reduces body weight and metabolic disturbances but also corrects menstrual patterns and recovers ovulation and even conception (11–13). However, some women cannot tolerate the gastrointestinal side effects of metformin; vitamin B_{12} deficiency with the long-term use of metformin is also a cause of some concern (14).

Rosiglitazone, a peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist, has been widely used to treat non-insulin-dependent diabetes. Though studies have shown that rosiglitazone may ameliorate insulin resistance, hyperandrogenemia, menstrual disturbances, and ovulation (15, 16), the quality and certainty of the evidence have been limited.

There has been a large number of studies comparing the efficacy of metformin and rosiglitazone in women with PCOS (17, 18), but few studies have focused on the effectiveness of their combination in the obese subpopulation. In our current study, we designed a prospective, randomized, controlled trial to compare the clinical and biochemical-metabolic effects of metformin, rosiglitazone, and their combination in obese, insulin-resistant Chinese women with PCOS. Meanwhile, lifestyle changes such as dietary adjustments and physical exercise were also incorporated.

MATERIALS AND METHODS

Study Population

Women diagnosed with PCOS according to the Rotterdam criteria (19) were recruited for the study between December 2013 and September 2016 at the Reproductive Endocrinology Division, West China Second University Hospital of Sichuan University, People's Republic of China. The inclusion criteria for this study were as follows: [1] women from 18 to 35 years of age; [2] patients with obesity, a body mass index (BMI) ≥ 25 kg/m^2 (20); and [3] patients exhibiting insulin resistance, homeostatic model assessment of insulin resistance (HOMA-IR) index ≥ 2.77 (21). The exclusion criteria were as follows: [1] patients with hyperprolactinemia, hypo- or hyperthyroidism, or abnormal liver, kidney, or heart function; [2] patients affected by hypertension, diabetes mellitus, or severe mental illness or with a personal history of cardiovascular events; [3] patients who had taken oral contraceptives, glucocorticoids, antiandrogen agents, ovulation induction agents, diabetic drugs, or other steroid agents within 3 months.

Study Procedure

This prospective, randomized, open-label study was registered in the Chinese Clinical Trial Registry Center (ChiCTR-TRC-13003642). The ethics committee of the West China Second University Hospital of Sichuan University approved this study (no. 2010-016), and informed consent was obtained from each participant.

Calculation of the sample size was based on a predicted mean difference in HOMA-IR of 0.7 between metformin alone and metformin plus rosiglitazone in previous data (22) using the PASS (power analysis and sample size) system (23). To determine that an analysis of variance would have 80% power ($\beta = 0.2$) to detect a statistically significant difference (two-tailed P value of 0.05), each group consisted of 51 cases, assuming a common standard deviation of 1.25. A sample of 204 cases was finally planned with an expected 15% loss of follow-up and 10% withdrawals.

Medical information from all participants was reviewed. Data on the age of menarche, duration of menstrual periods, menstrual cycle, fertility desires, and history of infertility was recorded. Oligomenorrhea was defined as menstrual cycle lasting more than 35 days or a menstrual pattern of fewer than eight periods per year. Amenorrhea was defined as the absence of menstruation for more than 6 months or absence of menses over three periods according to the woman's original menstrual cycle. Abnormal uterine bleeding was defined as bleeding from the uterine corpus that was abnormal in volume, regularity, and/or timing in nonpregnant women. Infertility was identified when a couple had failed to achieve a pregnancy in regular and noncontraceptive intercourse over at least 1 year.

Androgen-related symptoms of hirsutism and acne were evaluated based on the modified Ferriman-Gallwey (mF-G) scale (24) and the Global Acne Grading System (GAGS) (25), respectively. Hirsutism was defined as a total mF-G score of ≥ 5 in Chinese women (26), and acne severity was graded

as none (total score: 0 points), mild (1–18 points), moderate (19–30 points), severe (31–38 points), or very severe (>38 points).

All participants underwent body height and weight measurements while wearing light clothing in bare feet. An inextensible anthropometric tape was used to gauge waist circumference and hip circumference while the participants stood erect with arms at their sides and feet positioned close together. We calculated BMI as the body weight (kg) divided by the square of the body height (m^2). We defined abdominal obesity as a waist circumference of greater than 80 cm according to the World Health Organization's criteria for obesity in the Asian population (20).

Peripheral blood samples were collected from participants' elbow veins after a 12-hour overnight fasting in the early follicular phase (days 3–5) of a spontaneous menstrual cycle or progestin-induced withdrawal bleeding in the case of amenorrhea. Serum levels of estradiol, progesterone, testosterone, luteinizing hormone, follicle-stimulating hormone, prolactin, and fasting insulin (FINS) were measured using chemiluminescent immunoassay (ADVIA Centaur; Siemens) with intra- and interassay variability less than 5.0%. Fasting glucose (FPG) was measured by the hexokinase method (ADVI2400; Siemens) with intra- and interassay variability less than 2.5%. We calculated HOMA-IR using the following equation: FINS (mIU/L) × FPG (mmol/L)/22.5. The levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL), and high-density cholesterol (HDL) were measured by an enzymatic method (ADVI 2400; Siemens) with intra- and interassay variability less than 7.5%. The predicted risks (TC/HDL and LDL/HDL ratio) of cardiovascular disease also were calculated.

A total of 204 eligible women with a PCOS diagnosis were randomly allocated to the treatment group according to computer-generated random numbers, using a block randomization method (1:1:1) with random block size of 6 or 10. Group 1 comprised 68 participants who received an oral administration of metformin at 1,500 mg/day. Group 2 comprised 67 participants who received an oral administration of rosiglitazone at 4 mg/day. Group 3 comprised 69 participants who received metformin at 1,000 mg/day plus rosiglitazone at 4 mg/day. The therapy continued for 6 months. The participants were prescribed oral micronized progesterone capsules (Yimaxin, Zhejiang Xianju Pharmaceutical) at 200 mg/day continuously for 10 days to induce withdrawal bleeding when the menstrual cycle lasted beyond 2 months.

During the study, all participants were advised to undergo lifestyle modification, including dietary adjustments and moderate-strength physical exercises three times a week for 40 minutes per session. They were asked to record their daily dietary and exercise activities, which were monitored through hospital visits, phone messages, or a WeChat mobile application. The investigators provided timely query resolution and advice according to the monthly feedback of the participants. Meanwhile, the participants were asked to use barrier contraception to avoid conception during intercourse.

Follow-up was performed to evaluate their clinical (menstrual status, mF-G and GAGS score) and anthropometric (body weight and waist and hip circumference) parameters at months 3 and 6 of the study. The hormone and metabolic parameters of all participants were measured at the 6-month follow-up evaluation.

Statistical Analysis

The intention-to-treat analysis included all randomized participants (n = 204). All data were analyzed using SPSS software (version 19.0; IBM). The continuous variables are expressed as mean ± standard deviation (SD) or 95% confidence intervals, and discrete quantitative variables are expressed as median values (P25, P75). We have assessed the data for normality using the Shapiro-Wilk test. For continuous variables with normal distribution, a paired sample *t*-test was performed to compare between the pretreatment and posttreatment parameters within a group. A one-way analysis of variance was performed for comparison among three groups. Bonferroni's test was used as the post hoc test.

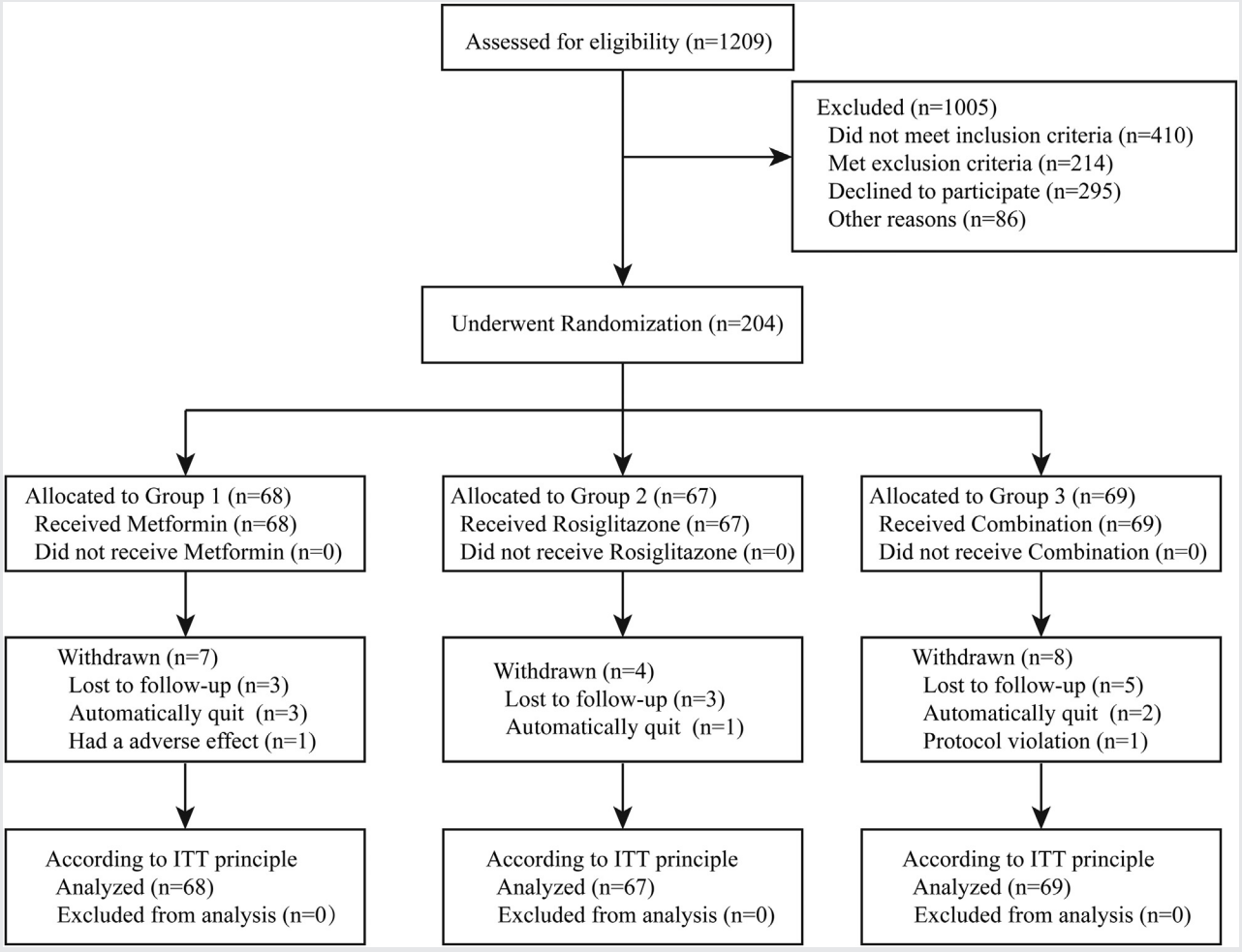
For continuous variables without normal distribution or discrete quantitative variables, the Wilcoxon signed-rank test was performed for comparisons between pretreatment and posttreatment parameters within a group. The Kruskal-Wallis test was applied to assess differences among the three groups. If values were statistically significant, the option of pairwise comparisons in SPSS was selected as the post hoc test. Except for multiple comparisons, a two-tailed $P < .05$ was considered statistically significant. For multiple comparisons, $P < .025$ was considered statistically significant.

RESULTS

From December 2013 to September 2016, 1,209 women received a PCOS diagnosis at our outpatient clinic. Among these patients, 204 matched the inclusion criteria and were enrolled in our study. Nineteen patients withdrew from the study, and the remaining 185 patients completed the study. The participant flow is described in Figure 1.

Most participants experienced menstrual disturbances such as oligomenorrhea (n = 106) and amenorrhea (n = 89). Sixty-three patients had hirsutism with an mF-G score of 3 (0, 6), 125 women had acne with a GAGS score of 8 (0, 25), and 91 married women had failed to conceive within 1 year. The mean (minimum–maximum) age and the age of menarche among the 204 participants was 25.95 ± 4.36 (18–35) years and 12.49 ± 1.08 (11–14) years, respectively. The mean body weight, height, and BMI were 69.96 ± 8.62 (50–98.40) kg, 159.14 ± 5.70 (140–172) cm, and 27.54 ± 2.21 (25.00–34.96) kg/m^2, respectively. The mean waist circumference, hip circumference, and waist-to-hip ratio (WHR) were 93.14 ± 7.48 (78–120) cm, 100.35 ± 5.74 (89–118) cm, and 0.93 ± 0.06 (0.78–1.08), respectively. Of the 204 participants, the 182 (89.21%) with waist circumferences of greater than 80 cm were considered to have abdominal obesity. The mean serum testosterone level was 0.65 ± 0.22(0.10–1.17) ng/mL. The mean FPG, FINS, and HOMA-IR were 5.47 ± 0.46 (4.23–6.90) mmol/L, 22.45 ± 8.21 (9.53–55.49) mIU/L, and 5.41 ± 2.15 (2.83–11.32), respectively. The mean TC, TG, HDL, and LDL levels were 4.54 ± 0.95 (1.12–6.17) mmol/L, 1.83 ± 0.61 (0.58–5.6) mmol/L, 1.31 ±

FIGURE 1



Flow diagram of the randomized controlled trial. Progress of the randomized controlled trial includes recruitment, enrollment, randomization, withdrawal, and completion.

Li. Insulin sensitizers in obese PCOS women. Fertil Steril 2019.

0.23 (0.72–2.60) mmol/L, and 2.93 ± 0.69 (0.96–4.59) mmol/L, respectively. In addition, the basic clinical, endocrine, and metabolite characteristics showed no statistically significant differences among the three study groups (Table 1).

After 6 months of treatment, the menstrual pattern showed improvements in most participants ($P<.001$), but the difference among the three groups was not statistically significant. The mF-G score decreased although the difference was not statistically significant. The decrease in GAGS scores was statistically significant in each group ($P<.001$). The decreases in mF-G and GAGS were not statistically significantly different among the three groups ($P>.05$). The body weight, BMI, waist circumference, WHR, serum testosterone level, and metabolic parameters (FPG, FINS, HOMA-IR, TC, TG, LDL, TC/HDL, and LDL/HDL) statistically significantly decreased in all three groups except for HDL levels, which were elevated (Table 2).

The waist circumference, WHR, FPG, FINS, and HOMA-IR evidently decreased after 6 months of treatment, but there were no statistically significant differences among the three groups. The body weight and BMI in group 1 were statistically significantly decreased compared with those in the two other groups ($P<.025$). The serum testosterone level in group 2 declined less compared with that of the two other groups ($P<.025$). The plasma TC and TG levels in the rosiglitazone users (groups 2 and 3) statistically significantly decreased compared with the levels in the patients who received only metformin (group 1). However, the decrease in the TC/HDL and LDL/HDL ratios showed no difference between the rosiglitazone users and metformin users (Table 3). The above comparisons within a group and between groups were based on intention-to-treat analysis.

All patients were instructed to take metformin at an initial dosage of 500 mg/day and gradually add 500 mg every week. At the beginning of metformin administration, 17 patients experienced mild gastrointestinal symptoms, which disappeared within 3 days. When metformin was administered at a dosage of 1,000 mg/day, 37 patients encountered

TABLE 1

The baseline characteristics of 204 obese women with PCOS and insulin resistance.

Characteristic	Group 1 (n = 68)	Group 2 (n = 67)	Group 3 (n = 69)
Age (y)	25.84 ± 4.48	26.04 ± 4.49	25.96 ± 4.02
Menarche age (y)	12.32 ± 0.85	12.31 ± 0.79	12.84 ± 0.74
Menstrual cycle (d)	65.25 ± 20.42	65.04 ± 21.08	67.48 ± 22.74
Weight (kg)	70.04 ± 8.08	69.82 ± 9.58	70.01 ± 8.27
Height (cm)	158.81 ± 6.06	158.78 ± 6.41	159.83 ± 4.49
BMI (kg/m^2)	27.70 ± 2.05	27.59 ± 2.41	27.33 ± 2.17
Waist circumference (cm)	93.40 ± 7.25	93.08 ± 7.72	92.95 ± 7.58
Hip circumference (cm)	100.55 ± 5.41	100.36 ± 5.41	100.15 ± 5.68
WHR	0.93 ± 0.062	0.93 ± 0.057	0.93 ± 0.060
mF-G	3 (0, 6)	3 (0, 6)	3 (0, 6)
GAGS	8 (0, 25)	8 (0, 27)	9 (0, 25)
E_2 (pg/mL)	47.33 ± 14.64	47.56 ± 12.73	47.93 ± 11.50
P (ng/mL)	0.58 ± 0.22	0.54 ± 0.11	0.59 ± 0.12
PRL (ng/mL)	11.73 ± 3.87	11.88 ± 4.39	11.54 ± 4.12
LH (mU/mL)	9.98 ± 3.42	9.89 ± 4.02	10.10 ± 4.06
FSH (mU/mL)	5.81 ± 1.91	5.88 ± 1.84	6.03 ± 1.83
T (ng/mL)	0.66 ± 0.17	0.65 ± 0.25	0.65 ± 0.25
FPG (mmol/L)	5.38 ± 0.41	5.56 ± 0.51	5.47 ± 0.44
FINS (mIU/L)	22.56 ± 8.30	22.20 ± 8.75	22.57 ± 7.68
HOMA-IR	5.38 ± 1.96	5.56 ± 2.49	5.49 ± 2.00
TG (mmol/L)	1.81 ± 0.60	1.84 ± 0.62	1.83 ± 0.61
TC (mmol/L)	4.54 ± 0.92	4.57 ± 1.07	4.50 ± 0.87
LDL (mmol/L)	2.92 ± 0.79	2.94 ± 0.68	2.94 ± 0.58
HDL (mmol/L)	1.29 ± 0.19	1.33 ± 0.24	1.31 ± 0.26
TC/HDL	3.50 ± 0.39	3.40 ± 0.58	3.48 ± 0.63
LDL/HDL	2.23 ± 0.36	2.22 ± 0.49	2.28 ± 0.51

Note: Values are mean ± standard deviation or median and interquartile range. BMI = body mass index; E_2 = estradiol; FSH = follicle-stimulating hormone; FINS = fasting insulin; FPG = fasting plasma glucose; GAGS = global acne grading system; HDL = high-density cholesterol lipoprotein; HOMA-IR = homeostatic model assessment of insulin resistance; LDL = low-density cholesterol lipoprotein; LH = luteinizing hormone; mF-G = modified Ferriman–Gallwey; P = progesterone; PCOS = polycystic ovary syndrome; PRL = prolactin; T = testosterone; TC = total cholesterol; TG = triglycerides; WHR = waist-to-hip ratio.

Li. Insulin sensitizers in obese PCOS women. Fertil Steril 2019.

mild, bearable gastrointestinal symptoms that lasted 1 to 3 weeks. When metformin was administered at a dosage of 1,500 mg/day, 51 patients experienced nausea, loss of appetite, diarrhea, and dizziness. Most of these patients gradually adapted within 1 to 5 weeks, except for one patient who could not tolerate a dosage of 1,500 mg/day and withdrew from our study with a dosage reduced to 1,000 mg/day. No side effects related to rosiglitazone were reported throughout the study.

TABLE 2

The clinical, hormonal, and metabolic parameters of 204 obese women with PCOS and insulin resistance after 6 months insulin-sensitizers plus lifestyle modification.

Parameter	Group 1 (n = 68)	Group 2 (n = 67)	Group 3 (n = 69)
Menstrual cycle (d)	46.19 ± 13.35[a]	45.07 ± 17.50[a]	43.65 ± 15.14[a]
Weight (kg)	63.23 ± 7.01[a]	66.42 ± 8.03[a]	66.47 ± 8.10[a]
BMI (kg/m^2)	25.02 ± 1.86[a]	26.27 ± 1.93[a]	25.94 ± 2.22[a]
Waist circumference (cm)	89.55 ± 7.50[a]	90.32 ± 7.07[a]	90.28 ± 7.07[a]
WHR	0.89 ± 0.060[a]	0.90 ± 0.052[a]	0.90 ± 0.058[a]
mF-G	2 (0, 6)	2 (0, 6)	2 (0, 6)
GAGS	0 (0, 16)[a]	2 (0, 17)[a]	0 (0, 15)[a]
T (ng/mL)	0.50 ± 0.18[a]	0.53 ± 0.20[a]	0.46 ± 0.19[a]
FPG (mmol/L)	5.09 ± 0.34[a]	5.20 ± 0.65[a]	5.14 ± 0.58[a]
FINS (mIU/L)	15.97 ± 5.74[a]	15.77 ± 4.37[a]	15.65 ± 5.17[a]
HOMA-IR	3.61 ± 1.31[a]	3.70 ± 1.34[a]	3.63 ± 1.50[a]
TG (mmol/L)	1.47 ± 0.60[a]	1.32 ± 0.24[a]	1.29 ± 0.68[a]
TC (mmol/L)	4.10 ± 1.15[a]	4.05 ± 1.05[a]	3.78 ± 0.76[a]
LDL (mmol/L)	2.24 ± 0.82[a]	2.22 ± 0.66[a]	2.22 ± 0.79[a]
HDL (mmol/L)	1.48 ± 0.24[a]	1.48 ± 0.25[a]	1.38 ± 0.27[a]
TC/HDL	2.74 ± 0.60[a]	2.70 ± 0.49[a]	2.78 ± 0.63[a]
LDL/HDL	1.48 ± 0.42[a]	1.48 ± 0.29[a]	1.59 ± 0.71[a]

Note: Values are mean ± standard deviation or median and interquartile range. BMI = body mass index; FINS = fasting insulin; FPG = fasting plasma glucose; GAGS = global acne grading system; HDL = high-density cholesterol lipoprotein; HOMA-IR = homeostatic model assessment of insulin resistance; LDL = low-density cholesterol lipoprotein; mF-G = modified Ferriman–Gallwey; PCOS = polycystic ovary syndrome; T = testosterone; TC = total cholesterol; TG = triglycerides; WHR = waist-to-hip ratio.

[a] $P < .001$, statistically significant differences within group.

Li. Insulin sensitizers in obese PCOS women. Fertil Steril 2019.

TABLE 3

Changes in clinical, hormonal, and metabolic parameters for 204 obese women with PCOS and insulin resistance in the three different intervention groups.

Parameter	Group 1 (n = 68)	Group 2 (n = 67)	Group 3 (n = 69)
Menstrual cycle (d)	−19.06 (−21.80 to −16.31)	−19.97 (−23.13 to −16.81)	−23.83 (−27.46 to −20.19)
Weight (kg)[a]	−6.81 (−7.51 to −6.10)	−3.40 (−4.15 to −2.65)	−3.54 (−4.17 to −2.91)
BMI (kg/m^2)[a]	−2.68 (−2.94 to −2.41)	−1.32 (−1.60 to −1.04)	−1.38 (−1.63 to −1.14)
Waist circumference (cm)	−3.85 (−4.62 to −3.09)	−2.76 (−3.16 to −2.36)	−2.67 (−3.07 to −2.27)
WHR	−0.039 (−0.047 to −0.031)	−0.027 (−0.031 to −0.023)	−0.027 (−0.031 to −0.22)
mF-G	0 (0, 0)	0 (0, 0)	0 (0, 0)
GAGS	0 (−4, 0)	0 (−5, 0)	0 (−5, 0)
T (ng/mL)[b]	−0.161 (−0.178 to −0.145)	−0.125 (−0.142 to −0.107)	−0.187 (−0.212 to −0.161)
FPG (mmol/L)	−0.281 (−0.332 to −0.231)	−0.353 (−0.407 to −0.299)	−0.324 (−0.373 to −0.276)
FINS (mIU/L)	−6.585 (−7.757 to −5.414)	−6.426 (−7.844 to −5.008)	−6.924 (−8.049 to −5.799)
HOMA-IR	−1.769 (−2.056 to −1.482)	−1.858 (−2.249 to −1.467)	−1.866 (−2.164 to −1.567)
TG (mmol/L)[a]	−0.341 (−0.389 to −0.293)	−0.524 (−0.619 to −0.430)	−0.536 (−0.592 to −0.481)
TC (mmol/L)[c]	−0.437 (−0.506 to −0.368)	−0.520 (−0.576 to −0.464)	−0.722 (−0.797 to −0.647)
LDL (mmol/L)	−0.670 (−0.750 to −0.591)	−0.724 (−0.847 to −0.602)	−0.726 (−0.811 to −0.640)
HDL (mmol/L)[a,b,c]	0.193 (0.168 to 0.218)	0.147 (0.130 to 0.165)	0.071 (0.060 to 0.081)
TC/HDL	−0.756 (−0.838 to −0.674)	−0.703 (−0.762 to −0.645)	−0.701 (−0.774 to −0.628)
LDL/HDL	−0.747 (−0.827 to −0.667)	−0.740 (−0.851 to −0.629)	−0.659 (−0.735 to −0.584)

Note: Values are mean and 95% confidence interval or median and interquartile range. Statistically significant differences for multiple comparisons: $P < .025$. BMI = body mass index; FINS = fasting insulin; FPG = fasting plasma glucose; GAGS = global acne grading system; HDL = high-density cholesterol lipoprotein; HOMA-IR = homeostatic model assessment of insulin resistance; LDL = low-density cholesterol lipoprotein; mF-G = modified Ferriman–Gallwey; PCOS = polycystic ovary syndrome; T = testosterone; TC = total cholesterol; TG = triglycerides; WHR = waist-to-hip ratio.

[a] $P < .025$ for group 1 vs. group 2 and group 3.

[b] $P < .025$ for group 2 vs. group 1 and group 3.

[c] $P < .025$ for group 3 vs. group 1 and group 2.

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DISCUSSION

In this prospective, randomized, controlled study, we assessed the effects of different insulin sensitizers and lifestyle modifications on the clinical and endocrine-metabolic profiles of obese, insulin-resistant women with PCOS. As expected, the two types of insulin sensitizers not only improved the metabolic profiles but also recovered the menstrual pattern and lessened hyperandrogenism, with results consistent with previous reports (15, 17, 27). The anthropometric parameters such as weight, BMI, waist circumference, and WHR statistically significantly decreased in the three study groups; the remarkable decrease in BMI observed with the administration of rosiglitazone alone differed from that in previous reports (28, 29). A possible explanation may be the incorporation of additional dietary modification and physical activity.

Whether metformin or rosiglitazone is more strongly recommended for PCOS remains controversial. In 2004, Baillargeon et al. (29) showed statistically significant improvement in insulin sensitivity with metformin treatment in non-obese women with PCOS when compared with rosiglitazone. However, some studies showed that rosiglitazone improved insulin resistance better than metformin in women with PCOS (30, 31), with a greater effect on hyperandrogenism and menstrual pattern (32). Few studies have compared the effects of metformin, rosiglitazone, and combined metformin and rosiglitazone therapy (22, 29, 30). In our study, the combined administration of metformin and rosiglitazone for 6 months was not superior to individual administration for the amelioration of metabolic disturbances, which contrasts with the previous studies (22, 32).

It has been reported that metformin (1,500 mg/day) in conjunction with lifestyle management can statistically significantly reduce body weight; this effect has been attributed to the pharmacologic action of metformin on weight loss (33, 34). Meanwhile, lifestyle modification—including dietary adjustments and exercise activities—can also improve weight loss (2). In addition, severe but temporary gastrointestinal side effects caused by metformin at a dosage of 1,500 mg/day may result in rapid weight loss, although we found no statistically significant difference with women taking rosiglitazone alone or in combination with a lower dosage of metformin (1,000 mg/day). Besides ameliorating changes in glucose metabolic parameters, after 6 months of therapy rosiglitazone induced a greater decrease in plasma TC and TG levels (the latter, in particular), when used alone or in combination with metformin.

The ligand-activated transcription factor PPAR-γ, which regulates lipid and glucose metabolism, and rosiglitazone, a PPAR-γ agonist, can improve lipid metabolism in obese, insulin-resistant women with PCOS. A previous study reported that rosiglitazone did not improve parameters associated with lipid metabolism such as TC and TG when compared with placebo (35). The differences in that study may be due to the study population, sample size, or duration of regimen. However, our study revealed that the most substantial increase in plasma HDL level occurred in the metformin-only users, followed by the rosiglitazone-only users. The users of metformin and rosiglitazone in combination showed the lowest increase.

The risk predictors of cardiovascular disease including TC/HDL and LDL/HDL ratio showed no statistically significant difference among the three study groups. This indicates that their lipid metabolism was comparable after 6 months of therapy with different insulin sensitizers.

Our study sample size was calculated based on data sourced from previous studies, and our design was a

prospective, randomized, controlled study without blinding. This design may have introduced some bias into our study. A limitation of our study is that it was conducted at a single center; typically a multicentric study is preferred. In addition, we did not investigate the recovery of ovulation.

Considering the benefits of metformin on body weight loss, we suggest that metformin in conjunction with lifestyle modification should be considered as the first-line regimen for obese (BMI ≥ 25 kg/m^2) and insulin-resistant Chinese women with PCOS, to manage endocrine and metabolic disorders and further modify the menstrual pattern. Rosiglitazone alone or in combination with low-dosage metformin should be recommended to those with abnormal plasma lipid levels, as the plasma TC and TG profiles were statistically significantly reduced after 6 months of treatment with rosiglitazone.

REFERENCES

1. Li R, Zhang Q, Yang D, Li S, Lu S, Wu X, et al. Prevalence of polycystic ovary syndrome in women in China: a large community-based study. Hum Reprod 2013;28:2562–9.
2. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Clin Endocrinol 2018; 40:188–95.
3. Teede HJ, Joham AE, Paul E, Moran LJ, Loxton D, Jolley D, et al. Longitudinal weight gain in women identified with polycystic ovary syndrome: results of an observational study in young women. Obesity (Silver Spring) 2013;21: 1526–32.
4. Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2012;18:618–37.
5. Vrbikova J, Hainer V. Obesity and polycystic ovary syndrome. Obes Facts 2009;2:26–35.
6. Stepto NK, Cassar S, Joham AE, Hutchison SK, Harrison CL, Goldstein RF, et al. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic-hyperinsulaemic clamp. Hum Reprod 2013;28:777–84.
7. Liou TH, Yang JH, Hsieh CH, Lee CY, Hsu CS, Hsu MI. Clinical and biochemical presentations of polycystic ovary syndrome among obese and nonobese women. Fertil Steril 2009;92:1960–5.
8. Chen L, Xu WM, Zhang D. Association of abdominal obesity, insulin resistance, and oxidative stress in adipose tissue in women with polycystic ovary syndrome. Fertil Steril 2014;102:1167–74.e4.
9. Lim SS, Norman RJ, Davies MJ, Moran LJ. The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. Obes Rev 2013;14: 95–109.
10. Kataoka J, Tassone EC, Misso M, Joham AE, Stener-Victorin E, Teede H, et al. Weight management interventions in women with and without PCOS: a systematic review. Nutrients 2017;9:996.
11. Pasquali R. Metformin in women with PCOS. Endocrine 2015;48:422–6.
12. Naderpoor N, Shorakae S, de Courten B, Misso ML, Moran LJ, Teede HJ. Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. Hum Reprod Update 2015;21:560–74.
13. Sun X, Zhang D, Zhang W. Effect of metformin on ovulation and reproductive outcomes in women with polycystic ovary syndrome: a meta-analysis of randomized controlled trials. Arch Gynecol Obstet 2013;288:423–30.
14. Liu Q, Li S, Quan H, Li J. Vitamin B12 status in metformin treated patients: systematic review. PLoS One 2014;9:e100379.
15. Lam PM, Tam WH, Ma RC, Cheung LP, Tsui MH, Tong PC, et al. The reproductive and metabolic effect of rosiglitazone on Chinese women with polycystic ovarian syndrome—a double-blind randomized placebo-controlled study. Fertil Steril 2011;96:445–51.
16. Sepilian V, Nagamani M. Effects of rosiglitazone in obese women with polycystic ovary syndrome and severe insulin resistance. J Clin Endocrinol Metab 2005;90:60–5.
17. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitizing drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligomenorrhoea and subfertility. Cochrane Database Syst Rev 2012;5:CD003053.
18. Mitkov M, Pehlivanov B, Terzieva D. Metformin versus rosiglitazone in the treatment of polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2006;126:93–8.
19. The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19:41–7.
20. World Health Organization Western Pacific Region, IASO IOTF. The Asia Pacific perspective: redefining obesity and its treatment. Sydney, Australia: Health Communications Australia; 2000.
21. Bonora E, Targher G, Alberiohe M, Nonadonna RC, Saggiani F, Zeners MB, et al. Homeostasis model assessment closely mirrors the glucose clamp techniques in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Dibetes Care 2000;23: 57–63.
22. Liao L, Tian YJ, Zhao JJ, Xin Y, Xing HY, Dong JJ. Metformin versus metformin plus rosiglitazone in women with polycystic ovary syndrome. Chin Med J 2011;124:714–8.
23. Machin D, Campbell MJ, Tan SB, Tan SH. Sample size tables for clinical studies. 2th ed. Oxford: Blackwell Science; 1997.
24. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. J Clin Endocrinol Metab 1961;21:1440–7.
25. Doshi A, Zahheer A, Stiller MJ. A comparison of current acne grading systems and proposal of a novel system. Int J Dermatol 1997;36:416–8.
26. Zhao X, Ni R, Li L, Mo Y, Huang J, Huang M, et al. Defining hirsutism in Chinese women: a cross-sectional study. Fertil Steril 2011;96:792–6.
27. Ito-Yamaguchi A, Suganuma R, Kumagami A, Hashimoto S, Yoshida-Komiya H, Fujimori K. Effects of metformin on endocrine, metabolic milieus and endometrial expression of androgen receptor in patients with polycystic ovary syndrome. Gynecol Endocrinol 2015;31:44–7.
28. Yilmaz M, Karakoc A, Toruner FB, Cakir N, Tiras B, Ayvaz G, et al. The effects of rosiglitazone and metformin on menstrual cyclicity and hirsutism in polycystic ovary syndrome. Gynecol Endocrinol 2005;21:154–60.
29. Baillargeon JP, Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Nestler JE. Effects of metformin and rosiglitazone, alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity. Fertil Steril 2004;82:893–902.
30. Legro RS, Zaino RJ, Demers LM, Kunselman AR, Gnatuk CL, Williams NI, et al. The effects of metformin and rosiglitazone, alone and in combination, on the ovary and endometrium in polycystic ovary syndrome. Am J Obstet Gynecol 2007;196:402.e1–10.
31. Steiner CA, Janez A, Jensterle M, Reisinger K, Forst T, Pfützner A. Impact of treatment with rosiglitazone or metformin on biomarkers for insulin resistance and metabolic syndrome in patients with polycystic ovary syndrome. J Diabetes Sci Tech 2007;1:211–7.
32. Yilmaz M, Biri A, Karakoç A, Törüner F, Bingöl B, Cakir N, et al. The effects of rosiglitazone and metformin on insulin resistance and serum androgen levels in obese and lean patients with polycystic ovary syndrome. J Endocrinol Invest 2005;28:1003–8.
33. Lee A, Morley JE. Metformin decreases food consumption and induces weight loss in subjects with obesity with type II non-insulin-dependent diabetes. Obes Res 1998;6:47–53.
34. Malin SK, Kashyap SR. Effects of metformin on weight loss: potential mechanisms. Curr Opin Endocrinol Diabetes Obes 2014;21:323–9.
35. Rautio K, Tampanainen JS, Ruokonen A, Morin-Papunen LC. Endocrine and metabolic effect of rosiglitazone in overweight women with polycystic ovary syndrome: a randomized placebo-controlled study. Hum Reprod 2006;21: 1400–7.