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META-ANALYSIS

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The effectiveness of metformin, oral contraceptives, and lifestyle modification in improving the metabolism of overweight women with polycystic ovary syndrome: a network meta-analysis

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Abstract

Purpose We designed a network meta-analysis that investigated relatively different interventions that included the effects of metformin, oral contraceptives, and lifestyle modification on the metabolic parameters of patients with polycystic ovary syndrome. In addition, we searched for eligible interventions that improved the metabolism of glucose and lipids.

Methods We searched the PubMed, EMBASE, and Cochrane Central databases from inception to May 2018. Publication types that were categorized as randomized controlled trials met our inclusion criteria. The main outcome included the homeostasis model assessment of insulin resistance, total cholesterol, low-density lipoprotein cholesterol, and total triglycerides. We performed both a pairwise meta-analysis and a network meta-analysis to evaluate the mean difference value and 95% credibility intervals, and we calculated the surface cumulative rank curve.

Results There were a total of 12 kinds of interventions: metformin, 2 mg cyproterone acetate plus 0.05 mg ethinylestradiol (EE/CA), 0.15 mg desogestrel plus 0.03 mg ethinylestradiol (EE/DSG), and 3 mg drospirenone plus 0.03 mg ethinylestradiol (EE/DRSP), lifestyle, exercise, diet, metformin + lifestyle, metformin + diet, EE/CA + lifestyle, metformin + EE/CA, and EE/DRSP + lifestyle from the 20 eligible RCTs that were included in this study. Our meta-analysis results showed that metformin + lifestyle (MD = −2.04, 95% CrI = −3.64 to −0.41), EE/CA + lifestyle (MD = −2.23, 95% CrI = −4.11 to −0.35), and EE/DRSP + lifestyle (MD = −2.59, 95% CrI = −4.66 to −0.50) resulted in lower in the levels of total cholesterol. Women treated with metformin + lifestyle (MD = −1.82, 95% CrI = −2.88 to −0.79), EE/CA + lifestyle (MD = −2.25, 95% CrI = −3.58 to −1.08), or EE/DRSP + lifestyle (MD = −2.29, 95% CrI = −3.69 to −1.07) exhibited significantly lower low-density lipoprotein cholesterol when compared with the placebo group. There was no significant difference between any of the interventions compared with a placebo in the levels of homeostasis model assessment of insulin resistance and total triglycerides. The surface cumulative rank curve revealed that metformin + lifestyle might be the best intervention with respect to the improvement of the homeostasis model of assessment insulin resistance and EE/DRSP + lifestyle appeared to be the best intervention for the reduction of total cholesterol and low-density lipoprotein cholesterol. Moreover, the metformin + diet intervention was more effective in reducing the level of total triglycerides.

Conclusions For overweight polycystic ovary syndrome patients, our evidence revealed that EE/CA and EE/SRSP combined with metformin or lifestyle changes can reduce the adverse effects on glucose and lipid metabolism of the use of oral contraceptive agents alone. Conventional PCOS treatments, such as metformin, EE/CA, and EE/DRSP, combined with lifestyle control can be particularly effective in improving the homeostasis model assessment of insulin resistance and lipid metabolism.

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Keywords Polycystic ovary syndrome · Interventions · Metabolism · Network meta-analysis · Randomized controlled trials

Introduction

Polycystic ovary syndrome (PCOS), as a common and complex endocrine disease that affects up to 13% of women of reproductive age, is characterized by oligoovulation or anovulation, elevated androgen levels, and polycystic ovary changes in ultrasound readings [1]. Although women with PCOS often suffer from infertility or menstrual disorders, they are also more prone to systemic endocrine disorders, not only reproductive endocrine disorders but also insulin resistance, which could lead to abnormal glucose and lipid metabolism or even cardio-cerebrovascular diseases, especially in overweight PCOS patients [2]. However, doctors and patients often neglect the adverse and long-term effects of abnormal glucose and lipid metabolism because of the main treatment demands related to infertility or menstrual disorders.

Currently, PCOS therapies include ovulation induction agents, insulin sensitizers, oral contraceptive agents, surgery, and lifestyle modification [3–7]. Ovulation induction agents are often used to stimulate follicle development and have a short treatment time [8], so few studies have focused on their effects on metabolic status in PCOS patients. However, metformin, as an insulin sensitizer combined with ovulation induction agents could improve ovulation and pregnancy rates [9], and could also reduce blood glucose and improve insulin resistance. On the other hand, metformin can produce many side effects such as nausea, stomach pain, and diarrhea, when used alone [10]. In addition, the commonly used oral contraceptive agents such as ethinylestradiol and cyproterone acetate tablets, desogestrel and ethinylestradiol tablets, and drospirenone and ethinylestradiol tablets could reduce androgen levels and regulate menstruation to normal but increase the risk of venous thrombosis and metabolic abnormality in long-term usage [11, 12]. Furthermore, laparoscopic ovarian drilling reduces androgen levels by destroying the interstitial tissue of the ovary, and after the surgery, patients exhibit lower glucose levels or glucose/insulin ratios [13]. Moreover, lifestyle modification could produce a similar reduction in blood glucose and insulin levels as metformin does in PCOS women [14].

However, PCOS is a lifelong disorder, especially regarding the metabolic effects, and the treatment should be long term [15]. The effect of different interventions for PCOS patients on metabolism and which intervention is most effective remain to be verified. For this reason, we designed this network meta-analysis (NMA) to compare the effects of different interventions on metabolism in overweight women with PCOS.

Materials and methods

Literature search

This meta-analysis was registered with the PROSPERO international prospective register of systematic reviews and the registration number is CRD 42018097086. We searched the medical literature for relevant studies using Pubmed, EMBASE, and Cochrane Central from inception to May 2018. A total of 2291 records were identified using electronic search strategies; in addition, one relevant record was obtained from the references list of the included studies. We used both free text words and medical subject heading (MeSH) terms combining keywords: ("Polycystic ovary syndrome" [Mesh] OR "PCOS" OR "stein-leventhal syndrome") AND ("Metformin" [Mesh] OR "oral contraceptive agent" OR "OCP" OR "diane" OR "cyproterone acetate plus ethinylestradiol" OR "marvelon" OR "desogestrel plus ethinylestradiol" OR "yasmin" OR "drospirenone plus ethinylestradiol" OR "Life Style" [Mesh] OR "Exercise" [Mesh] OR "Diet" [Mesh] OR "laparoscopic ovarian drilling"), and limited the publication type to randomized controlled trials (RCTs). There were no language or district restrictions.

Three types of oral contraceptive agents were investigated: 2 mg cyproterone acetate plus 0.05 mg ethinylestradiol (EE/CA), 0.15 mg desogestrel plus 0.03 mg ethinylestradiol (EE/DSG), and 3 mg drospirenone plus 0.03 mg ethinylestradiol (EE/DRSP). Lifestyle modification consisted of both exercise and diet control. Exercise included strength training or aerobic exercise such as regular walking, jogging, or cycling. Diet control indicated that each subject was assessed by a dietitian or nutritionist and consumed a regular diet to control calorie intake. Since the aim of ovulation induction agents was confined to follicular development and could not be used for long, our goal was to assess the effects of long-term (at least 4 weeks) interventions on metabolism, so the ovulation induction agents were not included in this meta-analysis.

The records were reviewed independently by two groups: A.W. and T.M., and Q.L. and C.S. Then, we summarized the included studies. Disagreements were solved by consensus together with M.L.

Table 1 Main characterisitcs of studies included in the network meta-analysis

Study	Year	Region	Interventions	Size	Follow-up	Outcomes
Lord et al. [20]	2006	UK	Metformin vs placebo	31	12 weeks	2, 3, 4
Gambineri et al. [21]	2006	Italy	Metformin + diet vs diet	39	12 months	3, 4
Tang et al. [22]	2006	UK	Metformin + lifestyle vs lifestyle	122	6 months	2, 4
Vigorito et al. [23]	2007	Italy	Lifestyle vs diet	90	3 months	2, 3, 4
Ma et al. [24]	2007	China	Metformin + lifestyle vs lifestyle	43	3 months	2, 3, 4
Hutchison et al. [25]	2008	Australia	Metformin + lifestyle vs EE/CA + lifestyle	38	3 months	1, 2, 3, 4
Thomson et al. [26]	2008	Australia	Diet vs lifestyle	52	20 weeks	1, 2, 3, 4
Kebapcilar et al. [27]	2009	Turkey	Metformin + EE/CA vs EE/CA	43	3 months	1, 2, 3, 4
Kebapcilar et al. [28]	2010	Turkey	Metformin vs metformin + EE/CA vs EE/CA	36	3 months	1, 2, 3, 4
Kriplani et al. [29]	2010	India	EE/DSG vs EE/DRSP	58	6 months	1, 2, 3, 4
Fux Otta et al. [30]	2010	Argentina	Metformin + lifestyle vs lifestyle	29	4 months	1, 2, 3, 4
Bhattacharya et al. [31]	2012	India	EE/CA vs EE/DSG vs EE/DRSP	150	12 months	1
Bonakdaran et al. [32]	2012	Iran	Metformin vs placebo	33	3 months	1
Esfahanian et al. [33]	2012	Iran	Metformin vs diet	30	3 months	1, 2, 3, 4
Curi et al. [34]	2012	Brazil	Metformin vs lifestyle	27	6 months	1
Amiri et al. [35]	2014	Iran	Metformin + diet vs diet	51	6 months	2, 3, 4
Almenning et al. [36]	2015	Norway	Exercise vs placebo	25	10 weeks	1, 2, 3, 4
Feng et al. [37]	2015	China	Metformin vs metformin + EE/CA	82	3 months	1, 2, 3, 4
Wang et al. [38]	2016	China	EE/CA + lifestyle vs EE/DRSP + lifestyle	68	3 months	1, 2, 3, 4
Song et al. [39]	2017	China	Metformin + EE/CA vs EE/CA	160	12 weeks	1, 2, 3, 4

Interventions: *EE/CA* 2 mg cyproterone acetate plus 0.05 mg ethinylestradiol, *EE/DSG* 0.15 mg desogestrel plus 0.03 mg ethinylestradiol, *EE/DRSP* 3 mg drospirenone plus 0.03 mg ethinylestradiol

Outcomes: 1 homeostasis model assessment of insulin resistance, 2 total cholesterol, 3 low-density lipoprotein cholesterol, 4 total triglycerides

Inclusion and exclusion criteria

Inclusion criteria

(1) PCOS women aged 18–49 years with an average body mass index (BMI) ≥ 25 (kg/m^2); (2) two out three of the following criteria, according to the Rotterdam Consensus criteria: PCOS diagnosed with polycystic ovaries, clinical or biochemical signs of hyperandrogenism, and oligomenorrhea or amenorrhea; (3) RCT; (4) included at least one main outcome; (5) comparisons between the relevant interventions; (6) the calculation formula of the homeostasis model assessment of insulin resistance (HOMA-IR) was fasting blood glucose (mmol/L) × fasting blood insulin (mIU/L)/22.5; and (7) the intervention time was at least 4 weeks.

Exclusion criteria

(1) PCOS patients under 18 years of age or over 49 years of age with an average BMI <25 (kg/m^2); (2) non-RCT; (3) no main outcome; (4) combination with other unrelated drugs such as ovulation-inducting agents, other contraceptives, or insulin sensitizers; (5) comparison with no relevant controls; and (6) patients with other diseases such as congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting neoplasm, hyperprolactinemia, kidney or liver disease, and so on.

Outcomes, data extraction, and assessment of quality of methods

The main outcomes included HOMA-IR, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and total triglycerides (TGs).

Data were extracted as shown in Table 1: study, year, region, interventions, size, follow-up, and outcomes. If one record had no available data, especially for the main outcomes, we actively contacted the author and then removed the record if the author did not reply.

The included studies were assessed for quality using the Cochrane Risk of Bias tool for RCTs [16], which consists of seven items: random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias.

Statistical analysis

First, we carried out a pairwise meta-analysis to directly compare the different PCOS interventions. We unified the unit of the outcomes previously reported [17] and the units of TC, LDL-c, and TGs were converted to mmol/L. The weighted mean difference (WMD) and 95% confidence interval (95% CI) between two groups were synthesized using the mean difference (MD) and standard deviation, and sample size or the data were converted from the MD and sample standard deviation at the end point between two groups [18]. In this pairwise meta-analysis, the I^2 and Q tests were used to assess the heterogeneity of the treatment effects, which was deemed significant when P was <0.05 or I^2 was more than 50%. When there was significant heterogeneity, the random effects model was used. Moreover, funnel plots were created by Stata software (version 14.0, StataCorp, College Station, TX) and were used for publication bias.

Second, the NMA was performed with a Bayesian framework to compare different interventions with R software (version 3.5.0, MathSoftCorp, AT&T Bell Laboratories). The analysis model was based on the definition of likelihood and prior probability. After using the rJAGS package to perform 20,000 simulations and 5000 simulations as a burn-in phase, we confirmed the convergence and calculated the pooled estimates of MD and 95% credibility interval (CrI) to compare the 12 kinds of interventions to each other. Additionally, the surface under the curve ranking area (SUCRA) was calculated to rank the different interventions. Compared with other interventions, one intervention showed a higher SUCRA value, so it might have a greater effect on the end point [19]. The consistency assumption of direct evidence and indirect evidence was assessed by the node-splitting method. When the results showed that the direct evidence of the outcomes was consistent with indirect evidence (P values were >0.05), the consistency model was adopted.

Results

Characteristics of studies included

As Fig. 1 shows, one additional reference was manually found by the reviewers. Among the total 2292 records, 1110 records were duplicates and were removed. Then, 1026 records were removed after reading the title and abstracts, leaving 156 studies. The full-text articles were reviewed and 20 records [20–39] were eventually included in this NMA. The included studies were published between 2006 and 2017. Since there was no eligible records related to laparoscopic ovarian drilling, 12 kinds of interventions were included: metformin, EE/CA, EE/DSG, EE/DRSP, lifestyle, exercise, diet, metformin + lifestyle, metformin + diet, EE/CA + lifestyle, metformin + EE/CA, and EE/DRSP + lifestyle, as shown in Fig. 2.

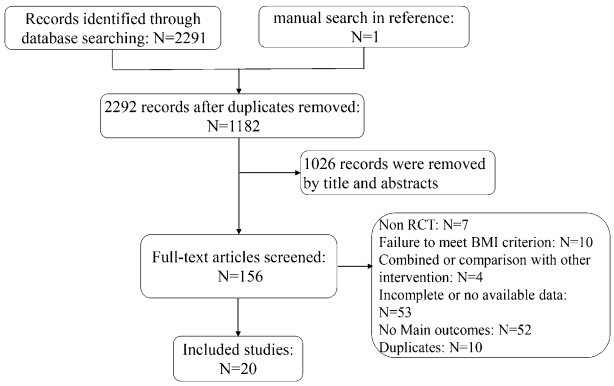

Fig. 1 Flow diagram of the process of identifying, including and excluding studies identified in the literature search for randomized controlled trials comparing different interventions for polycystic ovary syndrome

Quality assessment of the included studies

Among the 20 studies included, 1 study used a high-risk random sequence generation method [32], 3 studies did not describe the method used to generate random sequences [27, 28, 39], and other studies had a low risk. We evaluated 7 studies and found that they had an unclear bias risk because they did not describe an acceptable allocation concealing method [27–29, 32, 33, 38, 39], and others described an acceptable method of allocation concealment. Eleven studies did not describe the blinding method and had a high risk of not blinding participants and personnel [24–29, 33, 34, 36, 38, 39]. However, the outcomes included in this meta-analysis were objective, so all studies included had a low risk of blinding related to the blinding of the outcome assessment. Four studies had high drop-out rates during follow-up, so we rated them as having a high risk of attrition bias [24, 33, 34, 38]. All of the included studies had a low risk of other biases.

Pairwise meta-analysis

We performed 15 direct comparisons and calculated the MDs and 95% CIs. The results are illustrated in Table 2.

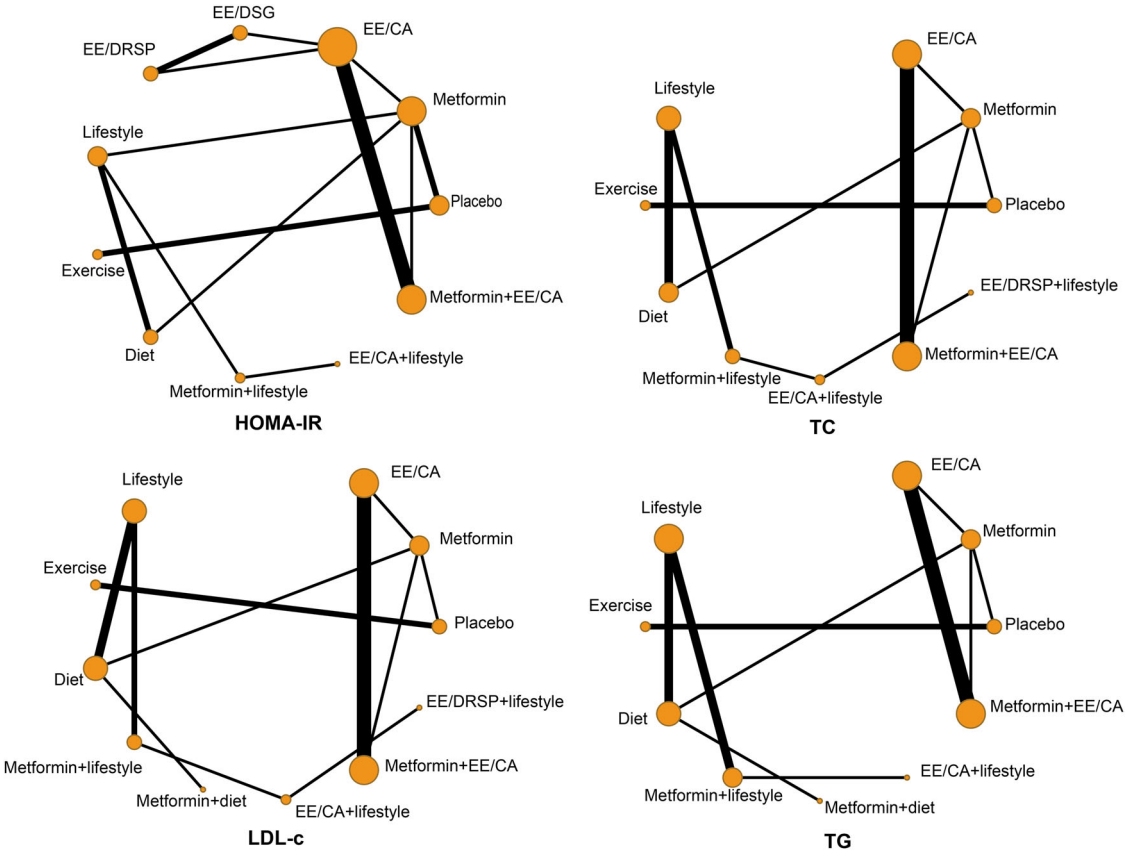

Fig. 2 Network plots of different interventions for polycystic ovary syndrome treatment. The width of the line is directly proportional to the number of treatments for each pair; the area of the circle represents the cumulative number of patients per intervention. EE/CA 2 mg cyproterone acetate plus 0.05 mg ethinylestradiol, EE/DSG 0.15 mg desogestrel plus 0.03 mg ethinylestradiol, EE/DRSP 3 mg drospirenone plus 0.03 mg ethinylestradiol, HOMA-IR homeostasis model assessment of insulin resistance, TC total cholesterol, LDL-c low-density lipoprotein cholesterol, TGs total triglycerides

Table 2 Metabolic profiles of PCOS interventions by pairwise meta-analysis

Comparison	HOMA-IR	TC	LDL-c	TGs
Metformin vs placebo	0.62 (−0.46, 1.70)	–0.87 (–1.58, –0.16)[a]	–0.97 (–1.70, –0.24)[a]	0.10 (–0.38, 0.58)
Metformin vs EE/CA	−0.90 (−1.55, −0.26)[a]	–0.36 (–0.91, 0.19)	0.20 (–0.34, 0.38)	0.15 (–0.13, 0.43)
Metformin vs lifestyle	0.54 (0.22, 0.87)[a]	_[b]	_[b]	_[b]
Metformin vs diet	0.35(−0.51,1.21)	0.57 (–0.25, 1.39)	0.44 (–0.09, 0.97)	0.35 (–0.24, 0.94)
Metformin vs metformin + EE/CA	0.20 (−0.45, 0.85)	0.03 (–0.55, 0.61)	0.16 (–0.21, 0.53)	0.28 (0.04, 0.52)[a]
EE/CA vs EE/DSG	1.53 (−0.10, 3.16)	_[b]	_[b]	_[b]
EE/CA vs EE/DRSP	0.25 (−1.40, 1.90)	_[b]	_[b]	_[b]
EE/CA vs metformin + EE/CA	0.49 (0.24, 0.74)[a]	0.19 (0.02,0.36)[a]	0.03 (–0.10, 0.17)	0.00 (–0.11, 0.11)
EE/DSG vs EE/DRSP	−0.04 (−0.55, 0.47)	–0.31 (–0.62, –0.00)[a]	0.29 (0.06, 0.52)[a]	−0.16 (–0.34, 0.02)
Lifestyle vs diet	−0.31 (−0.88, 0.27)	–0.13 (–0.30, 0.04)	–0.10 (–0.32, 0.13)	0.02 (–0.08, 0.13)
Lifestyle vs metformin + lifestyle	_[b]	0.43 (0.08, 0.78)[a]	0.36 (0.07, 0.65)[a]	–0.06 (–0.33, 0.21)
Exercise vs placebo	−0.69 (–2.71, 0.78)	–0.16 (–0.46, 0.77)	–0.15 (–0.78, 0.48)	0.16 (–0.06, 0.38)
Diet vs metformin + diet	1.26 (0.36, 2.16)[a]	_[b]	0.26 (–0.31, 0.83)	0.77 (–0.12, 1.66)
Metformin + lifestyle vs EE/CA + lifestyle	_[b]	0.20 (–0.51, 0.91)	0.50 (–0.21, 1.21)	–0.10 (–0.65, 0.45)
EE/CA + lifestyle vs EE/DRSP + lifestyle	0.20 (–3.33, 3.73)	–0.36 (–0.18, 0.90)	0.06 (–0.31, 0.43)	_[b]

PCOS polycystic ovary syndrome, *EE/CA* 2 mg cyproterone acetate plus 0.05 mg ethinylestradiol, *EE/DSG* 0.15 mg desogestrel plus 0.03 mg ethinylestradiol, *EE/DRSP* 3 mg drospirenone plus 0.03 mg ethinylestradiol, *HOMA-IR* homeostasis model assessment of insulin resistance, *TC* total cholesterol, *LDL-c* low-density lipoprotein cholesterol, *TGs* total triglycerides

[a]Values mean significance

[b]Not available

The HOMA-IR data demonstrated that the HOMA-IR levels of patients treated with metformin were relatively lower than those in the EE/CA treatment group (WMD = −0.90, 95% CI = –1.55 to –0.26) and higher than those in the lifestyle group (WMD = 0.54, 95% CI = 0.22 to 0.87). Women who were treated with metformin combined with EE/CA exhibited lower HOMA-IR levels than women who were treated with EE/CA (WMD = 0.49, 95% CI = 0.24 to 0.74), and the HOMA-IR levels of women who were treated with metformin combined with diet were lower than women who were in the diet-only group (WMD = 1.26, 95% CI = 0.36 to 2.16) (Table 2).

According to the TC data, the TC levels of women who were treated with metformin (WMD = –0.87, 95% CI = −1.58 to −0.16) were significantly lower than the TC levels of women who were given a placebo. The TC levels of women treated with EE/DSG (WMD = −0.31, 95% CI = −0.62 to −0.00) were lower than the TC levels of women treated with EE/DRSP. Women treated with metformin combined with EE/CA exhibited lower TC levels than women who were treated with EE/CA (WMD = 0.19, 95% CI = 0.02 to 0.36), and women treated with metformin combined with lifestyle exhibited lower TC levels than women who only modified their lifestyle (WMD = 0.43, 95% CI = 0.08 to 0.78) (Table 2).

For LDL-c levels, patients treated with metformin (WMD = −0.97, 95% CI = −1.70 to −0.24) had lower LDL-c levels than those treated with a placebo. Women who were treated with EE/DRSP had lower LDL-c levels than women who were treated with EE/DSG (WMD = 0.29, 95% CI = 0.06 to 0.52). Moreover, women who were treated with metformin combined with lifestyle showed lower LDL-c levels than women who only modified their lifestyle (WMD = 0.36, 95% CI = 0.07 to 0.65) (Table 2).

Compared with metformin only (WMD = 0.28, 95% CI = 0.04 to 0.52) (Table 2), metformin combined with EE/CA was more effective in reducing TGs.

Network meta-analysis

As illustrated in Tables 3–6 and Fig. 3, the results of different interventions for PCOS were compared by NMA.

Compared with the placebo, there was no statistical significance for any of the interventions based on HOMA-IR level. However, patients treated with metformin + lifestyle had lower HOMA-IR levels than those treated with metformin (MD = 1.88, 95% CrI = 0.61 to 3.14), EE/CA (MD = 2.47, 95% CrI = 0.98 to 3.98), lifestyle (MD = 1.30, 95% CrI = 0.19 to 2.38), diet (MD = 1.55, 95% CrI = 0.26 to 2.84), and metformin + EE/CA (MD = 1.96, 95% CrI = 0.44 to 3.46) (Table 3). Moreover, patients who were treated with metformin combined with EE/CA showed lower HOMA-IR levels than patients who were treated with EE/CA alone (MD = 0.52, 95% CrI = 0.09 to 1.00) (Table 3).

With respect to TC levels, women who were treated with lifestyle (MD = −1.59, 95% CrI = −3.09 to −0.06), diet (MD = −1.43, 95% CrI = −2.88 to −0.00), metformin + lifestyle (MD = −2.04, 95% CrI = −3.64 to −0.41), EE/CA + lifestyle (MD = −2.23, 95% CrI = −4.11 to −0.35), and EE/DRSP + lifestyle (MD = −2.59, 95% CrI = −4.66 to −0.50) (Fig. 3 and Table 4) exhibited lower TC levels than women who received a placebo.

Similarly, women treated with metformin (MD = −0.92, 95% CrI = −1.76 to −0.17), EE/CA (MD = −0.97, 95% CrI = −1.90 to −0.20), lifestyle (MD = −1.46, 95% CrI = −2.48 to −0.51), diet (MD = −1.36, 95% CrI = −2.33 to −0.44), metformin + lifestyle (MD = −1.82, 95% CrI = −2.88 to −0.79), metformin + diet (MD = −1.60, 95% CrI = −2.76 to −0.56), EE/CA + lifestyle (MD = −2.25, 95% CrI = −3.58 to −1.08), metformin + EE/CA (MD = −1.01, 95% CrI = −1.94 to −0.23), and EE/DRSP + lifestyle (MD = −2.29, 95% CrI = −3.69 to −1.07) (Fig. 3 and Table 5) had significantly lower LDL-c levels than women who received a placebo.

This NMA revealed that there was no statistical significance of any of the interventions compared with the placebo, and there was no statistical significance between the interventions in TG levels (Fig. 3 and Table 6).

Surface under the curve ranking area

As the results of SUCRA illustrated, metformin + lifestyle, EE/CA + lifestyle, and exercise had the largest three SUCRA values in the level of HOMA-IR. EE/DRSP + lifestyle, EE/CA + lifestyle, and metformin + lifestyle showed the largest three SUCRA values for the reduction of TC and LDL-c. Metformin + diet, diet, and lifestyle had the largest three values for the reduction in TG levels (Table 7).

Inconsistency test between direct and indirect evidence

For the levels of HOMA-IR, TC, LDL-c. and TGs, the results showed that the direct evidence of the outcomes were consistent with the indirect evidence (*P* values were >0.05), so the consistency model was adopted (Fig. 4).

Discussion

Some researchers believe that PCOS is closely related to metabolic syndrome because of the abnormal glucose and lipid metabolism [40]. This disorder may cause serious complications such as hyperglycemia, hypertension, hyperlipidemia, and so on [41]. However, most patients are

Table 3 Network meta-analysis results of PCOS intervention about HOMA-IR

	Placebo	Metformin	EE/CA	EE/DSG	EE/DRSP	Lifestyle	Exercise	Diet	Metformin + lifestyle	EE/CA + lifestyle	Metformin + EE/CA
HOMA-IR	Placebo	0.67 (−0.50, 1.93)	1.28 (−0.09, 2.79)	0.36 (−1.82, 2.47)	0.50 (−1.80, 2.63)	0.08 (−1.28, 1.51)	−0.73 (−2.21, 0.86)	0.36 (−1.03, 1.80)	−1.21 (−2.98, 0.60)	−1.52 (−5.44, 2.68)	0.75 (−0.60, 2.28)
	−0.67 (−1.93, 0.50)	Metformin	0.63 (−0.16, 1.46)	−0.33 (−2.03, 1.54)	−0.22 (−1.89, 1.74)	−0.58 (−1.25, 0.09)	−1.37 (−3.37, 0.56)	−0.31 (−1.06, 0.48)	−1.88 (−3.14, −0.61)[a]	−2.24 (−5.96, 1.83)	0.11 (−0.73, 0.92)
	−1.28 (−2.79, 0.09)	−0.63 (−1.46, 0.16)	EE/CA	−0.91 (−2.58, 0.71)	−0.77 (−2.46, 0.90)	−1.19 (−2.26, −0.20)[a]	−2.01 (−4.25, 0.04)	−0.93 (−2.02, 0.17)	−2.47 (−3.98, −0.98)[a]	−2.84 (−6.84, 1.33)	−0.52 (−1.00, −0.09)[a]
	−0.36 (−2.47, 1.82)	0.33 (−1.54, 2.03)	0.91 (−0.71, 2.58)	EE/DSG	0.11 (−0.55, 1.00)	−0.30 (−2.26, 1.55)	−1.10 (−3.65, 1.45)	−0.00 (−1.89, 1.84)	−1.57 (−3.80, 0.59)	−2.00 (−5.94, 2.50)	0.38 (−1.30, 2.10)
	−0.50 (−2.63, 1.80)	0.22 (−1.74, 1.89)	0.77 (−0.90, 2.46)	−0.11 (−1.00, 0.55)	EE/DRSP	−0.38 (−2.42, 1.43)	−1.20 (−3.90, 1.31)	−0.13 (−2.06, 1.68)	−1.66 (−3.96, 0.42)	−2.15 (−6.05, 2.48)	0.26 (−1.50, 1.98)
	−0.08 (−1.51, 1.28)	0.58 (−0.09, 1.25)	1.19 (0.20, 2.26)[a]	0.30 (−1.55, 2.26)	0.38 (−1.43, 2.42)	Lifestyle	−0.81 (−2.89, 1.23)	0.27 (−0.37, 0.94)	−1.30 (−2.38, −0.19)[a]	−1.67 (−5.36, 2.38)	0.66 (−0.35, 1.76)
	0.73 (−0.86, 2.21)	1.37 (−0.56, 3.37)	2.01 (−0.04, 4.25)	1.10 (−1.45, 3.65)	1.20 (−1.31, 3.90)	0.81 (−1.23, 2.89)	Exercise	1.08 (−1.00, 3.17)	−0.47 (−2.81, 1.85)	−0.85 (−4.93, 3.82)	1.48 (−0.54, 3.71)
	−0.36 (−1.80, 1.03)	0.31 (−0.48, 1.06)	0.93 (−0.17, 2.02)	0.00 (−1.84, 1.89)	0.13 (−1.68, 2.06)	−0.27 (−0.94, 0.37)	−1.08 (−3.17, 1.00)	Diet	−1.55 (−2.84, −0.26)[a]	−1.96 (−5.70, 2.23)	0.41 (−0.72, 1.49)
	1.21 (−0.60, 2.98)	1.88 (0.61, 3.14)[a]	2.47 (0.98, 3.98)[a]	1.57 (−0.59, 3.80)	1.66 (−0.42, 3.96)	1.30 (0.19, 2.38)[a]	0.47 (−1.85, 2.81)	1.55 (0.26, 2.84)[a]	Metformin + lifestyle	−0.40 (−4.01, 3.30)	1.96 (0.44, 3.46)[a]
	1.52 (−2.68, 5.44)	2.24 (−1.83, 5.96)	2.84 (−1.33, 6.84)	2.00 (−2.50, 5.94)	2.15 (−2.48, 6.05)	1.67 (−2.38, 5.36)	0.85 (−3.82, 4.93)	1.96 (−2.23, 5.70)	0.40 (−3.30, 4.01)	EE/CA + lifestyle	2.33 (−1.79, 6.31)
	−0.75 (−2.28, 0.60)	−0.11 (−0.92, 0.73)	0.52 (0.09, 1.00)[a]	−0.38 (−2.10, 1.30)	−0.26 (−1.98, 1.50)	−0.66 (−1.76, 0.35)	−1.48 (−3.71, 0.54)	−0.41 (−1.49, 0.72)	−1.96 (−3.46, −0.44)[a]	−2.33 (−6.31, 1.79)	Metformin + EE/CA

PCOS polycystic ovary syndrome, *EE/CA* 2 mg cyproterone acetate plus 0.05 mg ethinylestradiol, *EE/DSG* 0.15 mg desogestrel plus 0.03 mg ethinylestradiol, *EE/DRSP* 3 mg drospirenone plus 0.03 mg ethinylestradiol, *HOMA-IR* homeostasis model assessment of insulin resistance

[a]Values mean significance

Table 4 Network meta-analysis results of PCOS intervention about TC

	Placebo	Metformin	EE/CA	Lifestyle	Exercise	Diet	Metformin + lifestyle	EE/CA + lifestyle	Metformin + EE/CA	EE/DRSP + lifestyle
TC	Placebo	−0.87 (−1.84, 0.10)	−0.59 (−1.85, 0.67)	−1.59 (−3.09, −0.06)[a]	0.14 (−0.63, 0.92)	−1.43 (−2.88, −0.00)[a]	−2.04 (−3.64, −0.41)[a]	−2.23 (−4.11, −0.35)[a]	−0.79 (−2.04, 0.49)	−2.59 (−4.66, −0.50)[a]
	0.87 (−0.10, 1.84)	Metformin	0.27 (−0.49, 1.06)	−0.72 (−1.86, 0.44)	1.01 (−0.22, 2.26)	−0.56 (−1.62, 0.48)	−1.17 (−2.48, 0.13)	−1.36 (−3.03, 0.25)	0.08 (−0.71, 0.87)	−1.72 (−3.53, 0.14)
	0.59 (−0.67, 1.85)	−0.27 (−1.06, 0.49)	EE/CA	−1.00 (−2.40, 0.40)	0.74 (−0.72, 2.21)	−0.84 (−2.15, 0.46)	−1.44 (−2.97, 0.06)	−1.62 (−3.44, 0.16)	−0.20 (−0.57, 0.19)	−1.99 (−3.98, 0.02)
	1.59 (0.06, 3.09)[a]	0.72 (−0.44, 1.86)	1.00 (−0.40, 2.40)	Lifestyle	1.73 (0.01, 3.41)[a]	0.14 (−0.34, 0.65)	−0.45 (−1.04, 0.13)	−0.64 (−1.79, 0.47)	0.80 (−0.59, 2.21)	−1.01 (−2.40, 0.44)
	−0.14 (−0.92, 0.63)	−1.01 (−2.26, 0.22)	−0.74 (−2.21, 0.72)	−1.73 (−3.41, −0.01)[a]	Exercise	−1.59 (−3.20, 0.03)	−2.18 (−3.95, −0.39)[a]	−2.37 (−4.40, −0.32)[a]	−0.93 (−2.41, 0.54)	−2.73 (−4.92, −0.50)[a]
	1.43 (0.00, 2.88)[a]	0.56 (−0.48, 1.62)	0.84 (−0.46, 2.15)	−0.14 (−0.65, 0.34)	1.59 (−0.03, 3.20)	Diet	−0.59 (−1.39, 0.16)	−0.78 (−2.04, 0.41)	0.65 (−0.65, 1.97)	−1.14 (−2.65, 0.32)
	2.04 (0.41, 3.64)[a]	1.17 (−0.13, 2.48)	1.44 (−0.06, 2.97)	0.45 (−0.13, 1.04)	2.18 (0.39, 3.95)[a]	0.59 (−0.16, 1.39)	Metformin + lifestyle	−0.20 (−1.14, 0.79)	1.25 (−0.26, 2.80)	−0.55 (−1.83, 0.74)
	2.23 (0.35, 4.11)[a]	1.36 (−0.25, 3.03)	1.62 (−0.16, 3.44)	0.64 (−0.47, 1.79)	2.37 (0.32, 4.40)[a]	0.78 (−0.41, 2.04)	0.20 (−0.79, 1.14)	EE/CA + lifestyle	1.43 (−0.34, 3.27)	−0.35 (−1.21, 0.47)
	0.79 (−0.49, 2.04)	−0.08 (−0.87, 0.71)	0.20 (−0.19, 0.57)	−0.80 (−2.21, 0.59)	0.93 (−0.54, 2.41)	−0.65 (−1.97, 0.65)	−1.25 (−2.80, 0.26)	−1.43 (−3.27, 0.34)	Metformin + EE/CA	−1.80 (−3.81, 0.21)
	2.59 (0.50, 4.66)[a]	1.72 (−0.14, 3.53)	1.99 (−0.02, 3.98)	1.01 (−0.44, 2.40)	2.73 (0.50, 4.92)[a]	1.14 (−0.32, 2.65)	0.55 (−0.74, 1.83)	0.35 (−0.47, 1.21)	1.80 (−0.21, 3.81)	EE/DRSP + lifestyle

PCOS polycystic ovary syndrome, *EE/CA* 2 mg cyproterone acetate plus 0.05 mg ethinylestradiol, *EE/DRSP* 3 mg drospirenone plus 0.03 mg ethinylestradiol, *TC* total cholesterol

[a]Values mean significance

Table 5 Network meta-analysis results of PCOS intervention about LDL-c

	Placebo	Metformin	EE/CA	Lifestyle	Exercise	Diet	Metformin + lifestyle	Metformin + diet	EE/CA + lifestyle	Metformin + EE/CA	EE/DRSP + lifestyle
LDL-c	Placebo	−0.92 (−1.76, −0.17)[a]	−0.97 (−1.90, −0.20)[a]	−1.46 (−2.48, −0.51)[a]	−0.17 (−0.89, 0.44)	−1.36 (−2.33, −0.44)[a]	−1.82 (−2.88, −0.79)[a]	−1.60 (−2.76, −0.56)[a]	−2.25 (−3.58, −1.08)[a]	−1.01 (−1.94, −0.23)[a]	−2.29 (−3.69, −1.07)[a]
	0.92 (0.17, 1.76)[a]	Metformin	−0.08 (−0.45, 0.31)	−0.51 (−1.16, 0.09)	0.78 (−0.53, 1.82)	−0.41 (−1.01, 0.12)	−0.86 (−1.62, −0.20)[a]	−0.69 (−1.49, 0.09)	−1.27 (−2.42, −0.36)[a]	−0.12 (-0.49, 0.28)	−1.33 (−2.54, −0.34)[a]
	0.97 (0.20, 1.90)[a]	0.08 (−0.31, 0.45)	EE/CA	−0.44 (−1.21, 0.25)	0.81 (−0.45, 1.97)	−0.34 (−1.07, 0.29)	−0.78 (−1.67, −0.06)[a]	−0.61 (−1.49, 0.24)	−1.20 (−2.42, −0.21)[a]	–0.02 (−0.23, 0.15)	−1.24 (−2.55, −0.23)[a]
	1.46 (0.51, 2.48)[a]	0.51 (−0.09, 1.16)	0.44 (−0.25, 1.21)	Lifestyle	1.31 (−0.13, 2.50)	0.10 (−0.16, 0.38)	−0.34 (−0.68, −0.04)[a]	−0.17 (−0.82, 0.48)	−0.76 (−1.62, −0.03)[a]	0.41 (−0.30, 1.19)	−0.79 (−1.79, 0.01)
	0.17 (−0.44, 0.89)	−0.78 (−1.82, 0.53)	−0.81 (−1.97, 0.45)	−1.31 (−2.50, 0.13)	Exercise	−1.21 (−2.36, 0.25)	−1.67 (−2.92, −0.23)[a]	−1.45 (−2.78, −0.13)[a]	−2.09 (−3.57, −0.41)[a]	−0.84 (−2.00, 0.40)	−2.14 (−3.65, −0.47)[a]
	1.36 (0.44, 2.33)[a]	0.41 (−0.12, 1.01)	0.34 (−0.29, 1.07)	−0.10 (−0.38, 0.16)	1.21 (−0.25, 2.36)	Diet	−0.43 (−0.90, −0.04)[a]	−0.29 (−0.82, 0.32)	−0.83 (−1.78, −0.09)[a]	0.30 (−0.34, 1.03)	−0.87 (−1.95, −0.02)[a]
	1.82 (0.79, 2.88)[a]	0.86 (0.20, 1.62)[a]	0.78 (0.06, 1.67)[a]	0.34 (0.04, 0.68)[a]	1.67 (0.23, 2.92)[a]	0.43 (0.04, 0.90)[a]	Metformin + lifestyle	0.17 (−0.51, 0.90)	−0.43 (−1.20, 0.27)	0.74 (0.02, 1.61)[a]	−0.45 (−1.37, 0.33)
	1.60 (0.56, 2.76)[a]	0.69 (−0.09, 1.49)	0.61 (−0.24, 1.49)	0.17 (−0.48, 0.82)	1.45 (0.13, 2.78)[a]	0.29 (−0.32, 0.82)	−0.17 (−0.90, 0.51)	Metformin + diet	−0.57 (−1.72, 0.34)	0.58 (−0.28, 1.44)	−0.61 (−1.85, 0.41)
	2.25 (1.08, 3.58)[a]	1.27 (0.36, 2.42)[a]	1.20 (0.21, 2.42)[a]	0.76 (0.03, 1.62)[a]	2.09 (0.41, 3.57)[a]	0.83 (0.09, 1.78)[a]	0.43 (−0.27, 1.20)	0.57 (−0.34, 1.72)	EE/CA + lifestyle	1.15 (0.19, 2.39)[a]	−0.05 (−0.46, 0.43)
	1.01 (0.23, 1.94)[a]	0.12 (−0.28, 0.49)	0.02 (−0.15, 0.23)	−0.41 (−1.19, 0.30)	0.84 (−0.40, 2.00)	−0.30 (−1.03, 0.34)	−0.74 (−1.61, −0.02)[a]	−0.58 (−1.44, 0.28)	−1.15 (−2.39, −0.19)[a]	Metformin + EE/CA	−1.21 (−2.49, −0.21)[a]
	2.29 (1.07, 3.69)[a]	1.33 (0.34, 2.54)[a]	1.24 (0.23, 2.55)[a]	0.79 (−0.01, 1.79)	2.14 (0.47, 3.65)[a]	0.87 (0.02, 1.95)[a]	0.45 (−0.33, 1.37)	0.61 (−0.41, 1.85)	0.05 (−0.43, 0.46)	1.21 (0.21, 2.49)[a]	EE/DRSP + lifestyle

PCOS polycystic ovary syndrome, *EE/CA* 2 mg cyproterone acetate plus 0.05 mg ethinylestradiol, *EE/DRSP* 3 mg drospirenone plus 0.03 mg ethinylestradiol, *LDL-c* low-density lipoprotein cholesterol

[a]Values mean significance

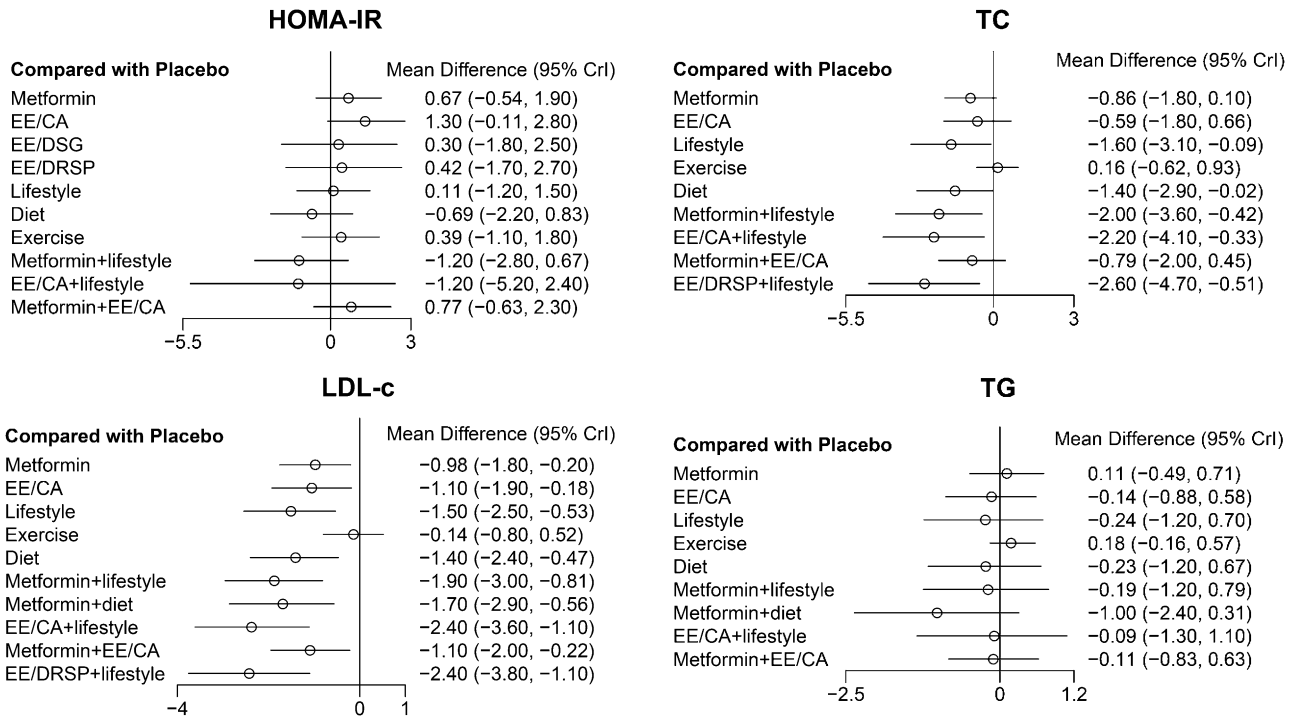

Fig. 3 Mean difference (95% credibility interval (CrI)) for the network comparison of polycystic ovary syndrome interventions for HOMA-IR, TC, LDL-c, and TGs. Both the mean difference and 95% CrI are less than zero; that is to say, the intervention is beneficial for reducing the parameter. EE/CA 2 mg cyproterone acetate plus 0.05 mg ethinylestradiol, EE/DSG 0.15 mg desogestrel plus 0.03 mg ethinylestradiol, EE/DRSP 3 mg drospirenone plus 0.03 mg ethinylestradiol, HOMA-IR homeostasis model assessment of insulin resistance, TC total cholesterol, LDL-c low-density lipoprotein cholesterol, TGs total triglycerides

diagnosed with PCOS because of irregular menstruation or infertility; thus, in most cases, the focus of attention lies on irregular menstruation or infertility, ignoring the possible long-term effects of PCOS on abnormal glucose and lipid metabolism. Therefore, in early treatment, doctors should pay more attention to monitoring and choosing effective treatments for glucose and lipid metabolism and should inform patients about the risks associated with this disorder.

The pairwise meta-analysis (Table 2) indicated that metformin combined with EE/CA or lifestyle had better effects on overweight PCOS patients with respect to reducing the levels of HOMA-IR, TC, LDL-c, and TGs. Some studies have revealed that oral contraceptive agents can decrease peripheral insulin receptors [42] and induce subclinical abnormalities in carbohydrate metabolism [43]. However, according to the results of the pairwise meta-analysis, metformin combined with EE/CA could be a better intervention to improve glucose metabolism.

Our NMA (Fig. 3) revealed that for the HOMA-IR level, the same results were obtained as were found in the pairwise meta-analysis: metformin combined with EE/CA or lifestyle had better effects in terms of the HOMA-IR level than metformin, EE/CA, or lifestyle alone (Table 3). Meanwhile, lifestyle, diet, metformin + lifestyle, EE/CA + lifestyle, and EE/DRSP + lifestyle could be effective in reducing TC (Table 4), and most interventions, with the exception of exercise, could reduce LDL-c (Table 5) in the overweight PCOS patients. However, none of the interventions exhibited differences in reducing TG levels (Table 6). In addition to the adverse effects on glucose metabolism, some studies have suggested that in women with PCOS, the use of oral contraceptive agents is associated with significant changes in lipid profiles, including elevated LDL-c [44]. These consequences come from the adverse effects of estrogen and the androgen progesterone on lipid metabolism [45]. However, our study showed that oral contraceptive agents especially EE/CA and EE/DRSP combined with lifestyle modification, could significantly reduce TC and LDL-c. Lifestyle modification was a comprehensive approach in the areas of nutrition, behavior, and physical activity that consisted of both diet and exercise control [46]. Diet control was mostly a hypocaloric diet, and aerobic exercise was the main form of exercise control. Lifestyle modification alone could be effective in reducing lipid parameters. When combined with EE/CA or EE/DRSP, the lifestyle modification could reduce the adverse effects of contraceptives on lipid metabolism. Thus, the combined therapies can not only normalized abnormal menstruation, but also might improve lipid metabolism in overweight PCOS patients.

According to the SUCRA values (Table 7), three interventions may be particularly effective in improving

Table 6 Network meta-analysis results of PCOS intervention about TGs

	Placebo	Metformin	EE/CA	Lifestyle	Exercise	Diet	Metformin + lifestyle	Metformin + diet	EE/CA + lifestyle	Metformin + EE/CA
TGs	Placebo	0.10 (−0.51, 0.71)	−0.13 (−0.90, 0.58)	−0.26 (−1.25, 0.67)	0.18 (−0.17, 0.56)	−0.26 (−1.17, 0.65)	−0.20 (−1.26, 0.78)	−1.01 (−2.36, 0.29)	−0.13 (−1.38, 1.10)	−0.10 (−0.83, 0.63)
	−0.10 (−0.71, 0.51)	Metformin	−0.24 (−0.67, 0.18)	−0.36 (−1.15, 0.37)	0.08 (−0.61, 0.79)	−0.36 (−1.06, 0.32)	−0.31 (−1.19, 0.50)	−1.11 (−2.33, 0.10)	−0.21 (−1.34, 0.85)	−0.21 (−0.62, 0.21)
	0.13 (−0.58, 0.90)	0.24 (−0.18, 0.67)	EE/CA	−0.13 (−1.00, 0.75)	0.32 (−0.47, 1.16)	−0.13 (−0.94, 0.72)	−0.07 (−1.04, 0.88)	−0.89 (−2.17, 0.47)	0.02 (−1.16, 1.19)	0.03 (−0.18, 0.29)
	0.26 (−0.67, 1.25)	0.36 (−0.37, 1.15)	0.13 (−0.75, 1.00)	Lifestyle	0.45 (−0.55, 1.52)	−0.00 (−0.28, 0.34)	0.06 (−0.31, 0.39)	−0.76 (−1.72, 0.29)	0.15 (−0.63, 0.89)	0.17 (−0.72, 1.05)
	−0.18 (−0.56, 0.17)	−0.08 (–0.79, 0.61)	−0.32 (−1.16, 0.47)	−0.45 (−1.52, 0.55)	Exercise	−0.44 (−1.43, 0.54)	−0.38 (−1.51, 0.65)	−1.19 (−2.60, 0.16)	−0.31 (−1.64, 0.97)	−0.29 (−1.10, 0.51)
	0.26 (−0.65, 1.17)	0.36 (−0.32, 1.06)	0.13 (−0.72, 0.94)	0.00 (−0.34, 0.28)	0.44 (−0.54, 1.43)	Diet	0.06 (−0.44, 0.48)	−0.76 (−1.71, 0.22)	0.14 (−0.71, 0.93)	0.16 (−0.67, 0.96)
	0.20 (−0.78, 1.26)	0.31 (−0.50, 1.19)	0.07 (−0.88, 1.04)	−0.06 (−0.39, 0.31)	0.38 (−0.65, 1.51)	−0.06 (−0.48, 0.44)	Metformin + lifestyle	−0.80 (−1.85, 0.27)	0.09 (−0.60, 0.74)	0.11 (−0.84, 1.07)
	1.01 (−0.29, 2.36)	1.11 (−0.10, 2.33)	0.89 (−0.47, 2.17)	0.76 (−0.29, 1.72)	1.19 (−0.16, 2.60)	0.76 (−0.22, 1.71)	0.80 (−0.27, 1.85)	Metformin + diet	0.89 (−0.39, 2.18)	0.92 (−0.41, 2.22)
	0.13 (−1.10, 1.38)	0.21 (−0.85, 1.34)	−0.02 (−1.19, 1.16)	−0.15 (−0.89, 0.63)	0.31 (−0.97, 1.64)	−0.14 (−0.93, 0.71)	−0.09 (−0.74, 0.60)	−0.89 (−2.18, 0.39)	EE/CA + lifestyle	0.01 (−1.15, 1.21)
	0.10 (−0.63, 0.83)	0.21 (−0.21, 0.62)	−0.03 (−0.29, 0.18)	−0.17 (−1.05, 0.72)	0.29 (−0.51, 1.10)	−0.16 (−0.96, 0.67)	−0.11 (−1.07, 0.84)	−0.92 (−2.22, 0.41)	−0.01 (–1.21, 1.15)	Metformin + EE/CA

PCOS polycystic ovary syndrome, *EE/CA* 2 mg cyproterone acetate plus 0.05 mg ethinylestradiol, *TGs* total triglycerides

Table 7 SUCRA values and ranks of PCOS interventions among end-point outcomes

Interventions	HOMA-IR		TC		LDL-C		TGs	
	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank	SUCRA	Rank
Metformin	0.29	8	0.40	6	0.27	9	0.23	8
EE/CA	0.05	10	0.26	8	0.33	8	0.54	4
EE/DSG	0.48	5	–[a]	–[a]	–[a]	–[a]	–[a]	–[a]
EE/DRSP	0.42	7	–[a]	–[a]	–[a]	–[a]	–[a]	–[a]
Lifestyle	0.58	4	0.63	4	0.58	5	0.59	3
Exercise	0.75	3	0.08	9	0.08	10	0.22	9
Diet	0.43	6	0.56	5	0.51	6	0.60	2
Metformin + lifestyle	0.88	1	0.81	3	0.78	3	0.53	5
Metformin + diet	–[a]	–[a]	–[a]	–[a]	0.68	4	0.94	1
EE/CA + lifestyle	0.76	2	0.83	2	0.92	2	0.45	7
Metformin + EE/CA	0.27	9	0.39	7	0.38	7	0.49	6
EE/DRSP + lifestyle	–[a]	–[a]	0.93	1	0.93	1	–[a]	–[a]

SUCRA surface under the cumulative ranking curve, *PCOS* polycystic ovary syndrome, *EE/CA* 2 mg cyproterone acetate plus 0.05 mg ethinylestradiol, *EE/DSG* 0.15 mg desogestrel plus 0.03 mg ethinylestradiol, *EE/DRSP* 3 mg drospirenone plus 0.03 mg ethinylestradiol, *HOMA-IR* homeostasis model assessment of insulin resistance, *TC* total cholesterol, *LDL-c* low-density lipoprotein cholesterol, *TGs* total triglycerides

[a]Not available

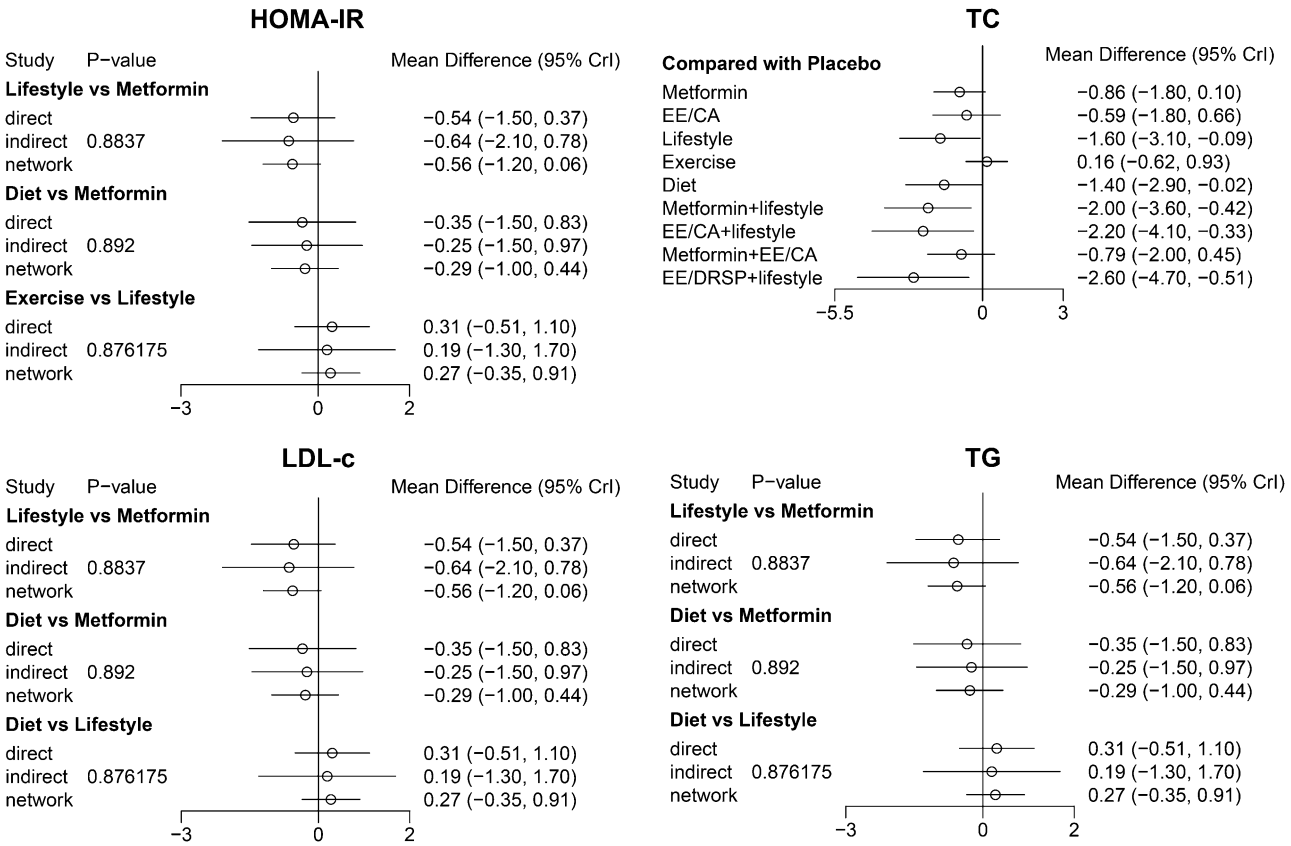

Fig. 4 Node-splitting method for assessing the consistency of HOMA-IR, TC, LDL-c, and TG levels, *P* values were >0.05, which showed that the direct evidence of the outcomes was consistent with the indirect evidence. HOMA-IR homeostasis model assessment of insulin resistance, TC total cholesterol, LDL-c low-density lipoprotein cholesterol, TGs total triglycerides

HOMA-IR and reducing lipid levels: metformin + lifestyle, EE/CA + lifestyle, and EE/DRSP + lifestyle. In our study, metformin + lifestyle was the most effective with respect to the improvement of HOMA-IR. In addition, EE/DRSP + lifestyle appeared to be the best intervention for reducing TC and LDL-c. Moreover, metformin + diet was more effective in reducing TG levels. In brief, oral contraceptive agents, especially EE/CA and EE/DRSP combined with lifestyle or metformin could not only improve insulin resistance but can also decrease TC and LDL-c. Metformin + lifestyle could be the best way to improve insulin resistance, while metformin + diet could be the best way to reduce TG levels. These combined therapies would be the better choice for metabolic disorders in overweight PCOS patients.

Nevertheless, it is essential to discuss some key issues that existed in our study. First, we included 20 RCTs, but some interventions were missing due to the lack of studies. The EE/DRSP + lifestyle intervention only appeared in the studies investigating TC and LDL-c, so we could not summarize the effectiveness on all the metabolic markers. Second, we limited the average BMI to ≥ 25 (kg/m^2); thus, the conclusions are only applicable to overweight PCOS patients. Moreover, the intervention time and the dose of metformin, exercise volume, and diet control would be the target of future analysis. However, the conclusions and limitations of this study may provide some directions for the design of new trials.

In conclusion, our evidence revealed that for overweight PCOS patients, oral contraceptive agents such as EE/CA and EE/SRSP, combined with metformin or lifestyle control can reduce the adverse effects on glucose and lipid metabolism that result from oral contraceptive agents used alone. Metformin + lifestyle, EE/CA + lifestyle, and EE/DRSP + lifestyle are particularly effective in improving HOMA-IR and reducing the levels of TC and LDL-c. Moreover, metformin + diet is more effective in reducing TG levels. These results provide clinical guidance for the treatment of PCOS, demonstrating that lifestyle control combined with conventional treatment of PCOS such as metformin, EE/CA, and EE/DRSP is the best way to improve HOMA-IR levels and lipid metabolism in overweight PCOS patients. Hence, large-scale clinical trials are urgently needed to study the appropriate dosage of metformin, exercise volume, and dietary control.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. G. Bozdag, S. Mumusoglu, D. Zengin, E. Karabulut, B.O. Yildiz, The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. Hum. Reprod. **31**, 2841–2855 (2016)
2. S. Mahalingaiah, E. Diamanti-Kandarakis, Targets to treat metabolic syndrome in polycystic ovary syndrome. Expert Opin. Ther. Targets **19**, 1561–1574 (2015)
3. S.F. De Medeiros, Risks, benefits size and clinical implications of combined oral contraceptive use in women with polycystic ovary syndrome. Reprod. Biol. Endocrinol. **15**, 93 (2017)
4. N. Naderpoor, S. Shorakae, B. de Courten, M.L. Misso, L.J. Moran, H.J. Teede, Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. Hum. Reprod. Update **21**, 560–574 (2015)
5. R. Davidson, T. Motan, C. Korownyk, Clomiphene for anovulatory infertility. Can. Fam. Physician **62**, 492 (2016)
6. S. Mitra, P.K. Nayak, S. Agrawal, Laparoscopic ovarian drilling: an alternative but not the ultimate in the management of polycystic ovary syndrome. J. Nat. Sci. Biol. Med. **6**, 40–48 (2015)
7. A.P. Delitala, G. Capobianco, G. Delitala, P.L. Cherchi, S. Dessole, Polycystic ovary syndrome, adipose tissue and metabolic syndrome. Arch. Gynecol. Obstet. **296**, 405–419 (2017)
8. R.S. Legro, Ovulation induction in polycystic ovary syndrome: current options. Best Pract. Res. Clin. Obstet. Gynaecol. **37**, 152–159 (2016)
9. H. Abu Hashim, A. Wafa, M. El Rakhawy, Combined metformin and clomiphene citrate versus highly purified FSH for ovulation induction in clomiphene-resistant PCOS women: a randomised controlled trial. Gynecol. Endocrinol. **27**, 190–196 (2011)
10. H. Nasri, M. Rafieian-Kopaei, Metformin: current knowledge. J. Res. Med. Sci. **19**, 658–664 (2014)
11. K.G. Piparva, J.G. Buch, Deep vein thrombosis in a woman taking oral combined contraceptive pills. J. Pharmacol. Pharmacother. **2**, 185–186 (2011)
12. R. Sitruk-Ware, A. Nath, Metabolic effects of contraceptive steroids. Rev. Endocr. Metab. Disord. **12**, 63–75 (2011)
13. M. Api, H. Görgen, A. Cetin, Laparoscopic ovarian drilling in polycystic ovary syndrome. Eur. J. Obstet. Gynecol. Reprod. Biol. **119**, 76–81 (2005)
14. J.P. Domecq, G. Prutsky, R.J. Mullan, A. Hazem, V. Sundaresh, Lifestyle modification programs in polycystic ovary syndrome: systematic review and meta-analysis. J. Clin. Endocrinol. Metab. **98**, 4655–4663 (2013)
15. H.F. Escobar Morreale, Polycystic ovary syndrome: definition, aetiology, diagnosis and treatment. Nat. Rev. Endocrinol. **14**, 270–284 (2018)
16. J.J. Deeks, J.P. Higgins, D.G. Altman, Assessing risk of bias in included studies. in *Cochrane Handbook or Systematic Reviews of Interventions Version 5.1.0*, ed. by J.P. Higgins, S. Green (The Cochrane Collaboration, UK, 2011), Chapter 8
17. B. Bruner, K. Chad, D. Chizen, Effects of exercise and nutritional counseling in women with polycystic ovary syndrome. Appl. Physiol. Nutr. Metab. **31**, 384–391 (2006)
18. S.P. Hozo, B. Djulbegovic, I. Hozo, Estimating the mean and variance from the median, range, and the size of a sample. BMC Med. Res. Methodol. **5**, 13 (2005)
19. A.E. Georgia Salantia, Adesb, P.A. John, Ioannidis: graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J. Clin. Epidemiol. **64**, 163–171 (2011)
20. J. Lord, R. Thomas, B. Fox, U. Acharya, T. Wilkin, The effect of metformin on fat distribution and the metabolic syndrome in

women with polycystic ovary syndrome—a randomised, double-blind, placebo-controlled trial. BJOG **113**, 817–824 (2006)
21. A. Gambineri, L. Patton, A. Vaccina, M. Cacciari, A.M. Morselli-Labate, C. Cavazza, U. Pagotto, R. Pasquali, Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. J. Clin. Endocrinol. Metab. **91**, 3970–3980 (2006)
22. T. Tang, J. Glanville, C.J. Hayden, D. White, J.H. Barth, A.H. Balen, Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study. Hum. Reprod. **21**, 80–89 (2006)
23. C. Vigorito, F. Giallauria, S. Palomba, T. Cascella, F. Manguso, R. Lucci, A. De Lorenzo, D. Tafuri, G. Lombardi, A. Colao, F. Orio, Beneficial effects of a three-month structured exercise training program on cardiopulmonary functional capacity in young women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. **92**, 1374–1384 (2007)
24. LK Ma, L.N. Jin, Q. Yu, L. Xu, Effect of lifestyle adjustment, metformin and rosiglitazone in polycystic ovary syndrome. Zhonghua. Fu. Chan. Ke. Za. Zhi. **42**, 294–297 (2007)
25. S.K. Hutchison, C. Harrison, N. Stepto, C. Meyer, Teede Hj, Retinol-binding protein 4 and insulin resistance in polycystic ovary syndrome. Diabetes Care **31**, 1427–1432 (2008)
26. R.L. Thomson, J.D. Buckley, M. Noakes, P.M. Clifton, R.J. Norman, G.D. Brinkworth, The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. J. Clin. Endocrinol. Metab. **93**, 3373–3380 (2008)
27. L. Kebapcilar, A. Yuksel, G. Bozkaya et al. Effects of an EE/CA compared with EE/CA-metformin on serum ADMA levels in women with polycystic ovary syndrome. Cent. Eur. J. Med. **4**, 423–427 (2009). https://doi.org/10.2478/s11536-009-0074-x
28. L. Kebapcilar, C.E. Taner, A.G. Kebapcilar, A. Alacacioglu, I. Sari, Comparison of four different treatment regimens on coagulation parameters, hormonal and metabolic changes in women with polycystic ovary syndrome. Arch. Gynecol. Obstet. **281**, 35–42 (2010)
29. A. Kriplani, A.J. Periyasamy, N. Agarwal, V. Kulshrestha, A. Kumar, A.C. Ammini, Effect of oral contraceptive containing ethinyl estradiol combined with drospirenone vs. desogestrel on clinical and biochemical parameters in patients with polycystic ovary syndrome. Contraception **82**, 139–146 (2010)
30. C. Fux Otta, M. Wior, G.S. Iraci, R. Kaplan, D. Torres, M.I. Gaido, E.P. Wyse, Clinical, metabolic, and endocrine parameters in response to metformin and lifestyle intervention in women with polycystic ovary syndrome: A randomized, double-blind, and placebo control trial. Gynecol. Endocrinol. **26**, 173–178 (2010)
31. S.M. Bhattacharya, A. Jha, Comparative study of the therapeutic effects of oral contraceptive pills containing desogestrel, cyproterone acetate, and drospirenone in patients with polycystic ovary syndrome. Fertil. Steril. **98**, 1053–1059 (2012)
32. S. Bonakdaran, Z. Mazloom Khorasani, B. Davachi, J. Mazloom Khorasani, The effects of calcitriol on improvement of insulin resistance, ovulation and comparison with metformin therapy in PCOS patients: a randomized placebo- controlled clinical trial. Iran. J. Reprod. Med. **10**, 465–472 (2012)
33. F. Esfahanian, M.M. Zamani, R. Heshmat, F. Moini nia, Effect of metformin compared with hypocaloric diet on serum C-reactive protein level and insulin resistance in obese and overweight women with polycystic ovary syndrome. J. Obstet. Gynaecol. Res. **39**, 806–813 (2012)
34. D.D. Curi, A.M. Fonseca, J.A. Marcondes, J.A. Almeida, V.R. Bagnoli, J.M. Soares Jr, E.C. Baracat, Metformin versus lifestyle changes in treating women with polycystic ovary syndrome. Gynecol. Endocrinol. **28**, 182–185 (2012)
35. M. Amiri, M. Golsorkhtabaramiri, S. Esmaeilzadeh, F. Ghofrani, A. Bijani, L. Ghorbani et al. Effect of metformin and flutamide on anthropometric indices and laboratory tests in obese/overweight PCOS women under hypocaloric diet. J. Reprod. Infertil. **15**, 205–213 (2014)
36. I. Almenning, A. Rieber-Mohn, K.M. Lundgren, T. Shetelig Løvvik, K.K. Garnæs, T. Moholdt, Effects of high intensity interval training and strength training on metabolic, cardiovascular and hormonal outcomes in women with polycystic ovary syndrome: a pilot study. PLoS ONE **10**, 1–16 (2015)
37. W. Feng, Y.Y. Jia, D.Y. Zhang, H.R. Shi, Management of polycystic ovarian syndrome with Diane-35 or Diane-35 plus metformin. Gynecol. Endocrinol. **32**, 147–150 (2016)
38. Q.Y. Wang, Y. Song, W. Huang, L. Xiao, Q.S. Wang, G.M. Feng, Comparison of drospirenone- with cyproterone acetate-containing oral contraceptives, combined with metformin and lifestyle modifications in women with polycystic ovary syndrome and metabolic disorders: a prospective randomized control trial. Chin. Med. J. (Engl.). **129**, 883–890 (2016)
39. J. Song, X. Ruan, M. Gu, L. Wang, H. Wang, A.O. Mueck, Effect of orlistat or metformin in overweight and obese polycystic ovary syndrome patients with insulin resistance. Gynecol. Endocrinol. **34**, 413–417 (2017)
40. M. Jové, I. Pradas, A. Naudí, S. Rovira-Llopis, C. Bañuls, M. Rocha, M. Portero-Otin, A. Hernández-Mijares, V.M. Victor, R. Pamplona, Lipidomics reveals altered biosynthetic pathways of glycerophospholipids and cell signaling as biomarkers of the polycystic ovary syndrome. Oncotarget **9**, 4522–4536 (2018)
41. C.J. Glueck, R. Papanna, P. Wang, N. Goldenberg, L. Sieve-Smith, Incidence and treatment of metabolic syndrome in newly referred women with confirmed polycystic ovarian syndrome. Metabolism **52**, 908–915 (2003)
42. R. De Pirro, F. Forte, A. Bertoli, A.V. Greco, R. Lauro, Changes in insulin receptors during oral contraception. J. Clin. Endocrinol. Metab. **52**, 29–33 (1981)
43. I.F. Godsland, C. Walton, C. Felton, A. Proudler, A. Patel, V. Wynn, Insulin resistance, secretion, and metabolism in users of oral contraceptives. J. Clin. Endocrinol. Metab. **74**, 64–70 (1992)
44. M. Amiri, F. Ramezani Tehrani, F. Nahidi, A. Kabir, F. Azizi, E. Carmina, Effects of oral contraceptives on metabolic profile in women with polycystic ovary syndrome: a meta-analysis comparing products containing cyproterone acetate with third generation progestins. Metabolism **73**, 22–35 (2017)
45. A. Nath, R. Sitruk-Ware, Different cardiovascular effects of progestins according to structure and activity. Climacteric **12**, 96–101 (2009)
46. K.M. Hoeger, L. Kochman, N. Wixom, K. Craig, R.K. Miller, D. S. Guzick, A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: a pilot study. Fertil. Steril. **82**, 421–429 (2004)