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Meta-Analysis

Metformin and Combined Oral Contraceptive Pills in the Management of Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis

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Abstract

Context: Polycystic ovary syndrome (PCOS) affects more than 1 in 10 women.

Objective: As part of the 2023 International PCOS Guidelines update, comparisons between combined oral contraceptive pills (COCP), metformin, and combination treatment were evaluated.

Data Sources: Ovid Medline, Embase, PsycINFO, All EBM, and CINAHL were searched.

Study Selection: Women with PCOS included in randomized controlled trials (RCTs).

Data Extraction: We calculated mean differences and 95% CIs regarding anthropometrics, metabolic, and hyperandrogenic outcomes. Meta-analyses and quality assessment using GRADE were performed.

Data Synthesis: The search identified 1660 publications; 36 RCTs were included. For hirsutism, no differences were seen when comparing metformin vs COCP, nor when comparing COCP vs combination treatment with metformin and COCP. Metformin was inferior on free androgen index (FAI) (7.08; 95% CI 4.81, 9.36), sex hormone binding globulin (SHBG) (−118.61 nmol/L; 95% CI −174.46, −62.75) and testosterone (0.48 nmol/L; 95% CI 0.32, 0.64) compared with COCP. COCP was inferior for FAI (0.58; 95% CI 0.36, 0.80) and SHBG (−16.61 nmol/L; 95% CI −28.51, −4.71) compared with combination treatment, whereas testosterone did not differ. Metformin lowered insulin (−27.12 pmol/L; 95% CI −40.65, −13.59) and triglycerides (−0.15 mmol/L; 95% CI −0.29, −0.01) compared with COCP. COCP was inferior for insulin (17.03 pmol/L; 95% CI 7.79, 26.26) and insulin resistance (0.44; 95% CI 0.17, 0.70) compared with combination treatment.

Conclusions: The choice of metformin or COCP treatment should be based on symptoms, noting some biochemical benefits from combination treatment targeting both major endocrine disturbances seen in PCOS (hyperinsulinemia and hyperandrogenism).

Key Words: polycystic ovary syndrome, metformin, combined oral contraceptive pill, meta-analysis, hirsutism, weight

Polycystic ovary syndrome (PCOS) affects approximately 10% of women globally (1) and is characterized by chronic anovulation, oligo/amenorrhea, hyperandrogenism, polycystic ovarian morphology, and metabolic and psychological manifestations. PCOS is associated with hyperinsulinemia, insulin resistance, and increased body mass index (BMI). Higher BMI can increase risks of gestational diabetes, type 2 diabetes, and cardiovascular disease (2, 3, 4). Insulin enhances ovarian and adrenal androgen secretion, exaggerating hyperandrogenic symptoms in PCOS (5). Androgen excess favors visceral fat deposition and lipid dysfunction with a vicious cycle of worsening of hyperinsulinemia and insulin resistance (6). To

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break the vicious cycle, both insulin resistance and hyperandrogenism are key treatment targets in PCOS.

Metformin is an insulin-sensitizing drug, known to inhibit gluconeogenesis and lipogenesis (7) and prevent weight gain by influencing appetite regulatory pathways in the brain (8). Several studies have shown that metformin may improve biochemical hyperandrogenism and anovulation (9, 10). Generally combined oral contraceptive pills (COCP) are regarded as more effective than metformin for the management of hyperandrogenism and menstrual regulation in PCOS (11, 12).

COCP, containing estrogen and progestin components, are primarily used as contraception. Due to their direct endometrial effects, COCPs are also used among women with PCOS to regulate the menstrual cycle. A recent systematic review by our group found COCP to be effective in improving menstrual cyclicity and hirsutism in PCOS, with limited evidence for hirsutism (13). COCPs containing cyproterone acetate (CPA) might be more effective in reducing hirsutism compared to conventional COCPs (14, 15); however, the use of COCPs containing CPA is not recommended as first-line treatment due to the increased risk of venous thromboembolism in the general population (12, 16). Overall, finding the most favorable medical treatment for PCOS remains challenging. To treat insulin resistance, hyperandrogenism, irregular cycles, and metabolic features, a medical treatment combining COCP and metformin has been suggested (17).

We performed a systematic review and meta-analysis of the most up-to-date evidence regarding metformin and COCP in the management of clinical and hormonal outcomes in women with PCOS. Results will directly inform the 2023 International Evidence-based Guideline for the Assessment and Management of PCOS. Subgroup analyses based on BMI and age (adolescent and adult), as well as type of COCP (with or without CPA) were performed to further inform recommendations regarding the optimal treatment for the individual patient.

Table 1. Population, intervention, comparison and outcome (PICO) of the systematic review and meta-analysis

PICO elements	Keywords
Patients	Females with PCOS (diagnosed by Rotterdam, NIH, or AES) of any ethnicity and weight. Subgroups: Adolescents (10-19 years), adults, BMI < 25 kg/m^2, BMI ≥ 25 kg/m^2 Exclusion criteria: Females without PCOS. Less than 2 years post menarche. Women with type 2 diabetes, comorbidities, or major depression
Intervention	All types of COCPs, metformin, or COCP + metformin For hirsutism, at least 6 months treatment, for other outcomes at least 3 months treatment. Subgroups: Progestins based on different androgenicity (containing or not containing CPA) Exclusion criteria: Nonoral formulation of contraceptives
Comparisons	As stated in intervention
Outcomes	Anthropometric: Weight, BMI, WHR Androgenicity: Hirsutism (FG score), FAI, testosterone and SHBG, DHEAS, androstenedione, irregular cycles Metabolic: Insulin resistance (HOMA-IR, Clamp, OGTT), cholesterol, LDL, HDL, triglycerides, CRP, PAI-1 levels Psychological: QoL, depression Adverse effects

Abbreviations: BMI, body mass index; COCP, combined oral contraceptive pills; CPA, cyproterone acetate; CRP, C-reactive protein; DHEAS, dehydroepiandrosterone sulfate; FAI, free androgen index; FG score, Ferriman Gallwey score; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; PAI-1, plasminogen activator inhibitor; PCOS, polycystic ovary syndrome; QoL, quality of life; WHR, waist to hip ratio; SHBG, sex hormone binding globulin.

Materials and Methods

This systematic review and meta-analysis was conducted as part of the 2023 update of the International Evidence-based Guidelines for the Assessment and Management of PCOS (18). We addressed the efficacy of (i) metformin compared to COCP; (ii) COCP monotherapy compared with metformin and COCP; and (iii) metformin monotherapy compared with metformin and COCP in women with PCOS for improving anthropometric, biochemical, clinical, and psychological outcomes.

Selection Criteria

The Population, Intervention, Comparison and Outcome (PICO) framework for this systematic review is outlined in Table 1 and was determined by an experienced, multidisciplinary, clinical research team (A.M., T.P., D.R., P.M.S., C.T.T., A.P., S.W., H.T.). Core outcomes were based on a Delphi process involving 700 clinicians, academic opinion leaders, and consumers (19). Outcomes included anthropometric, metabolic, androgenicity, and psychological outcomes, as well as adverse events (detailed in Table 1).

Data Sources

This systematic review and meta-analysis provide an update of a previous systematic review (12) conducted in 2017 to inform the International Evidence-based Guidelines for the Assessment and Management of PCOS (20). This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (21, 22). The study protocol was registered prior to full-text screening in PROSPERO (Registration number CRD42022345640).

Ovid Medline, Embase, PsycINFO, All EBM, and CINAHL were searched to identify relevant literature from 2017 until July 7, 2022. We also re-evaluated all articles, which were found in the search performed during the previous systematic review ranging from 1946 to 2017, as well as additional references identified from relevant systematic reviews. Details of the search strategy are presented in Supplementary Fig. S1 (23).

Study Selection

Two authors (J.M., M.F., or S.A.) independently screened each potential study on title and abstract with the use of COVIDENCE. The same authors performed the full-text screening to determine the final included studies. If there was any doubt about inclusion, the study was reviewed and discussed in a larger group (J.M., M.F., S.A., and C.T.T.).

Quality Appraisal of the Evidence

Quality appraisal of the included studies, in terms of risk of bias (RoB), was performed by J.M. and M.F. using RoB2 (24). Individual quality items included methods of

randomization and group allocation; blinding of patients, carers, investigators, or outcome assessors; methods of outcome assessment and reporting; methods of data analysis; statistical issues; and trial pre-registration. Disagreements were resolved by discussion and re-inspection of the full-text article. Each study was adjudged as having an overall low RoB, some concerns, or high RoB. We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) method to estimate the certainty of the evidence (25). GRADE assessments were conducted in duplicate by J.M. and M.F.

Data Extraction

Two independent reviewers (J.M. and M.F.) extracted data from included studies, using a specially developed data extraction form according to selection criteria. Extracted data included a description of the study (authors, country, year of publication, setting, diagnostic criteria for PCOS), participants (mean age and BMI), intervention (dose and duration of metformin and COCP) and study results according to outcome. All units were recalculated to SI units and SD.

Statistical Analysis

Meta-analyses were performed using Review Manager 5.4.1. For continuous outcomes we calculated mean differences (MD) and 95% CI and for dichotomous outcomes odds ratios (ORs) and 95% CI. Due to clinical heterogeneity from differences in metformin dose, type of COCP, and duration of treatment, random effects models were used for the meta-analyses.

We performed subgroup analyses according to BMI, age (adults and adolescents), and type of COCP. Regarding BMI, studies were sorted into 3 categories; those with participants with a BMI < 25 kg/m^2, those with a BMI ≥ 25 kg/m^2, and studies using other BMI cutoffs (BMI not classified). Participants aged 10 to 19 years were classified as adolescents. Subgroup analyses according to type of COCP were classified into COCP containing CPA and other COCP.

Funnel plots were inspected for the assessment of publication bias.

Results

Study Selection

From 1660 search results, 450 articles were chosen for full-text review. In addition, we screened 176 full texts from the previous search in 2017 (12). After full-text review, 36 randomized controlled trials (RCTs) in 46 publications were identified (Fig. 1). Of these, 25 RCTs compared metformin with COCP, 17 compared COCP with metformin and COCP, and 6 compared metformin with metformin and COCP. Study characteristics are presented in Table 2. The RCTs were performed in Europe (n = 9) (26-40) North America (n = 4) (41-44), the Middle East (n = 14) (45-58), Asia (n = 8) (59-66), and Australia (n = 1) (67-70) between 2000 and 2021. Intervention durations ranged from 3 to 24 months, with 6 months of follow-up being the most commonly reported data. Metformin doses ranged from 500 mg to 2000 mg daily, with 1500 to 2000 mg daily being the most common dose (in 28 of the 36 studies). Regarding COCP, all studies used 30 to 35 µg ethinylestradiol (EE), 20 studies used CPA as the progestin compound, 14 studies used other progestins, and 2 studies had one study arm with participants using EE/drospirenone and another arm with those using EE/CPA (26, 40). Four studies involved adolescents (41, 42, 44, 49) and the remainder focused on adults.

Risk of Bias

In our systematic review, 2 studies fulfilled the criteria for low RoB, 14 had some concerns, and 20 had a high RoB. All studies adequately described the PCOS diagnostic criteria and inclusion and exclusion criteria. The most common reason for a high RoB was bias arising from the randomization process. The second most common reason was missing outcome data. RoB assessments of the included studies are shown in Fig. 2.

Meta-analyses

Results on metformin compared with COCP are shown in Table 3. Subgroup analyses are shown in Supplementary Tables S1 and S2 (23), also illustrated in Supplementary Fig. S2 (subgroups according to BMI) (23), Supplementary Fig. S3 (subgroups according to adults/adolescents) (23), and Supplementary Fig. S4 (subgroups according to COCP with or without CPA) (23).

Combination treatment (COCP and metformin) compared with COCP monotherapy is presented in Table 4, with subgroup analysis reported in Supplementary Table S3 and Supplementary Fig. S5 (23). Results on combination treatment vs metformin monotherapy are presented in Table 5, with subgroup analysis in Supplementary Table S4 and Supplementary Fig. S6 (23).

We found no evidence of publication bias in the funnel plots.

Anthropometric Outcomes

Metformin vs COCP

Regarding overall results on weight, BMI, and waist to hip ratio (WHR), no differences were found (Table 3).

In subgroup analyses according to BMI and adults/adolescents no differences were seen on weight, BMI and WHR (Supplementary Table S1; Supplementary Figs. S2 and S3) (23).

In subgroup analyses comparing metformin with COCP with and without CPA (Supplementary Table S2; Supplementary Fig. S4) (23) there were no differences in weight. Nevertheless, BMI was lower with metformin when compared with EE/CPA (MD −0.99 kg/m^2; 95% CI, −1.74 to −0.23), but not when compared with COCP without CPA.

COCP vs combination

COCP alone compared with combination treatment with COCP and metformin showed no differences in weight, WHR, or BMI (Table 4).

Metformin vs combination

Metformin was superior in lowering WHR (MD −0.03; 95% CI, −0.06 to −0.01) compared with metformin, with no difference in BMI (Table 5).

Clinical and Biochemical Hyperandrogenism

Metformin vs COCP

No difference was seen in hirsutism in the overall analysis but regarding biochemical hyperandrogenism, metformin was

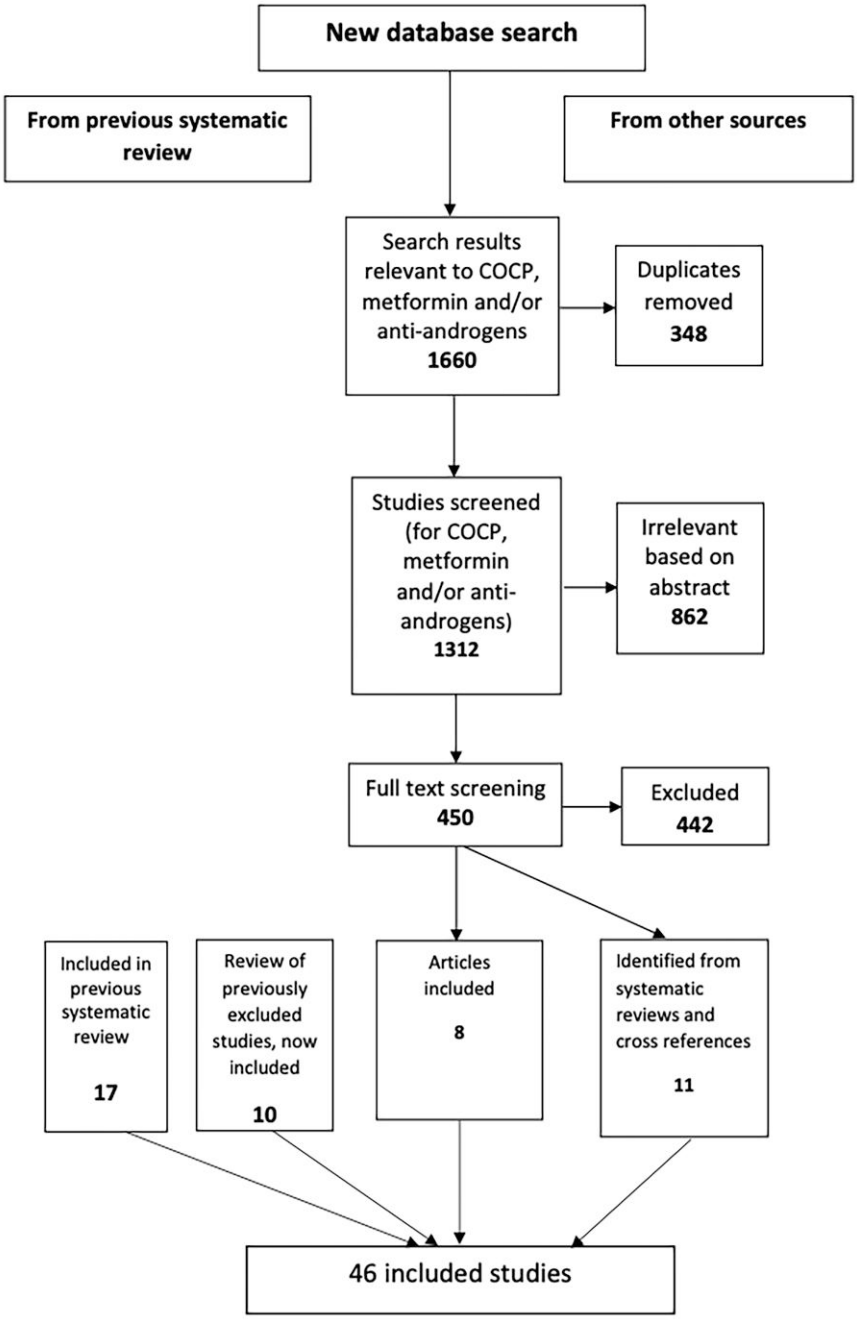

Figure 1. Included studies are shown in the PRISMA flowchart. The search was performed for 3 medical treatments (combined oral contraceptive pills [COCP], metformin, and anti-androgens) as part of the update of the PCOS guidelines. Results comparing COCP, metformin, and combined COCP and metformin were included in this systematic review.

inferior to COCP on free androgen index (FAI) (MD 7.08; 95% CI, 4.81 to 9.36), sex hormone binding globulin (SHBG) (MD −118.61 nmol/L; 95% CI, −174.46 to −62.75), and testosterone (MD 0.48 nmol/L; 95% CI, 0.32 to 0.64) (Table 3).

Subgroup analysis categorized by BMI (Supplementary Table S1; Supplementary Fig. S2) (23) showed that in women with PCOS and a BMI < 25 kg/m^2, metformin was less effective than COCP in treating hirsutism (MD 1.73; 95% CI, 0.07 to 3.40) and improving FAI (MD 5.78; 95% CI, 2.82 to 8.73), total testosterone (MD 0.56 nmol/L; 95% CI, 0.29 to 0.83), and SHBG (MD −168 nmol/L; 95% CI, −211 to −124).

In women with a BMI ≥25 kg/m^2, there was no difference in hirsutism when comparing metformin with COCP. For biochemical hyperandrogenism, metformin was inferior for FAI (MD 9.05; 95% CI, 6.44 to 11.66); total testosterone (MD 0.40 nmol/L; 95% CI, 0.15 to 0.66), and SHBG (MD −96 nmol/L; 95% CI, −121 to −72).

The type of COCP did not influence the overall results regarding clinical and biochemical hyperandrogenism (Supplementary Table S2; Supplementary Fig. S4) (23).

Table 2. Characteristics of included studies

Study ID	RoB	Comparisons	Country, duration	N	Mean age (years)	Mean BMI	PCOS	Menarche age	Smokers	Comments
Aghamohammadzadeh 2010	High	C: 35 μg EE + CPA 2 mg M: Metformin 1000 mg/day	Iran 3 + 6 months	C = 30 M = 30	All 23.4 ± 8.1	All 25.57 ± 5.4	NIH	NR	NR	Adults BMI not classified
Allen 2005	Mod	C: 35 μg EE + 0.25 mg NOR/day M: Metformin 1000 mg/day	USA 6 months	C = 15 M = 16	C: 15.3 (12.5-21) M: 15.4 (13.1-18.4)	C: 40.1 ± 2.1 M: 37.3 ± 1.3	Author defined			Adolescents BMI > 25
Al-Zubeidi 2015	High	C: 30 μg EE + 1 mg NORA/day M: Metformin 2000 mg/day	USA 6 months	C = 10 M = 12	C: 16 (15-17) M: 16 (14-18)	C: 33.4 ± 9 M: 33.7 ± 6	NIH	>2 years post menarche	NR	Adolescents BMI not classified
Bilgir 2009	High	C: 35 μg EE + 2 mg CPA C + M: 35 μg EE + 2 mg CPA + Metformin 1700 mg/day	Turkey 3 months	C = 20 C + M = 20	1: 24.3 ± 5.7 2: 25.2 ± 4.6	C: 28.2 ± 6.0 M: 28.2 ± 4.3	Rott	NR	Nonsmokers	Adults BMI not classified
Bodur 2018	High	C: 30 μg EE + 3 mg DRSP M: Metformin 1700 mg C + M: 30 μg EE + 3 mg DRSP + Metformin 1700 mg	Turkey 6 months	C = 17 M = 17 C + M = 12	1: 26.62 ± 4.92 2: 26.24 ± 3.96 3: 27.35 ± 5.65	C: 23.45 ± 3.40 M: 25.06 ± 3.08 C + M: 25.11 ± 3.75	Rott	NR	NR	Adults BMI not classified
Cetinkalp 2009	High	C: 35 μg EE + 2 mg CPA M: Metformin 2000 mg/day	Turkey 4 months	C = 33 M = 47	NR	C: 24.72 ± 4.1 M: 25.82 ± 6.1	Rott	NR	NR	Adults BMI not classified
Christakou 2014	Mod	C1: 35 μg EE +2 mg CPA C2: 30 μg EE + 3 mg DRSP M: Metformin 1700 mg/day	Greece 3 + 6 months	C1 = 38 C2:=36 M = 35	C1: 22 ± 0.6 C2: 23.2 ± 0.6 M: 21.5 ± 0.5	C1:21.80 ± 0.4 C2: 22.37 ± 0.5 M: 23.03 ± 0.7	NIH	NR	All nonsmokers	Adults BMI < 25 EE/DRSP used in meta-analysis
Cibula 2005	Mod	C: 35 μg EE + 250 μg NOR 21/7 CM: 35 μg EE + 250 μg NOR + Metformin 1500 mg/day	Czech Republic 6 months	C = 15 CM = 13	C: 23.2 ± 4.6 CM: 23.8 ± 5.4	C: 22.1 ± 3.1 CM: 24.7 ± 4.9	Author defined			Adults BMI not classified
Dardzinska 2014	Mod	C: 35μg EE + 2 mg CPA M: Metformin 1700 mg/day 2 months washout	Poland 4 months	Phase 1 C = 21 M = 14 Phase 2 C = 14 M = 7	C 1st: 24.9 [23.5;26.4] M 1st: 24.6 [23.0;26.3]	C 1st: 24.9 ± 4.4 M 1st: 25.1 ± 9.8C 1st: 24.9 [23.5;26.4] M 1st: 24.6 [23.0;26.3]	Rott	NR	20% of all	Adults BMI < 25 Crossover

(*continued*)

Table 2. Continued

Study ID	RoB	Comparisons	Country, duration	N	Mean age (years)	Mean BMI	PCOS	Menarche age	Smokers	Comments
Dorgham 2021	High	1: only laser 2: laser + metformin 500 mg 3: laser + 35 μg EE + 2 mg CPA	Egypt 6 months (results available also for 3 months)	1 = 50 2 = 50 3 = 50	NR	NR	Rott	NR	NR	Adults BMI not classified Facial hirsutism required
El Maghraby 2015	High	C: 30 μg EE + 15 mg progestin/day M: Metformin 1700 mg/day	Egypt 24 months (results available for 6, 12, 18, 24 m)	C = 33 M = 32	C: 16.90 ± 1.60 M: 17.20 ± 2.00	NR	Rott	NR	NR	Adolescents BMI not classified
Elter 2002	Mod	C: 35μg EE + 2 mg CPA 21/7 C + M: 35μg EE + 2 mg CPA + Metformin 1500 mg/day	Turkey 4 months	C = 20 C + M = 20	C: 23.45 ± 6.07 C + M: 24.90 ± 6.62	C: 21.83 ± 1.40 C + M: 22.74 ± 2.66	Author defined	NR	NR	Adults BMI < 25
Essah 2011	Low	C: 35 μg EE + 0.18/0.215/0.25 mg NOR (+ placebo) C + M: 35 μg EE + 0.18/0.215/0.25 mg NOR + Metformin 1500 mg/day	USA 3 months	C = 10 C + M = 9	NR (adults)	C: 32.6 ± 2.3 C + M: 36.2 ± 2.5	Rott	NR	All nonsmokers	Adults BMI not classified
Feng 2016	Mod	C: 35 μg EE + 2 mg CPA C + M: 35 μg EE + 2 mg CPA + Metformin 900-1700 mg/day	China 3 months	C = 41 C + M = 41 Implied	C: 28.57 ± 3.04 C + M: 27.86 ± 3.79	C: 27.77 ± 4.23 C + M: 29.46 ± 4.43	Rott	NR	NR	Adults BMI not classified
Fonseka 2020	Low	C1: EE/CPA (Diane-35, C2: EE/DES (Fermion) C1 + M: EE/CPA + Metformin (dose not specified) C2 + M: EE/DES + Metformin (dose not specified)	Sri Lanka 12 months	C1 = 20 C2 = 23 C1 + M = 26 C2 + M = 30	C1: 23.35 ± 5.10 C2: 22.39 ± 6.45 C1 + M: 24.81 ± 6.24 C2 + M: 27.90 ± 6.89	C1: 28.27 ± 6.94 C2: 26.74 ± 4.88 C1 + M: 27.93 ± 4.89 C2 + M: 27.20 ± 4.28	Rott	NR	NR	Adults BMI not classified
Glintborg 2014a Glintborg 2014b Altinok 2018 Glintborg 2017	High	C: 30 μg EE + 150 mg DSG M: Metformin 2000 mg/day C + M: 30 μg EE + 150 mg DSG + Metformin 2000 mg/day	Denmark 12 months	C = 23 M = 19 C + M = 23	Median, 25-75%ile: C: 28 (24; 32) M: 31 (24; 33) C + M: 30 (24; 31)	Median, 25-75%ile: C: 28.0 (22.9; 31.8) M: 25.9 (24.1; 29.6) C + M: 27.6 (24.3; 31.2)	Rott	NR	NR	Adults BMI not classified

(*continued*)

Table 2. Continued

Study ID	RoB	Comparisons	Country, duration	N	Mean age (years)	Mean BMI	PCOS	Menarche age	Smokers	Comments
Harborne 2003	High	C: 35μg EE + 2 mg CPA 21/7 M: Metformin 1500 mg/day	Scotland 12 months	C = 26 M = 26	C: 31.7 (26.8-36.5) M: 31.3 (27.9-34.7)	C: 31.8 (28.4-34.4) M: 31.7 (29.5-35.5)	Rott	NR	NR	Adults BMI > 25
Hoeger 2008	High	C: 30 μg EE + 0.15 mg DSG M: Metformin 1700 mg/day	USA 6 months	C = 10 M = 6	C: 15.4 ± 1.4 M: 15.4 ± 1.7	C: 37.8 ± 5.1 M: 36.1 ± 7.5	Rott	NR	All nonsmokers	Adolescents BMI > 25
Kaya 2012	High	C: 30 μg EE + 3 mg DRSP C + M: 30 μg EE + 3 mg DRSP + Metformin 1700 mg/day	Turkey 6 months	C = 19 C + M = 18	C:23.2 ± 5.4 C + M: 23.0 ± 4.5	C:26.4 ± 6.2 C + M:31.7 ± 7.3	AES	NR	NR	Adults BMI not classified
Kaya 2015	High	C: 30 μg EE + 3 mg DRSP C + M: 30 μg EE + 3 mg DRSP + Metformin 1700 mg/day	Turkey 6 months	C = 25 C + M = 25	C: 23 ± 5 C + M: 24 ± 4	C: 26.7 ± 5.7 C + M: 29.8 ± 6.9	AES	NR	excluded	Adults BMI not classified
Kebapcilar 2009	High	C: 35 μg EE + 2 mg CPA C + M: 35 μg EE + 2 mg CPA + Metformin 1700 mg/day	Turkey 3 months	C = 22 C + M = 21	C: 24.1 ± 5.6 C + M: 25.1 ± 4.4	C: 27.2 ± 6.2 C + M: 28.7 ± 4.4	Rott	NR	excluded	Adults BMI not classified
Kebapcilar 2010	High	C: 35 μg EE + 2 mg CPA C + M: 35 μg EE + 2 mg CPA + Metformin 1700 mg/day M: Metformin 1700 mg/day	Turkey 3 months	12/group	24.0 ± 5.4 years; for all	C: 28.7 ± 6 C + M: 27.6 ± 3 M: 27.8 ± 4	Rott	NR	excluded	Adults BMI not classified
Kilic 2011	Mod	C: 30 μg EE + 0.15 mg DSG M: Metformin 1700 mg/day	Turkey 6 months	Obese C = 25 M = 24 Nonobese C = 24 M = 23	Obese C:29.0 ± 3.5 M:28.7 ± 3.7 Nonobese C:26.7 ± 3.8 M:26.3 ± 3.0	Obese C:27.7 ± 0.9 M:31.5 ± 2.2 Nonobese C:21.6 ± 1.4 M: 23.3 ± 1.6	Rott	NR	excluded	Adults BMI <25 BMI > 25
Kumar 2018	Mod	C: 35 μg EE/ + 2 mg CPA M: Metformin 2000 mg/day C + M: 35 μg EE + 2 mg CPA + Metformin 2000 mg/day	India 6 months	C = 28 M:=30 C + M = 29	C: 22.9 (5) M: 22 (5.2) C + M: 24.1 (5.9)	C: 26.15 (4.9) M: 27.14 (6) C + M: 30.10 (5.5)	Rott	NR	NR	Adults BMI < 25
Luque-Ramírez 2009	Mod	C: 35 μg EE/2 mg CPA M: Metformin 1700 mg/day	Spain 6 months	C = 15 M = 19	C: 23.4 ± 5.6 M: 25.1 ± 6.6	C: 29.2 ± 5.7 M: 30.5 ± 6.9	NIH	NR	C:40% M: 42%	Adults BMI not classified

(*continued*)

Table 2. Continued

Study ID	RoB	Comparisons	Country, duration	N	Mean age (years)	Mean BMI	PCOS	Menarche age	Smokers	Comments
Lv 2005	High	C: 35 μg EE/2 mg CPA C + M: 35 μg EE/2 mg CPA + Metformin 500 mg/day	China 6 months	C = 25 C + M = 25	C: 24.4 ± 5.1 C + M: 24.5 ± 5.6	C: 21.8 ± 1.4 C + M:22.1 ± 20.2	Author defined	NR	NR	Adults BMI < 25
Meyer 2007 Burchall 2017 Hutchison 2008 Moran 2010	Mod	C1: 35μg EE + 2 mg CPA (high) C2: 20μg EE + 100μg LVG + 50 mg SPL (low dose)*** M: Metformin 2000 mg/day	Australia 6 months	C1 = 31 C2 = 33 M = 36	Average: 31 years	C1: 36.5 no SD C2: 35.5 no SD M: 36.3 no SD	NIH	NR	Excluded	Adults BMI not classified
Mhao 2016	High	C: EE 30 μg/CMA 2mg M: Metformin 1000 mg/day	Iraq 3 months	C = 10 M = 16	Age range, 14-40 years	C: 30.5 ± 5.3 M: 27.2 ± 5.4	NR	NR	NR	Adults BMI not classified
Morin-Papunen 2003a Morin-Papunen 2000 Morin-Papunen 2003b Rautio 2005	High High	C: 35μg EE + 2 mg CPA 21/7 M: Metformin 1000 mg/day for 3 months, then 2000 mg/day	Finland 6 months	Nonobese: C = 10 M = 10 Obese: C = 10 M = 8	Nonobese: C: 28.5 ± 1.7 (SE) M: 28.2 ± 1.4 Obese: C: 29.8 ± 1.0 (SE) M: 29.9 ± 1.5	Nonobese: C: 21.8 ± 0.7 (SE) M 22.5 ± 0.8 Obese: C: 37.2 ± 1.8 (SE) M 32.5 ± 1.1	Aligns with Rott			Adults BMI < 25 BMI > 25
Moro 2013	Mod	C: 30 μg EE + 3 mg DRSP M: Metformin 1500 mg/day C + M: 30 μg EE + 3 mg DRSP + Metformin 1500 mg/day	Italy 6 months	C: 25 M: 25 C + M: 26	C: 26 ± 3 M: 25 ± 5 C + M: 25 ± 4	Median (range) C: 23.7 (20.8-28.6) M: 25.1 (21.9-28.3) C + M:26.5(21.3-30)	Rott	NR	C: 36% M: 40% C + M: 38%	Adults BMI < 25
Ozgurtas 2008	High	C: 35 μg EE + 2 mg CPA M: Metformin 1700 mg/day	Turkey 3 months	C = 21 M = 20	NR (≥18 years)	C: 21.72 ± 1.24 M: 21.81 ± 1.27	Rott	NR	All nonsmokers	Adults BMI < 25
Panidis 2011	High	C1: 35 μg EE + 2 mg CPA C2: 30 μg EE + 3 mg DRSP M: Metformin 1700 mg/day	Greece 6 months	C1 = 15 C2 = 15 M = 15	C1: 20.67 ± 4.13 C2: 22.00 ± 2.07 M: 20.53 ± 3.09	C1: 21.04 + 1.97 C2: 21.69 + 2.33M: 21.83 + 1.73	NIH	NR	NR	Adults BMI < 25 EE/DRSP used in meta-analysis
Sahu 2019	Mod	C: 35 μg EE + 2 mg CPA 21/7 M: Metformin 1000 mg/day	India 6 months	C = 44 M = 42	C: 26.8 ± 4.2 M: 27.0 ± 5.2	C: 25.6 ± 2.7 M: 25.7 ± 2.6	Rott	NR	All nonsmokers	Adults BMI not classified
Song 2017 Ruan 2018	High	C: 35 μg EE + 2 mg CPA M: 35 μg EE + 2 mg CPA + Metformin 1500 mg/day	China 3 months	C = 60 M = 60	C: 27.68 ± 4.99 M: 28.63 ± 5.12	C: 28.64 ± 4.89 M: 27.00 ± 3.47	Rott	NR	C: 22% M: 25%	Adults BMI not classified

(*continued*)

Table 2. Continued

Study ID	RoB	Comparisons	Country, duration	N	Mean age (years)	Mean BMI	PCOS	Menarche age	Smokers	Comments
Wei 2012	Mod	C: 35 μg EE + 2 mg CPA + placebo C + M: 35 μg EE + 2 mg CPA + Metformin 1500 mg/day	China 3 months	C = 28 C + M = 30	"All female were reproductive-aged"	C: 24.9 ± 1.7 C + M: 24.7 ± 1.9	Rott	NR	All nonsmokers	Adults BMI not classified
Wu 2008 2015	Mod	C: 35μg EE + 2 mg CPA M: Metformin 1500 mg/day C + M: 35μg EE + 2 mg CPA + Metformin 1500 mg/day	China 3 months	Obese: C: 7 M: 7 C + M:6 Nonobese: C: 12 M: 11 C + M: 10	Obese: C: 25.0 ± 4.3 M: 25.6 ± 3.6 C + M: 24.5 ± 2.4 Nonobese: C: 26.1 ± 4.6 M: 25.6 ± 4.2 C + M: 25.8 ± 4.0	Obese: C: 25.3 ± 0.8 M: 25.6 ± 0.6 CM: 25.2 ± 1.0 Nonobese: C: 21.4 ± 1.6 M: 21.5 ± 1.8 CM: 21.6 ± 1.4	Rott	NR	Excluded	Adults BMI > 25 BMI < 25

Abbreviations: AES, Androgen Excess Society; BMI, body mass index; C, Oral contraceptive pill; CPA, cyproterone acetate; DRSP, drospirenone; DSG, desogestrel; EE, ethinylestradiol; LVG, levonorgestrel; M, metformin; NIH, National Institutes of Health; NOR, norgestimate; NR, Not reported, PCOS, polycystic ovary syndrome; RoB, risk of bias; Rott, Rotterdam; SPL, spironolactone.

COCP vs combination

No differences were noted in hirsutism between COCP alone and combination treatment. COCP alone was inferior to combination treatment for FAI (MD 0.58; 95% CI, 0.36 to 0.80), SHBG (MD −16.61 nmol/L; 95% CI, −28.51 to −4.71), dehydroepiandrosterone sulfate (DHEAS) (MD 0.93 μmol/L; 95% CI, 0.54 to 1.31), and androstenedione (MD 1.37 nmol/L; 95% CI, 0.14 to 2.60), whereas no differences were noted regarding total and free testosterone (Table 4; Supplementary Fig. S5 (23)).

Metformin vs combination

Metformin was inferior for DHEAS (MD 82.38 μmol/L; 95% CI, 15.43 to 149.36) and total testosterone (MD 0.64 nmol/L; 95% CI, 0.26 to 1.02). None of the identified studies reported hirsutism as an outcome for this comparison (Table 5; Supplementary Fig. S6 (23)).

Metabolic Outcomes

Metformin vs COCP

Metformin was more effective in lowering overall fasting insulin levels (MD −27.12 pmol/L; 95% CI, −40.65 to −13.59), total cholesterol (MD −0.40 mmol/L; 95% CI, −0.66 to −0.14), triglycerides (MD −0.15 mmol/L; 95% CI, −0.29 to −0.01), and C-reactive protein (CRP) levels (MD −11.31 nmol/L; 95% CI, −19.78 to −2.85) compared with COCP (Table 3). For fasting glucose, homeostatic model assessment for insulin resistance (HOMA-IR), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and plasminogen activator inhibitor 1 (PAI-1), there were no differences.

In subgroup analyses on women with a BMI ≥ 25 kg/m^2 (Supplementary Fig. S2; Supplementary Table S1) (23), the metformin-treated group had lower CRP (MD −33.09 nmol/L; 95% CI, −47.33 to −18.84) and HDL (MD −0.24 mmol/L; 95% CI, −0.38 to −0.09) compared with COCP. Fasting insulin was lower with metformin regardless of BMI (Supplementary Table S1; Supplementary Fig. S2) (23).

Metformin was superior to COCP for fasting insulin, both in adults (MD −22.17 pmol/L; 95% CI, −29.93 to −14.42) and adolescents (MD −30.03 pmol/L; 95% CI, −78.63 to −18.56). Metformin was also superior for total cholesterol, both in adults (MD −0.34 mmol/L; 95% CI, −0.60 to −0.08) and for adolescents (MD −1.12 mmol/L; 95% CI, −1.74 to −0.50) (Supplementary Table S1) (23). The type of COCP showed no major differences compared with the overall result (Supplementary Table S2) (23).

COCP vs combination

COCP alone increased fasting insulin (MD 17.03 pmol/L; 95% CI, 7.79 to 26.26), HOMA-IR (MD 0.44; 95% CI, 0.17 to 0.70), and CRP (MD 1.94 nmol/L; 95% CI, 0.05 to 3.84) compared with combination treatment (Table 4; Supplementary Fig. S5 (23)). In women with a BMI < 25 kg/m^2, COCP alone resulted in marginally higher glucose (MD 0.25 mmol/L; 95% CI, 0.07 to 0.43) compared with combination treatment.

Metformin vs combination

Metformin alone showed marginally lower fasting glucose (MD −0.33 mmol/L; 95% CI, −0.64 to −0.01) and CRP (MD

Figure 2. Risk of bias assessments of the included studies.

Table 3. Grade assessments and evidence profile on outcomes comparing metformin with combined oral contraceptive pills

	No. studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Met (n)	COCP (n)	Effect, random, MD (95% CI)	Favors	Certainty
Weight (kg)										
Overall	7	Serious[a]	Very serious[e]	No serious	Serious[b]	188	177	−1.25 kg (−12.95 to 10.44)	No difference	⊕◯◯◯ VERY LOW
Waist-hip ratio (WHR)										
Overall	7	Very serious[b]	Very serious[e]	Serious[f]	No serious	88	85	−0.02 (−0.03 to 0.00)	No difference	⊕◯◯◯ VERY LOW
BMI (kg/m^2)										
Overall	20	Serious[c]	Very serious[e]	No serious	No serious	401	390	−0.74 kg/m^2 (−1.58 to 0.09)	No difference	⊕◯◯◯ VERY LOW
Hirsutism (FG score)										
Overall	6	Very serious[b]	Very serious[e]	No serious	Serious[b]	120	127	0.72 (−1.40 to 2.85)	No difference	⊕◯◯◯ VERY LOW
Free androgen index (FAI)										
Overall	8	Very serious[b]	Very serious[e]	No serious	No serious	107	114	**7.08 (4.81 to 9.36)**	**COCP**	⊕⊕◯◯ LOW[i]
Sex hormone binding globulin (SHBG) (nmol/L)										
Overall	9	Very serious[b]	Very serious[e]	No serious	No serious	171	168	**−118.61 (−174.46 to −62.75)**	**COCP**	⊕⊕◯◯ LOW[i]
Dehydroepiandrosterone sulfate (DHEAS) (umol/L)										
Overall	7	Very serious[b]	Serious[d]	Serious[f]	No serious	170	160	**1.18 (0.17 to 2.18)**	**COCP**	⊕◯◯◯ VERY LOW
Androstendione (nmol/L)										
Overall	4	Very serious[b]	Serious[d]	No serious	No serious	66	70	**3.25 (1.46 to 5.04)**	**COCP**	⊕◯◯◯ VERY LOW
Total testosterone (nmol/L)										
Overall	17	Serious[c]	Serious[d]	No serious	No serious	323	321	**0.48 (0.32 to 0.64)**	**COCP**	⊕⊕◯◯ LOW
Free testosterone (pmol/L)										
Overall	4	Very serious[b]	Serious[d]	No serious	Serious[b]	107	91	**3.59 (1.41 to 5.78)**	**COCP**	⊕◯◯◯ VERY LOW
Fasting insulin (pmol/L)										
Overall	14	Serious[c]	Serious[d]	No serious	No serious	292	282	**−27.12 (−40.65 to −13.59)**	**Metformin**	⊕⊕◯◯ LOW
Fasting glucose (mmol/L)										
Overall	10	Very serious[b]	Serious[d]	No serious	No serious	210	201	−0.08 (−0.23 to 0.06)	No difference	⊕◯◯◯ VERY LOW
Homeostatic model assessment for insulin resistance (HOMA-IR)										
Overall	8	Serious[a]	Very serious[e]	Serious[f]	No serious	202	184	−0.60 (−1.24 to 0.05)	No difference	⊕◯◯◯ VERY LOW

(*continued*)

Table 3. Continued

	No. studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Met (n)	COCP (n)	Effect, random, MD (95% CI)	Favors	Certainty
Total cholesterol (mmol/L)										
Overall	13	Serious[c]	Very serious[e]	No serious	No serious	281	273	**−0.40 (−0.66 to −0.14)**	**Metformin**	⊕◯◯◯ VERY LOW
High-density lipoprotein (HDL) cholesterol (mmol/L)										
Overall	13	Serious[a]	Very serious[e]	No serious	No serious	283	267	−0.05 (−0.18 to 0.07)	No difference	⊕◯◯◯ VERY LOW
Low-density lipoprotein (LDL) cholesterol (mmol/L)										
Overall	13	Serious[a]	Serious[d]	No serious	No serious	281	273	−0.08 (−0.29 to 0.13)	No difference	⊕⊕◯◯ LOW
Triglycerides (mmol/L)										
Overall	13	Serious[a]	Serious[d]	No serious	No serious	277	264	**−0.15 (−0.29 to −0.01)**	**Metformin**	⊕⊕◯◯ LOW
C-reactive protein (CRP) (nmol/L)										
Overall	7	Serious[a]	Serious[d]	No serious	No serious	165	156	**−11.31 (−19.78 to −2.85)**	**Metformin**	⊕⊕◯◯ LOW
Plasminogen activator inhibitor-1 levels (PAI-1) (ng/mL)										
Overall	2	Very serious[b]	Serious[d]	Serious[f]	Very serious[g]	23	27	−1.05 (−24.65 to 22.54)	No difference	⊕◯◯◯ VERY LOW
Girls with restored menses										
Overall	5	Very serious[b]	No serious	No serious	No serious	85	82	**0.17 (0.05 to 0.57)**	**COCP**	⊕⊕◯◯ LOW

Bolding indicates a statistically significant MD ($P < .05$).
Abbreviations: COCP, combined oral contraceptive pills; MD, mean difference; RCT; randomized controlled trials; RoB; risk of bias.
[a]Downgraded once as all studies high or moderate RoB.
[b]Downgraded twice as all studies or all but one are high RoB.
[c]Downgraded once as studies high to moderate RoB.
[d]Downgraded once as I^2 is close to or >50% but CI partly overlapping.
[e]Downgraded twice as I^2 very high and CI not overlapping.
[f]Downgraded once as no adolescents in the overall group.
[g]Downgraded twice as there are very few studies.
[h]Downgraded once as the CI is wide.
[i]Upgraded once due to large effect.

Table 4. Grade assessments and evidence profile of outcomes in PCOS comparing COCP with metformin and COCP

No studies		Quality assessment					No. participants		Effect, random [95% CI]	Favors	Certainty
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP	COCP + Met			
Weight (kg)											
Overall	6	Serious[a]	No serious	No serious	No serious	None	125	124	MD 0.06 (−1.99 to 2.11)	No difference	⊕⊕⊕◯ MODERATE
Waist-hip ratio (WHR)											
Overall	7	Serious[a]	No serious	No serious	No serious	None	143	141	MD 0.00 (−0.02 to 0.01)	No difference	⊕⊕⊕◯ MODERATE
BMI (kg/m^2)											
Overall	14	Serious[a]	Serious[b]	No serious	No serious	None	284	279	MD −0.22 (−0.98 to 0.55)	No difference	⊕⊕◯◯ LOW
Hirsutism (FG score)											
Overall	3	Serious[a]	No serious	No serious	No serious	None	71	86	MD 0.99 (−0.35 to 2.32)	No difference	⊕⊕⊕◯ MODERATE
Free androgen index (FAI)											
Overall	6	Serious[a]	No serious	No serious	No serious	None	172	171	**MD 0.58 (0.36 to 0.80)**	**COCP + met**	⊕⊕⊕◯ MODERATE
Sex hormone binding globulin (SHBG) (nmol/L)											
Overall	7	Serious[a]	Serious[b]	No serious	No serious	None	177	175	**MD −16.61 (−28.51 to −4.71)**	**COCP + met**	⊕⊕◯◯ LOW
Dehydroepiandrosterone sulfate (DHEAS) (umol/L)											
Overall	9	Very serious[c]	No serious	No serious	No serious	None	231	231	**MD 0.93 (0.54 to 1.31)**	**COCP + met**	⊕⊕◯◯ LOW
Total testosterone (nmol/L)											
Overall	12	Serious[a]	No serious	No serious	No serious	None	290	287	MD 0.08 (−0.00 to 0.15)	No difference	⊕⊕⊕◯ MODERATE
Free testosterone (pmol/L)											
Overall	6	Very serious[c]	No serious	No serious	No serious	None	103	100	MD 0.96 (−0.35 to 2.27)	No difference	⊕⊕◯◯ LOW
Androstendione (nmol/L)											
Overall	6	Very serious[c]	Very serious[d]	No serious	No serious	None	159	157	**MD 1.37 (0.14 to 2.60)**	**COCP + met**	⊕◯◯◯ VERY LOW
Fasting insulin (pmol/L)											
Overall	14	Serious[a]	Serious[b]	No serious	No serious	None	319	314	**MD 17.03 (7.79 to 26.26)**	**COCP + met**	⊕⊕◯◯ LOW
Fasting glucose (mmol/L)											
Overall	9	Serious[a]	Serious[b]	No serious	No serious	None	244	239	MD 0.15 (−0.01 to 0.30)	No difference	⊕⊕◯◯ LOW
Homeostatic model assessment for insulin resistance (HOMA)											

(*continued*)

Table 4. Continued

No studies		Quality assessment					No. participants		Effect, random [95% CI]	Favors	Certainty
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP	COCP + Met			
Overall	10	Very serious[c]	No serious	No serious	No serious	None	272	268	**MD 0.44 (0.17 to 0.70)**	**COCP + met**	⊕⊕◯◯ LOW
Total cholesterol (mmol/L)											
Overall	14	Serious[a]	Serious[b]	No serious	No serious	None	350	349	MD 0.06 (−0.11 to 0.23)	No difference	⊕⊕◯◯ LOW
Low-density lipoprotein (LDL) cholesterol (mmol/L)											
Overall	14	Serious[a]	No serious	No serious	No serious	None	350	348	MD 0.04 (−0.07 to 0.15)	No difference	⊕⊕⊕◯ MODERATE
High-density lipoprotein (HDL) cholesterol (mmol/L)											
Overall	14	Serious[a]	Serious[b]	No serious	No serious	None	350	349	MD −0.07 (−0.15 to 0.02)	No difference	⊕⊕◯◯ LOW
Triglycerides (mmol/L)											
Overall	14	Serious[a]	Serious[b]	No serious	No serious	None	350	348	MD −0.02 (−0.12 to 0.07)	No difference	⊕⊕◯◯ LOW
C-reactive protein (CRP) (nmol/L)											
Overall	4	Serious[a]	No serious	No serious	No serious	None	74	68	**MD 1.94 (0.05 to 3.84)**	**COCP + met**	⊕◯◯◯ VERY LOW
Plasminogen activator inhibitor-1 levels (PAI-1) (ng/mL)											
Overall	2	Serious[a]	Serious[b]	No serious	Very serious[e]	None	27	21	MD −0.16 (−1.92 to 1.61)	No difference	⊕◯◯◯ VERY LOW
Health-related quality of life (HR-QoL)											
Overall	1	Serious[a]	Not applicable	Not applicable	Very serious[e]	None	23	23	Narrative review	No difference	⊕◯◯◯ VERY LOW

Bolding indicates a statistically significant MD ($P < .05$).
Abbreviations: COCP, combined oral contraceptive pills; MD, mean difference; Met, metformin; PCOS, polycystic ovary syndrome; RCT; randomized controlled trials; RoB; risk of bias.
[a]Downgraded once as the majority of evidence is at moderate or high RoB.
[b]Downgraded once due to I2 > 50%.
[c]Downgraded twice due to high RoB.
[d]Downgraded twice due to I2 > 50% and CI not overlapping.
[e]Downgraded twice due to very few patients.

Table 5. Grade assessments and evidence profile of outcomes in PCOS comparing metformin with metformin and combined oral contraceptive pills

No. studies		Risk of bias	Inconsistency	Indirectness	Imprecision	Met	Met + COCP	Effect, random, MD (95% CI)	Favors	Certainty
Waist-hip ratio (WHR)										
Overall	2	Serious[a]	No serious	No serious	Very serious[e]	18	16	**−0.03 (−0.06 to −0.01)**	**Metformin**	⊕◯◯◯ VERY LOW
BMI (kg/m^2)										
Overall	4	Serious[a]	Serious[b]	No serious	Serious[d]	60	57	−1.31 (−2.65 to 0.03)	No difference	⊕◯◯◯ VERY LOW
Dehydroepiandrosterone sulfate (DHEAS) (umol/L)										
Overall	2	Serious[a]	No serious	No serious	Serious[d]	60	58	**82.39 (15.43 to 149.36)**	**Metformin + COCP**	⊕⊕◯◯ LOW
Total testosterone (nmol/L)										
Overall	4	Serious[a]	Serious[b]	No serious	No serious	73	71	**0.64 (0.26 to 1.02)**	**Metformin + COCP**	⊕⊕◯◯ LOW
Fasting insulin pmol/L)										
Overall	4	Serious[a]	No serious	No serious	Serious[d]	60	57	−3.35 pmol/L (−17.67 to 10.97)	No difference	⊕⊕◯◯ LOW
Fasting glucose (mmol/L)										
Overall	2	Serious[a]	Serious[b]	Serious[e]	Very serious[e]	47	41	**−0.33 mmol/L (−0.64 to −0.01)**	**Metformin**	⊕◯◯◯ VERY LOW
Homeostatic model assessment for insulin resistance (HOMA-IR)										
Overall	3	Serious[a]	Very serious[c]	No serious	Serious[d]	59	53	−1.28 (−2.92 to 0.35)	No difference	⊕◯◯◯ VERY LOW
Total cholesterol (mmol/L)										
Overall	3	Serious[a]	Serious[b]	No serious	No serious	67	67	−0.61 mmol/L (−1.23 to 0.01)	No difference	⊕⊕◯◯ LOW
High-density lipoprotein (HDL) cholesterol (mmol/L)										
Overall	3	Serious[a]	No serious	No serious	No serious	67	67	−0.06 mmol/L (−0.17 to 0.04)	No difference	⊕⊕⊕◯ MODERATE
Low-density lipoprotein (LDL) cholesterol (mmol/L)										
Overall	3	Serious[a]	Serious[b]	No serious	No serious	67	67	−0.14 mmol/L (−0.46 to 0.17)	No difference	⊕⊕◯◯ LOW
Triglycerides (mmol/L)										
Overall	3	Serious[a]	Very serious[c]	No serious	No serious	67	67	−0.20 mmol/L (−0.72 to 0.31)	No difference	⊕◯◯◯ VERY LOW
C-reactive protein (CRP) (nmol/L)										
Overall	2	Serious[a]	No serious	No serious	Serious[d]	47	41	**−4.08 nmol/L (−6.01 to −2.16)**	**Metformin**	⊕⊕◯◯ LOW

Bolding indicates a statistically significant MD ($P < .05$).
Abbreviations: COCP, combined oral contraceptive pills; MD, mean difference; Met, metformin; PCOS, polycystic ovary syndrome; RCT; randomized controlled trials; RoB; risk of bias.
[a]Downgraded once as the studies are at moderate or high RoB.
[b]Downgraded once as I^2 is close to or >50% but CI partly overlapping.
[c]Downgraded twice as I^2 very high and CI not overlapping.
[d]Downgraded once as there are only a few studies.
[e]Downgraded twice as there are very few participants.

−4.08 nmol/L; 95% CI, −6.01 to −2.16), compared with a combination treatment (Table 5; Supplementary Fig. S6 (23)).

Cycle Regularity and Quality of Life Outcomes

Metformin was inferior to COCP on restoring regular menses overall (OR 0.17; 95% CI, 0.05 to 0.57), as well as in adults (OR 0.19; 95% CI, 0.05 to 0.72) and adolescents (OR 0.10; 95% CI, 0.01 to 1.92).

We were not able to perform a meta-analysis on health-related quality of life. Results from 3 identified studies (32, 42, 50) showed conflicting results and our overall assessment is that there is no difference in quality of life.

Side Effects

Due to lack of systematic reporting, where many studies do not report adverse effects at all or do not report in a similar manner, we were not able to perform a meta-analysis. However, the reports suggest more gastrointestinal side effects with metformin.

Discussion

Main Findings

This extensive systematic review and meta-analysis, including 36 RCTs, was performed to directly inform recommendations on the use of metformin and COCP in women with PCOS, as

part of the 2023 update of the International Evidence-based Guidelines on the Assessment and Treatment of PCOS. Our findings showed that metformin was superior to COCP for metabolic outcomes, especially in women with PCOS and a BMI ≥ 25 kg/m^2, whereas COCP was superior for improving cycle regularity and, in women with a BMI < 25 kg/m^2, for improving hirsutism. The combination of metformin and COCP was more effective for improving biochemical hyperandrogenism, insulin levels, and insulin resistance than COCP monotherapy.

Interpretation

Clinical and biochemical hyperandrogenism

For many patients with PCOS, medical treatment is indicated to treat clinical hyperandrogenism, including acne and hirsutism. For these symptoms, COCPs have been recommended as first-line treatment. In addition, COCPs regulate menstrual cycles and provide contraception (12, 15). In this study we confirm that COCP was superior to metformin for treatment of hirsutism in women with BMI < 25 kg/m^2, whereas evidence for other BMI groups was of very low quality. However, we found that COCP was superior in improving biochemical hyperandrogenism compared with metformin. A systematic review on COCP treatment in women with PCOS, including both RCTs and non-RCTs, suggested that COCP containing CPA might be more effective in improving hirsutism. However, no direct comparisons between different COCP were made, limiting the conclusions (15). General population studies have shown that CPA increases the risk of venous thromboembolism compared with other COCP (71, 72); hence, COCPs containing CPA are currently not recommended as first-line treatments for PCOS (20).

No differences were found regarding hirsutism between COCP and combination treatment. Nevertheless, combination treatment was more effective in improving FAI, SHBG, and DHEAS compared with COCP alone. One systematic review (17) studied hirsutism and acne in PCOS, comparing monotherapy with metformin or COCP with combination treatment, with monotherapy being less effective for hirsutism compared with combination treatment. However, that review also included studies with shorter treatment durations (3 months) hindering interpretation of their findings.

As high insulin levels increase luteinizing hormone–mediated ovarian androgen synthesis (73), combination treatment presumably targets several distinct mechanisms leading to improved clinical and biochemical hyperandrogenism. Thus, combination treatment theoretically offers several benefits. Importantly, additional high-quality prospective studies are needed to better ascertain the efficacy of these treatment regimens. We also recognize the importance of self-assessment of severity and impact on quality of life, over and above clinical assessment.

Anthropometric outcomes

Women with PCOS have an increased prevalence of the metabolic syndrome (74, 75). In our meta-analysis, there were no differences in weight, WHR, and BMI, but evidence was only available with very low certainty. Previously, metformin has been shown to improve BMI compared with placebo (76). A recent systematic review which included nonrandomized trials found that combined metformin, COCP, and antiandrogen treatment improved BMI and glucose tolerance (11). However, this study did not compare metformin monotherapy to a combination treatment with metformin and COCP. In our study the combination of COCP and metformin showed no benefit for anthropometric measures compared with COCP alone.

Metabolic outcomes

Hyperinsulinemia and insulin resistance play important roles in the pathophysiology of PCOS for both normal-weight women and women with obesity (2, 3, 73, 77). Metformin decreases insulin resistance and insulin levels. COCP does not have any major effects on carbohydrate metabolism in healthy women, whereas the effect on lipid metabolism depends on the level of estrogen and type of progestin, with potential negative effects (78, 79, 80, 81). Our systematic review confirms that metformin is superior in lowering fasting insulin levels, total cholesterol, and triglycerides compared with COCP, in line with findings reported previously (12).

Metformin can be used where COCPs are contradicted, in older women, women with obesity or medical conditions (such as migraine with aura, risk of venous thromboembolism or severe hypertension) or where pregnancy is desired. The major disadvantage of metformin treatment is the generally mild, usually self-limited, gastrointestinal side effects, limiting patient acceptance of appropriate doses. We also report that metformin lowered CRP compared with COCP treatment. CRP is often used as a metabolic risk marker and is associated with an increased risk of cardiovascular disease (82). Metformin has previously been shown to decrease CRP, both in obese and nonobese women, compared with placebo (83). COCP appears to increase CRP (79, 84, 85), yet the significance of these effects remains unknown.

Importantly, the addition of metformin to COCP improved insulin levels and insulin resistance, as compared with COCP alone. This is of special interest for women with PCOS with additional risk factors for type 2 diabetes, such as a high BMI (86, 87). Two systematic reviews found that adding metformin to COCP and anti-androgens improved BMI and glucose tolerance (11, 88).

Strengths and Limitations

This review presents the most up-to-date evidence on COCP and metformin treatment in women with PCOS. Strengths of the report include the rigorous processes, including PICO developed by clinicians, researchers, and patients; and the large number of RCTs included. Because critical appraisal is inherently subjective, both RoB and GRADE assessments were conducted by 2 authors independently. Several subgroup analyses were included to highlight benefits in population subgroups of interest. Limitations include those inherent in the included studies, with many studies having a high RoB, mainly due to often poorly described randomization processes or lack of blinding. Certainty of evidence was also affected by inconsistency of effect sizes and small sample sizes. Several studies did not provide data on BMI.

Identified research gaps include the lack of larger studies on adolescents with PCOS and on the comparison of metformin with combination treatment. Additional high-quality studies are needed to assess symptoms, especially related to clinical hyperandrogenism rather than biochemical markers of hyperandrogenism. Future directions include understanding

mechanisms of action and factors that may impact on medication responses, such as genotype and phenotype of PCOS.

Conclusion

Results from this extensive systematic review and meta-analysis will advise the pending 2023 PCOS guideline update. The guideline will recommend COCP to be used over metformin for management of irregular cycles and hirsutism, and metformin over COCP for metabolic indications in PCOS. While our meta-analyses indicated that the combined treatment with metformin and COCP improved biochemical hyperandrogenism, insulin levels, and insulin resistance more than COCP alone, no difference was seen in clinical outcomes.

For women with PCOS, the choice of treatment should be based on clinical symptoms. Combination treatment appears to be beneficial in high metabolic risk groups, targeting the 2 major endocrine disturbances seen: hyperinsulinemia and hyperandrogenism. Our results, including several subanalyses, add to the current evidence base and contribute toward reaching the ultimate goal of shared decision-making and effective, tailored, and individualized treatment for patients with PCOS.

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Author Contributions

This systematic review will inform the forthcoming 2023 update of the International Evidence-based Guideline on Assessment and Management of PCOS, led by H.T. Senior experts within the guideline working group included T.P., D.R., P.M.S., C.T.T., A.P., S.W., A.M. and H.T. C.C.T. and A.M. were part of the evidence team. The search, screening, and RoB and GRADE assessments were performed by J.M., M.F., and S.A. J.M. and M.F. did the data extraction. J.M. and M.F. drafted the first version of the manuscript, which was revised by the other authors. All authors approved of the final version of the manuscript.

Disclosures

J.M. reports a postdoc research grant from Orion Research Foundation. D.R. reports an honorarium from Novo Nordisk for a lecture on PCOS and obesity. Neither Orion nor Novo Nordisk had any influence on this work. The other authors have no conflicts to declare.

Data Availability

The data underlying this article are secondary, aggregated from already published work.

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