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ROLE OF INSULIN SENSITIZERS ON CARDIOVASCULAR RISK FACTORS IN POLYCYSTIC OVARIAN SYNDROME: A META-ANALYSIS

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Abstract

Objective: Polycystic ovarian syndrome (PCOS) is associated with an increase in cardiovascular (CV) risk factors such as insulin resistance, with accompanying hyperinsulinemia and hyperlipidemia, which are predisposing factors for type 2 diabetes mellitus and CV disease. The aim of this meta-analysis is to examine the effect of insulin sensitizers on clinical and biochemical features of PCOS and risk factors for CV disease.

Methods: A systematic literature review was conducted, and randomized controlled clinical trials were identified by a search of bibliographic databases: Medline database (from 1966 forward), EMBASE (January 1985 forward), and Cochrane Central Register of Controlled Trials. Reviews of reference lists further identified candidate trials. Data was independently abstracted in duplicate by 2 investigators using a standardized data-collection form. Articles without a comparison group and randomization allocation were excluded. Reviewers worked independently and in duplicate to determine the methodological quality of trials, then collected data on patient characteristics, interventions, and outcomes.

Results: Of 455 studies, 44 trials were eligible. A random effects model was used. Significant unadjusted results favoring treatment with insulin sensitizers were obtained for body mass index (BMI) (effect size [ES] of 0.58), waist to hip ratio (WHR) (ES of 0.02), low-density-lipoprotein cholesterol (LDL-C) (ES of 0.11), fasting insulin (ES of 2.82), fasting glucose (ES of 0.10), free testosterone (ES of 1.88), and androstenedione level (ES of 0.76).

Conclusion: Treatment with insulin sensitizers in women with PCOS results in improvement in CV factors such as BMI, WHR, LDL-C, fasting insulin, glucose, free testosterone, and androstenedione.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is an endocrine disorder characterized by oligo- or anovulation, biochemical or clinical hyperandrogenism, and polycystic ovarian morphology on ultrasound (1). PCOS is associated with an increase in cardiovascular risk factors such as insulin resistance (IR), with accompanying hyperinsulinemia, elevated lipid levels, central obesity, increased C-reactive protein, and changes in blood pressure. PCOS affects 5 to 10% of women of reproductive age (2–5) and is the most common cause of infertility in 5% of this age group (6). PCOS is also a common cause of early pregnancy loss (7) and pregnancy complications (8). IR, hyperinsulinemia, and obesity are the predisposing factors for type 2 diabetes mellitus (DM) and cardiovascular disease (CVD) in women with PCOS. Women with PCOS have a 7 to 10% increase in DM (9,10), decreased high-density-lipoprotein (HDL) cholesterol (HDL-C), increased low-density-lipoprotein (LDL) cholesterol (LDL-C) (11,12), increased triglycerides (TGs) (13,14), and increased risk of hypertension (15).

The primary abnormality affecting most women with PCOS is IR, which also plays a pathogenic role in metabolic syndrome (16–18). The prevalence of the metabolic syndrome in PCOS is 43 to 47% (19). Intra-abdominal fat accumulation plays an important role in the development of IR (20); features of PCOS such as IR and hyperandrogenism are found more in cases of obese women than in lean women (21). Hyperinsulinemia causes hyperandrogenemia by decreasing the level of sex hormone-binding globulin and increasing the gonadotropin-releasing hormone (GnRH)-stimulated release of luteinizing hormone (LH). According to Legro et al (10), the prevalence of metabolic abnormalities and cardiovascular risk factors is greater in women with PCOS as compared to those without PCOS. Given the above metabolic and phenotypic profile, women with PCOS are more prone to CVD (22). The Endocrine Society's clinical guidelines recommend the use of exercise therapy and calorie-restricted diets in the management of body weight in PCOS patients, as weight loss is likely beneficial for both reproductive and metabolic dysfunction in PCOS. Nonpharmacologic measures such as exercise, weight loss, and diet control have been shown to improve IR and ovulatory function (23) but are subject to short-and long-term nonadherence. The Endocrine Society's guidelines (24) also discourage the use of metformin as a first-line treatment for obesity management, prevention of pregnancy complications, or treatment of cutaneous manifestations in PCOS. Per the guidelines, metformin is recommended only for women with PCOS who have type 2 DM or impaired glucose tolerance and for whom lifestyle modification is insufficient. For women with PCOS who have menstrual irregularities but are unable to tolerate hormonal contraceptives, metformin is suggested as second-line therapy. Insulin sensitizers play a prime role in PCOS, as treating IR may lead to improvement in anovulation, hyperandrogenism, weight loss, and dyslipidemia. Two groups of insulin-sensitizer drugs, namely biguanide (metformin) and thiazolidinediones (TZDs) (rosiglitazone and pioglitazone) are used for treating IR in PCOS. Subsequent to the meta-analysis (25) reporting safety concerns about the use of rosiglitazone leading to cardiovascular morbidity, there has been concern associated with the use of TZDs. In addition to improving IR, TZDs have been shown to improve hyperandrogenemia (26,27). The first study showing efficacy of metformin in PCOS was published more than a decade ago (28).

The various outcomes studied with the treatment of PCOS include resumption of menstrual cycles, ovulation, and hirsutism. Small studies have shown mixed results regarding the impact of short-term treatment of PCOS on cardiovascular risk factors. In the absence of any long-term studies on the effect of metformin and/or TZDs in women with PCOS, neither metformin nor the TZDs emerge as the definitive drug of choice. This meta-analysis was conducted to investigate the evidence regarding the effect of insulin sensitizers on cardiovascular and DM risk factors in women with PCOS.

METHODS

Data collection was conducted by means of a systematic examination of all randomized control trials investigating the relationship between insulin-sensitizing drugs (metformin, rosiglitazone, and pioglitazone) and PCOS. Because the classification and diagnosis of PCOS have changed through the years, we included only studies involving cases diagnosed using the standard criteria for the time of the study (either 1990 National Institutes of Health criteria or 2003 Rotterdam criteria). Articles with net mean changes in clinical and/or biochemical outcomes such as weight, blood pressure, LDL, HDL, TGs, ovulation rate, LH to follicle-stimulating hormone (FSH) ratio, fasting insulin levels, testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS) with their corresponding variance or equivalent reported were selected. Articles lacking a comparison group and randomization allocation were excluded. Additionally, we excluded editorials, letters, and review articles. If the results of a study were published more than once, only those results from the most recent or complete article were included in our analyses.

Literature Search Strategy

All relevant published and unpublished clinical trials were identified by a search of bibliographic databases and hand search of relevant articles. The search was restricted to include only human studies. A search of the Medline database (from 1966 forward), Excerpta Medica database (January 1985 forward), and Cochrane Central Register of Controlled Trials was conducted using the medical subject headings “polycystic ovary syndrome,” “hyperandrogenism,” “hyperinsulinemia,” “plasminogen activator inhibitor-I,” “metformin,” “biguanide,” “thiazolidinediones,” “pioglitazone,” “rosiglitazone,” and the key words “glucophage,” “Actos,” and “Avandia.” Troglitazone was excluded, as it has been discontinued. The title and abstract of all identified articles were reviewed and those deemed ineligible were excluded. Articles that appeared to meet the above inclusion criteria were retrieved and reviewed. Two investigators from the group reviewed all potentially relevant studies independently. In selecting studies to use in the analysis, the above inclusion and exclusion criteria as listed in the “Methods” section were followed.

Data were independently abstracted in duplicate by 2 investigators using a standardized data-collection form. Discrepancies between investigators were resolved by discussion and by a third investigator who adjudicated any discrepancies. The data collected included: title, primary author’s name, year and source of publication, country of origin, study design (i.e., parallel or cross-over, open or single, or double blind), characteristics of the study population (sample size, comorbidity, distribution according to age, sex, and race,

inflammatory markers), duration of intervention, type of control used, and drug information. Data on clinical and biochemical parameters included mean baseline and net change values for blood pressure, weight, body mass index (BMI), waist to hip ratio (WHR), LDL, HDL, TGs, fasting insulin levels, fasting glucose levels, LH, FSH, LH:FSH ratio, testosterone, androstenedione, and DHEAS. Data were also obtained on the assessment of cardiovascular events, and the relative risk (or hazard ratio or odds ratio) of CVD events associated with this therapy and corresponding confidence interval, overall and for any subgroups. Figure 1 shows the PRISMA flowchart highlighting the literature search and included studies.

Statistical Analysis

For each analysis, data were converted to the same metric unit based on conversion formulas provided by each individual trial. The conversion factors were verified by standard clinical and reference laboratory values. Some trials provided SD, whereas others provided SE or SEM. Pooled variances were derived accordingly. We converted all SEs to SDs using the equation $SD = SE \times \sqrt{N}$, where N represents the sample size. Trials that did not report SD, SE, or sample variance for a given parameter were not included. We did not conduct a statistical analysis if only a small number of trials existed (i.e., $n < 5$), as it would result in less reliable conclusions.

Most of the studies presented results before and after treatment. We calculated the pooled estimates of treatment effect with 95% confidence interval (CI) for the standardized mean differences between the control and intervention arms after treatment. The arm receiving treatment with an insulin sensitizer was defined as the treatment arm, whereas the arm receiving treatment with other medical agents was defined as the control arm. We are reporting effect size (ES) to describe the standardized mean difference seen between the treatment and control groups. Results from a random effect model are reported (29). Statistical significance was evaluated for treatment effect and heterogeneity. The random effects model takes heterogeneity into account. Statistical analyses were carried out using STATA software, version 10.1.

RESULTS

There were many different treatment medications used in the control arm. The treatment measures included use of metformin, rosiglitazone, and pioglitazone, whereas the comparison groups included use of placebo, ethinyl estradiol (EE), EE + cyproterone acetate (CA), clomiphene citrate (CC), the GnRH goserelin, diet, exenatide, orlistat, spironolactone, and flutamide. A summary of different comparison groups used in this study is given in Table 1. The sample size of these studies ranged from 10 to 626 patients. None of the included studies had results on cardiovascular event outcomes. Only 6 studies had the TZDs rosiglitazone or pioglitazone in the treatment arm in our analysis. The remaining 38 studies had metformin as a single drug or in combination with other therapy, such as CC, EE + CA, and flutamide + oral contraceptive pills. Of the outcomes we evaluated, statistically significant results were obtained for BMI, WHR, LDL, fasting insulin, fasting glucose, free testosterone, and androstenedione with the use of insulin sensitizer. Table 1 also lists the characteristics of the 44 studies (6,30–72) that were used in the analyses.

Results of the ESs (all the studies [metformin and TZDs in the treatment group] were included) for all the variables in all the studies combined are presented in Figure 2. Remaining results of the ESs for individual variables are presented in Supplementary Figures 1 through 22. Analysis of 34 studies for BMI (Supplementary Fig. 1) resulted in an ES of 0.58 (95% CI, 0.17 to 0.98) favoring treatment with insulin sensitizers as compared to control treatments. This means the average subject in the treatment group lowered their BMI by 0.58 SEs when compared to the average subject in the control group. Analysis of the WHR in 20 studies revealed an ES of 0.02 (95% CI, 0.01 to 0.03) favoring treatment with insulin sensitizers (see Fig. 3). LDL-C (Supplementary Fig. 2) was analyzed in 17 studies and showed an ES of 0.11 (95% CI, 0.02 to 0.21) in favor of insulin sensitizers. Results favoring treatment with insulin sensitizers were obtained for fasting insulin (Supplementary Fig. 3), with an ES of 2.82 (95% CI, 1.13 to 4.52) from 32 studies. There was an ES of 0.10 (95% CI, 0.03 to 0.16) in fasting glucose (Supplementary Fig. 4) from an analysis of 26 studies, as expected, given that the action of insulin sensitizers is to decrease glucose level. Analysis of 14 studies showed a significant ES of 1.88 (95% CI, 0.58 to 3.18) for free testosterone (Supplementary Fig. 5) after treatment with insulin sensitizers. There was an ES of 0.76 (95% CI, 0.18 to 1.35) for androstenedione levels (Supplementary Fig. 6) from analysis of 19 studies. Metformin and TZDs are insulin sensitizers but do have different pleiotropic effects. To assess if there would be a difference in the results seen, we divided the studies according to whether it was metformin (n = 38) or TZD (n = 6) in the treatment arm. Results of the metformin-adjusted ES for all the variables are presented in Figure 4. In the studies using metformin, there was a significant ES favoring use of metformin for BMI (0.61; 95% CI, 0.18 to 1.03), WHR (0.02; 95% CI, 0.01 to 0.03), fasting insulin (2.59; 95% CI, 0.93 to 4.24), fasting glucose (0.08; 95% CI, 0.004 to 0.15), free testosterone (2.29; 95% CI, 0.86 to 3.73), and androstenedione (0.84; 95% CI, 0.24 to 1.43). The ES for LDL-C was no longer significant as seen in the combined metformin and TZD analysis. Results from the studies using TZDs (Fig. 5) in the treatment arm revealed that there was a significant ES for total cholesterol (0.2; 95% CI, 0.18 to 0.22), LDL-C (0.11; 95% CI, 0.09 to 0.13), and fasting glucose (0.23; 95% CI, 0.04 to 0.42) favoring use of TZDs. BMI, WHR, fasting insulin, free testosterone, and androstenedione were no longer significant.

The studies used in the meta-analysis had different agents used in the control arm of the studies. Considering the differing effects of the various medications used in the control arm of the studies, we further subgrouped the studies as follows: the placebo control group (n = 16), in which the control arm was a true placebo; the gonadotropin control group (n = 19), in which the studies used agents that act upon the GnRH axis in the control arm; and an anorexic agent treatment group (n = 3), in which agents or diets that lead to weight loss were used. Additionally, there were 6 studies that used more than one agent in the control arm, which were categorized in the combination group. In the placebo control group (results for all variables presented in Supplementary Fig. 7), significant ESs were seen for total cholesterol (0.12; 95% CI, 0.18 to 0.22), LDL-C (0.11; 95% CI, 0.09 to 0.13), and LH (0.59; 95% CI, 0.33 to 0.87) favoring treatment with insulin sensitizers (both metformin and TZDs combined). In the group of studies using agents affecting the GnRH axis, there were significant ESs seen for (see Supplementary Fig. 8) BMI (0.26; 95% CI, 0.48 to 2.05), WHR

(0.027; 95% CI, 0.01 to 0.05), fasting insulin (3.94; 95% CI, 1.45 to 6.43), and fasting glucose (0.17; 95% CI, 0.02 to 0.32). In the combination agents (without the anorexigenic agent studies) control group (Supplementary Fig. 9), significant ESs were obtained for HDL-C (0.46; 95% CI, 0.2 to 0.71) and free testosterone (15.25; 95% CI, 3.77 to 26.34) favoring treatment with the insulin sensitizers. In the anorexigenic agent control group (Supplementary Fig. 10), analyses did not show any significant benefit of treatment with these drugs on any of the parameters. Because there were only 3 studies in the anorexigenic agent treatment group, we combined these studies in the combination treatment group to see if inclusion of those studies would make a difference. In this group (Supplementary Fig. 11), a significant ES favoring the treatment arm was seen only for free testosterone (15.25; 95% CI, 3.76 to 26.74).

DISCUSSION

This meta-analysis demonstrates that treatment with insulin sensitizers (both metformin and TZDs combined) in women with PCOS resulted in improvement in BMI, WHR, LDL, fasting insulin, glucose, free testosterone, and androstenedione levels. Treatment with metformin resulted in significant change in BMI, WHR, fasting insulin and glucose, free testosterone, and androstenedione levels. In the TZD treatment group, favorable results were obtained for total cholesterol, LDL, and fasting glucose only. IR is the primary abnormality seen in women with PCOS. Intra-abdominal fat plays an important role in the development of IR, which is also associated with changes in lipids. The hallmark biochemical abnormality of IR is hypertriglyceridemia and low plasma HDL-C concentration. Plasma LDL-C concentrations in insulin-resistant subjects are the same as those in insulin-sensitive subjects; however, there is a qualitative change in LDL-C, resulting in “pattern B” distribution of LDL particles. This consists of smaller LDL particles that are more susceptible to oxidation and thus potentially more atherogenic. IR is also associated with hypertension and endothelial dysfunction. With all these characteristics, women with PCOS are at high risk for CVD and DM.

The effect of treatment of lipid abnormalities has certainly been studied extensively in patients with type 2 DM. Rosenson et al (73) compared the effects of rosuvastatin 10 mg, atorvastatin 10 mg, and placebo in patients with dyslipidemia and the metabolic syndrome. In the group with baseline TGs <2.26 mmol/L, rosuvastatin 10 mg showed a significantly greater percent change (–47%) in LDL-C as compared to 10 mg of atorvastatin (–39%; $P<.01$). The reduction in LDL-C seen with both statins was significantly greater than placebo (–3%; $P<.001$). Similarly, in the group with baseline TGs $\geq$ 2.26 mmol/L, the reduction in LDL-C was significantly greater with rosuvastatin 10 mg (–43%) in comparison to atorvastatin 10 mg (–37%; $P<.05$). As expected, reduction in LDL-C seen with both statins was significantly greater than placebo (2%; $P<.001$). A meta-analysis by Kearney et al (74) with data on >18,000 patients with DM from 14 randomized controlled trials of statin therapy with a mean follow-up of 4.3 years, showed that for each mmol/L reduction in LDL-C, there was a 9% proportional reduction in all-cause mortality and 13% reduction in vascular mortality.

Studies have shown that gemfibrozil and fenofibrate reduce TG levels by 20 to 50% in patients with very high TG levels (75). The Fenofibrate Intervention and Event Lowering in Diabetes study (76) assessed the effects of long-term treatment with fenofibrate to raise HDL-C and lower TG levels on coronary morbidity and mortality in patients with type 2 DM, aged 50 to 75 years, who were not taking statin therapy at study entry. At 5 years, 5.9% of patients in the placebo group and 5.2% in the fenofibrate group had a coronary event (relative reduction of 11%; hazard ratio [HR], 0.89; 95% CI, 0.75 to 1.05; $P = .16$). There was a significant relative reduction of 24% in nonfatal myocardial infarction (HR, 0.76; 95% CI, 0.62 to 0.94; $P = .01$) and a nonsignificant increase in coronary heart disease mortality (HR, 1.19; 95% CI, 0.90 to 1.57; $P = .22$). Whether the change in the cardiovascular risk factors with statin therapy as seen in patients with type 2 DM translates into a similar clinical benefit and better patient outcomes in women with PCOS in the long term is unknown.

The impact of interventions in the stages prior to DM has been studied as well. The Diabetes Prevention Program study (77) assessed the impact of intensive lifestyle change on hypertension, dyslipidemia, and cardiovascular events as compared to metformin therapy (850 mg twice daily) and placebo in 3,234 patients with impaired fasting glucose with a mean BMI of 34.0 kg/m². After an average follow-up of 2.8 years, the mean weight loss was 0.1, 1.2, and 5.6 kg in the placebo, metformin, and lifestyle-intervention groups respectively ($P < .001$). The incidence of DM was reduced by 58% in the lifestyle-intervention group and 31% in the metformin group compared to placebo. During the 10-year follow-up study (78), subjects in the intensive lifestyle-intervention group had partly regained weight. However, the reduction in the incidence of DM continued to remain higher in the lifestyle-intervention group (34%) as compared to metformin (18%) and placebo. Adherence to lifestyle intervention may certainly fluctuate.

Several anorexigenic agents have recently been approved for pharmacologic management of obesity. A guideline with several meta-analyses (79) showed that the pooled amount of weight loss seen is as follows: 4.45 kg at 12 months with sibutramine, 2.89 kg at 12 months with orlistat, and 3.6 kg at 6 months for phentermine. The controlled release combination agent, phentermine/topiramate (PHEN/TPM CR) is available in several strengths. In a double-blind, randomized, 52-week extension trial (80), the least-squares mean percentage changes from baseline in body weight were -1.8, -9.3, and -10.5% for placebo and PHEN/TPM CR 7.5/46-mg and 15/92-mg doses, respectively. Lorcaserin (81), an approved selective agonist of the serotonin 2C receptor, was shown to result in least squares mean weight loss of 4.7% (95% CI, 4.3 to 5.2%) with twice-daily dosing and 5.8% (95% CI, 5.5 to 6.2%) with the once-daily dose, as compared to 2.8% (95% CI, 2.5 to 3.2%) with placebo. Other medications approved for management of obesity include bupropion/naltrexone and liraglutide at the 3 mg dose (Saxenda). The effect of these recently approved drugs in women with PCOS has not been studied.

Addressing IR is a critical part of treating women with PCOS. There are data suggesting a positive effect of metformin on ovulation rate (6,59,82–86). However, very few studies have evaluated the effect of insulin sensitizers on cardiovascular risk factors and cardiovascular outcomes, specifically in women with PCOS. Our analysis showed significant decrease in

WHR, LDL, fasting glucose, free testosterone, and androstenedione with the use of insulin sensitizers as compared to placebo. The long-term effects of these changes in women with PCOS needs to be studied further.

Limitations

Due to a lack of data on TZD trials, it is difficult to comment on the role of TZDs in PCOS (though they are certainly used to address underlying IR). There was wide variation in the treatment measures used, which can be accountable for heterogeneity between studies, and the sample size in some studies was small. Given the different pleotropic effects of metformin and TZDs, we divided the studies into 2 groups (metformin and TZD) and analyzed them separately. Additionally, not all the studies used true placebo in the control arm. To prevent any confounding, the studies were divided into the various groups as stated based on the agent used in the control arm, and further sub-analyses were then conducted. Meta-analyses are limited by biases introduced through individual studies as well as biases introduced through the process of systematic review and quantitative summary.

CONCLUSION

Much remains to be understood about the underlying IR and pathophysiology of PCOS. Adequately powered longitudinal studies with sufficient sample sizes are required to prove any definite longer-term beneficial effects of insulin sensitizers, and years of follow-up will be required to obtain conclusive evidence on cardiovascular outcomes with the use of insulin sensitizers. Diet and exercise remain the first line of treatment in women with PCOS, with metformin remaining the most prescribed drug when lifestyle changes are insufficient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

DISCLOSURE

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Abbreviations:

BMI	body mass index
CI	confidence interval
CVD	cardiovascular disease
DM	diabetes mellitus
EE	ethinyl estradiol

ES	effect size
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HDL	high-density lipoprotein
HDL-C	high-density-lipoprotein cholesterol
HR	hazard ratio
IR	insulin resistance
LDL	low-density-lipo-protein
LDL-C	low-density-lipoprotein cholesterol
LH	luteinizing hormone
PCOS	polycystic ovarian syndrome
TGs	triglycerides
TZD	thiazolidinedione
WHR	waist to hip ratio

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Fig. 1.
Flowchart of study selection. *RCT* = randomized controlled trial.

Fig. 2.

Forest plot of effect size for all the variables for studies using metformin and thiazolidinediones. *BMI*= body mass index; *CI*= confidence interval; *DHEAS*= dehydroepiandrosterone sulfate; *ES*= effect size; *FSH*= follicle-stimulating hormone; *HDL*= high-density lipoprotein; *LDL*= low-density lipoprotein; *LH*= luteinizing hormone.

Fig. 3.

Forest plot for the variable waist to hip ratio for studies using both metformin and thiazolidinediones. *CI*= confidence interval; *ES*= effect size.

Fig. 4.

Forest plot of adjusted effect size for all the variables for the studies using metformin in the treatment arm. *BMI*= body mass index; *CI*= confidence interval; *DHEAS* = dehydroepiandrosterone sulfate; *ES* = effect size; *FSH* = follicle-stimulating hormone; *HDL* = high-density lipoprotein; *LDL* = low-density lipoprotein; *LH* = luteinizing hormone.

Fig. 5.

Forest plot of adjusted effect size for all the variables for the studies using thiazolidinediones in the treatment arm. *BMI* = body mass index; *CI* = confidence interval; *DHEAS* = dehydroepiandrosterone sulfate; *ES* = effect size; *FSH* = follicle-stimulating hormone; *HDL* = high-density lipoprotein; *LDL* = low-density lipoprotein; *LH* = luteinizing hormone.

Table 1

Characteristics of Included Studies

Author	Control/Placebo	Treatment
^a Nestler et al (6)	Placebo for 5 weeks	Metformin 500 mg TID for 5 weeks
^b Qubian et al (30)	1,200–1,400 kcal diet for 26 weeks	Metformin 850 mg BID for 26 weeks
^a Palomba et al (31)	Placebo for 12 months	Metformin 1,700 mg QD for 12 months
^c Elnashaer et al (32)	N-acetyl cysteine 1.8 g QD for 6 weeks	Metformin 1,500 mg QD for 6 weeks
^a Rautio et al (33)	Placebo for 16 weeks	Rosiglitazone 4 mg BID for 16 weeks
^a Gambineri et al (34)	Placebo 1 tablet BID for 12 months	Metformin 850 mg BID for 12 months
^a Lord et al (35)	Placebo for 3 months	Metformin 500 mg TID for 3 months
^a Rautio et al (36)	Placebo for 4.5 months	Rosiglitazone 4 mg QD for 2 weeks then 4 mg BID for 4 months
^d Allen et al (37)	Ethinyl estradiol/norgestimate (35 µg/0.25 mg) for 6 months	Metformin 500 mg BID for 2 weeks then 1,000 mg BID for the remaining 6 months
^a Tang et al (38)	Placebo BID for 6 months	Metformin 850 mg BID for 6 months
^c Lemay et al (39)	Ethinyl estradiol 35 µg + cyproterone acetate 2-mg pills for 6 months then OC pills + rosiglitazone for 6 months	Rosiglitazone 4 mg daily before breakfast for 6 months then rosiglitazone + OC pill for 6 months
^d Lv et al (40)	Cyproterone acetate (Diane 35) for 6 months	Cyproterone acetate (Diane 35) + metformin 500 mg QD for 6 months
^d Rautio et al (41)	Ethinyl estradiol 35 µg + cyproterone acetate 2 mg for 21 days/month followed by 7-day pill-free period for 6 months	Metformin 500 mg BID for 3 months and then 1,000 mg BID for 3 months
^d Sahin et al (42)	Flutamide 250 mg QD for 4 weeks	Metformin 850 mg TID for 4 weeks
^b Jayagopal et al (43)	Orlistat 120 mg TID for 3 months	Metformin 500 mg TID for 3 months
^d Meenakumari et al (44)	CC 50 mg QD for days 5–9 of menstrual cycle	Metformin 500 mg TID for 4 weeks then add CC 50 mg QD for days 5–9 of menstrual cycle
^c Sönmez et al (45)	100 mg clomiphene citrate + acarbose 100 mg TID for 3 months	100 mg clomiphene citrate + 850 mg metformin BID for 3 months
^d Liu et al (46)	Clomiphene citrate 50 mg for days 5–9 of menstrual cycle for 3 cycles	Metformin 500 mg TID for 3 months
^d Ibáñez and de Zegher (47)	OC pills for 21 days per month + flutamide 62.5 mg/day for 3 months	OC pill + flutamide 62.5 mg/day + metformin 850 mg QD for 3 months
^a Brettenthaler et al (48)	Placebo for 3 months	Pioglitazone 30 mg QD for 3 months

Author	Control/Placebo	Treatment
^c Ganie et al (49)	Spironolactone 25 mg BID for 6 months	Metformin 500 mg BID for 6 months
^d Zhang et al (50)	Clomiphene citrate 100 mg for 3 menstrual cycles	Rosiglitazone 4 mg QD for 3 menstrual cycles
^a Maciel et al (51)	Placebo for 6 months	Metformin 500 mg TID for 6 months
^d Ye et al (52)	Ethinyl estradiol 35 µg + cyproterone acetate 2 mg QD for 12 months	Metformin 500 mg TID for 12 months
^a Gambineri et al (53)	Placebo for 6 months	Metformin 850 mg BID for 6 months
^d Morin-Papunen et al (54)	Ethinyl estradiol 35 µg + cyproterone acetate 2 mg for 6 months	Metformin 500 mg BID 3 months then 1,000 mg for 3 months
^d Ciçek et al (55)	Goserelin 3.6 mg every 28 days for 3 months	Metformin 850 mg BID for 3 months
^d Shobokshi and Shaarawy (56)	100 mg clomiphene citrate for 5 days	100 mg clomiphene citrate for 5 days + 100 mg rosiglitazone for 12 weeks
^d George et al (57)	hMG 75 units increased by 75 units every 7–10 days if there is no ovulation	Metformin 500 mg TID for 6 months then add CC 150 mg QD
^d Morin-Papunen et al (58)	Diane Nova (ethinyl estradiol 35 µg + cyproterone acetate 2 mg) for 6 months	Metformin 500 mg BID for 3 months + 1,000 mg BID for 3 months
^a Chou et al (59)	Placebo for 12 weeks	Metformin 500 mg TID for 12 weeks
^c Pagotto et al (60)	Placebo + low-calorie diet for 28 weeks	Metformin 500 mg TID + low-calorie diet for 28 weeks
^d Elter et al (61)	Ethinyl estradiol 35 µg + cyproterone acetate 2 mg for 4 months	Metformin 500 mg BID + ethinyl estradiol 35 µg + cyproterone acetate 2 mg for 4 months
^d Ibáñez et al (62)	Flutamide 250 mg QD for 9 months	Metformin 1,275 mg QD for 9 months
^c Kocak et al (63)	Placebo + clomiphene citrate for 8 weeks	Metformin 850 mg BID + clomiphene citrate for 8 weeks
^a Jakubowicz et al (64)	Placebo for 4 weeks	Metformin 500 mg TID for 4 weeks
^a Vandermolen et al (65)	Placebo for 7 weeks	Metformin 500 mg TID for 7 weeks
^d Morin-Papunen et al (66)	Ethinyl estradiol 35 µg + cyproterone acetate 2 mg for 21 days/month followed by 7-day pill-free period for 6 months	Metformin 500 mg BID for 3 months followed by 1,000 mg BID for 3 months
^a Pasquali et al (67)	Placebo for 6 months	Metformin 850 mg BID for 6 months
^a Nestler et al (68)	Placebo for 4–8 weeks	Metformin 500 mg TID for 4–8 weeks
^d Wu et al (69)	Ethinyl estradiol 35 µg + cyproterone acetate 2 mg for 21 days/month followed by 7-day pill-free period for 3 months	Metformin 500 mg TID for 3 months
^b Elkind-Hirsch et al (70)	Exenatide 10 µg BID for 24 weeks	Metformin 1,000 mg BID for 24 weeks

Author	Control/Placebo	Treatment
^d Khorram et al (71)	Clomiphene citrate 100 mg QD on cycle days 5–9 only	Metformin 500 mg TID for 2 weeks + clomiphene citrate 100 mg per day on cycle days 5–9 only
^a Yarali et al (72)	Placebo for 6 weeks	Metformin 850 mg BID for 6 weeks

Abbreviations: BID = twice a day; CC = clomiphene citrate; hMG = human menopausal gonadotropin; OC = oral contraceptive; QD = once daily; TID = 3 times a day.

- ^aStudy was categorized in the true placebo group in the subanalysis.
- ^bStudy was categorized in the anorexigenic drugs group in the subanalysis.
- ^cStudy was categorized in the combination drugs group in the subanalysis.
- ^dStudy was categorized in the gonadotropin-releasing hormone agonist/antagonist group in the subanalysis.