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Systematic Review and Meta Analysis

Different kinds of oral contraceptive pills in polycystic ovary syndrome: a systematic review and meta-analysis

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Abstract

Objective: To compare between different combined oral contraceptive pills (COCPs) as part of the update of the International Evidence-Based Guidelines on the Assessment and Management of polycystic ovary syndrome (PCOS).

Design: A systematic review and meta-analysis was performed, Prospero CRD42022345640.

Methods: MEDLINE, EMBASE, All EBM, CINAHL, and PsycINFO was searched on July, 8, 2022, for studies including women with PCOS, comparing 2 different COCPs in randomized controlled trials.

Results: A total of 1660 studies were identified, and 19 randomized controlled trials (RCTs) were included.

Fourth-generation COCP resulted in lower body mass index (BMI) (mean difference [MD] 1.17 kg/m^2 [95% confidence interval {CI} 0.33; 2.02]) and testosterone (MD 0.60 nmol/L [95% CI 0.13; 1.07]) compared with third-generation agents, but no difference was seen in hirsutism.

Ethinyl estradiol (EE)/cyproterone acetate (CPA) was better in reducing hirsutism as well as biochemical hyperandrogenism (testosterone [MD 0.38 nmol/L {95% CI 0.33–0.43}]) and BMI (MD 0.62 kg/m^2 [95% CI 0.05–1.20]) compared with conventional COCPs.

There was no difference in hirsutism between high and low EE doses. No evidence regarding natural estrogens in COCP was identified.

Conclusion: With current evidence, combined regimens containing an antiandrogen (EE/CPA) may be better compared with conventional COCPs in reducing hyperandrogenism, but EE/CPA will not be recommended as a first-line COCP treatment by the pending PCOS guideline update, due to higher venous thrombotic events (VTE) risk in the general population. Later-generation progestins offer theoretical benefits, but better evidence on clinical outcomes is needed in women with PCOS.

Trial registration: The protocol for the systematic review was registered prospectively in Prospero, CRD42022345640.

Keywords: polycystic ovary syndrome, combined oral contraception, progestins, cyproterone acetate, hirsutism

Significance

This is the most up-to-date evidence on the effect of different oral contraceptive pills in polycystic ovary syndrome (PCOS) which along with broader evidence on the oral contraceptives, consumer preference, and multidisciplinary expertise directly informs the 2023 update of the evidence-based guidelines on assessment and treatment of PCOS.

Introduction

Combined oral contraceptive pills (COCPs) are a commonly prescribed treatment for women with polycystic ovary syndrome (PCOS), targeting key features including irregular menstrual cycles and clinical hyperandrogenism, also providing contraception and endometrial protection.[1] Clinical hyperandrogenism and irregular cycles adversely impact health-related quality of life (HRQoL) in women with PCOS.[2–4] In 2018, the first Evidence-Based International Guidelines for the assessment and management of PCOS was published,

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recommending that COCP *should* be recommended in adult women for the management of hyperandrogenism and/or irregular menstrual cycles.[1,5] Evidence-based data from the general population in conjunction with consumer preferences, multidisciplinary expertise, and robust guideline development processes informed these 2018 Guidelines. However, recommendations regarding the specific types or doses of estrogens or progestins to be used in women with PCOS could not be made due to a paucity of adequate data.

Combined oral contraceptive pills contain two active components, an estrogen and a progestogen.[6] The most commonly used estrogen in COCPs is ethinyl estradiol (EE); more recently COCPs containing other estrogens have become available. Combined oral contraceptive pills reduce hyperandrogenism due to the estrogen's hepatic effects to increase globulin production, including sex hormone binding globulins (SHBG) that bind to circulating testosterone, resulting in lower free testosterone concentrations.[7] However, the increased hepatic protein synthesis promoted by estrogens (particularly EE) also leads to hypercoagulability, resulting in an increased risk for venous thrombotic events (VTE) with COCP use. Combined oral contraceptive pill use essentially doubles the risk of VTE from 2–10 events/10 000 women-years to 7–10 events/10 000 women-years.[8,9] A French cohort study on the general population in over five million women showed that EE doses of 20 µg were associated with lower risks of pulmonary embolism, ischemic stroke, and myocardial infarction, compared with 30–40 µg,[10] with low absolute risks. Over the years, EE doses have been reduced, and more COCPs now use EE doses of 20–35 µg.[10,11] Interestingly, recent study showed that regiments containing natural estrogens seem to present lower risk for VTE compared with EE preparations.[12]

Progestogens refer to a class of compounds with progestational activity, whereas progestin refers to synthetic progestogens which act as progesterone agonists.[13] Progestins have been categorized into different generations, depending on time of introduction, and structural properties. Progestins vary in their androgenic activity depending on the binding affinity to the androgen receptor, the effect they have on decreasing SHBG, and the degree to which they bind to SHBG.[7,11,14] The later-generation progestins have been shown to result in higher SHBG increase compared with second-generation COCP in healthy women.[15] Progestins can also have mild metabolic effects, mainly on lipids, which may be relevant in PCOS as a high-risk metabolic condition.[16]

We conducted a systematic review and meta-analysis to provide evidence regarding specific COCPs for the 2023 update of the international PCOS guidelines.[17] We compared COCPs with high vs. low dose of EE, different estrogens, different generation progestins, COCP vs. progestin alone, and conventional COCPs vs. EE + cyproterone acetate (CPA) to inform recommendations and to guide future research.

Materials and methods

This work was conducted according to the PRISMA guidelines[18,19] and complies with the Declaration of Helsinki. The protocol (CRD42022345640) was prospectively registered in Prospero. Ethical consent was not needed as this work is based on already published data.

In the previous guideline, studies published before 2017 were assessed.[5] Using the same search string, the search was updated on July, 8, 2022, using the databases EMBASE, Medline, CINAHL, All EBM, and PsycINFO. The search addressed three treatments in relation to the PCOS guideline update: COCP, metformin, and antiandrogens.

Effects of COCP compared with no medical treatment have previously been reported.[20] This publication focuses on comparisons between different oral contraceptive pills.

Table S1 shows the search strategy in detail.

Study selection

The Patient, Intervention, Comparison and Outcomes (PICO) relevant here, shown in Table 1, was determined based on prioritized outcomes, established previously through a Delphi process involving 700 clinicians, academic opinion leaders, and consumers.[18] Covidence was used for assessments.[21] After duplicate removals, title and abstract screening was made in duplicate. Studies included in the previous guidelines, relevant for this PICO, were included, and the excluded list from the previous search was reviewed for comprehensiveness. Full text screening and extraction was done in duplicate. The risk of bias (RoB) assessments were done using RoB2,[22] and the tool Robvis was used for visualization.[23] The Grading of Recommendations,

Table 1. The patient, intervention, comparison, and outcomes (PICO) of this systematic review and meta-analysis.

PICO	Description
Patients:	Females with PCOS (diagnosed by Rotterdam, National Institutes of Health [NIH], or Androgen Excess and PCOS Society [previously Androgen Excess Society {AES}] criteria) of any ethnicity and weight. Subgroups: adolescents (10–19 years), adults, and smokers. Exclusion criteria: females without PCOS, <2 years post menarche, and women with type 2 diabetes, comorbidities, or major depression.
Intervention:	All types of COCPs, low 20 µg estrogens or less vs. standard or high 30 µg or more. Different generation progestins. Estradiol and natural. For hirsutism, a minimum of 6 months of treatment required. At least 3 months for all other outcomes. Exclusion criteria: Nonoral formulation of contraceptives.
Comparisons:	Same as intervention.
Outcomes:	Androgenicity: hirsutism measured by Ferriman Gallwey (FG) score, free androgen index (FAI), testosterone and sex hormone blinding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), androstenedione, and irregular cycles. Metabolic: insulin resistance measured by Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), clamp test, oral glucose tolerance test (OGTT), cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides, and C-reactive protein (CRP). Psychological: health-related quality of life (HRQoL) and depression. Anthropometric: weight, BMI, and waist-hip-ratio (WHR). Others: thromboembolic events and plasminogen activator inhibitor (PAI)-1 levels. Adverse effects.
Study type:	Randomized controlled trials. Evidence-based guidelines and systematic reviews for further references. *Limits:* English language. Limit to last 20 years given change in doses and progestins.

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Assessment, Development, and Evaluations (GRADE) approach was used to estimate the strength of evidence.[24] Both RoB and GRADE assessments were done in duplicate. When meta-analysis could be performed, review manager version 5.4.1. was used, with the random effect model. Funnel plots were inspected and there was no evidence of publication bias.

Results

A total of 1660 studies were identified in the search and 19 randomized controlled trials (RCTs) were included. A flow chart of included/excluded studies is shown in Figure 1.

Included studies, described in Table 2, had a duration between 3 and 24 months, were published 2002-2021, and originated from Europe ($n = 11$), Middle East ($n = 3$), and Asia ($n = 5$) (Table 2). Three included only adolescents. Four had a low RoB, 3 moderate risk, and 12 high RoB (Figure S1).

The progestins (abbreviations in brackets) identified in the included studies were:

- First generation: Chlormadinone acetate (CMA)
- Second generation: Levonorgestrel (LNG)
- Third generation: Desogestrel (DSG) and gestodene (GSD)
- Fourth generation: Drospirenone (DRSP) and dienogest (DNG)
- Other: CPA

COCP with low vs. high dose of EE: different estrogens

Two 12-month RCTs compared high (30–35 μg) vs. low (20 μg) EE doses.[25,26] A meta-analysis could not be performed. The only common outcome was hirsutism, but the studies reported hirsutism differently. The systematic review showed no difference in hirsutism. Groups were similar except for a greater high-dose EE increase in SHBG (mean change 167.4 ± 89.0 vs. 125.5 ± 124.6 nmol/L for high vs. low dose EE, respectively) (data not shown).

All identified studies used preparations containing EE, and thus, comparisons between different estrogens could not be done.

First-generation COCPs

No studies were identified comparing first-generation with second-generation COCPs and only one small study comparing first-generation with third-generation COCPs[27] (data not shown). Regarding first-generation vs. fourth-generation COCPs, four RCTs ranging from 3 to 24 months of duration were identified, all with a high RoB. All studies compared EE/CMA (first generation) with fourth-generation progestin DRSP/EE, with details given in Table 2.[27–30] In Yildizhan,[30] follow-ups were done at 6 monthly with 12-month follow-up used here to align to the other studies. Meta-analysis was performed for androgen levels and showed a greater decrease in DHEAS (mean difference [MD] 0.78 μmol/L [95% confidence interval {CI} 0.29; 1.27]) and androstenedione (MD 1.13 nmol/L [95% CI 0.64; 1.62]), favoring fourth-generation progestins, with no difference in SHBG and testosterone (Figure S2).

Results from the systematic review showed no difference in hirsutism; cholesterol and C-reactive protein (CRP) levels were lower after treatment with the fourth-generation progestin, compared with first generation. There were no differences in other outcomes (Table S2). Cycle regularity was not reported.

COCP with second-generation vs. COCP with third-generation progestins

Two RCTs were identified, both with a high RoB, comparing second-generation EE/LNG with the third-generation EE/DSG in both studies.[31,32] One was a crossover study, involving four arms,[31] with a 6-month treatment, a 6–8-week washout, and then a further 6 months with a COCP containing a different progestin. Results were presented using generalized estimating equations models at 6 months of therapy. The second study was a 6-month four-arm trial comparing COCPs with four different progestins on lipid profiles.[32] Since the studies report outcomes in different ways, a meta-analysis could not be performed. The crossover study showed greater changes in FAI, DHEAS, and SHBG, favoring the third-generation progestin. No other difference, including in hirsutism, was seen between the groups (Table S3). Cycle regularity was not reported.

COCP with second-generation vs. COCP with fourth-generation progestins

Two RCTs were identified,[31,32] and both had a high RoB. The progestins compared here were the second-generation progestin LNG vs. the fourth-generation DRSP. Since the studies report outcomes in different ways, a meta-analysis could not be performed. The crossover study showed greater change in FAI, DHEAS, and SHBG, favoring the fourth-generation progestin, with no difference for other outcomes, including hirsutism (Table S3). Cycle regularity was not reported.

COCP with third-generation vs. fourth generation progestins

Five RCTs were identified that compared third-generation (DSG and GSD) with fourth-generation progestins (DRSP and DNG). One, Bhattacharya (2012), was a 12-month trial with three arms, with EE/DSG ($n = 49$) and EE/DRSP ($n = 50$) relevant for this comparison.[33] The study had a low RoB. Another study, De Leo 2010, was 3-month trial with four arms, with the three arms EE/GSD ($n = 10$), EE/DSG ($n = 10$), and EE/DRSP ($n = 10$) relevant for this comparison.[27] The study had a high RoB.[27] This study had two third-generation progestins; when possible to include in a meta-analysis, the EE/DSG group was chosen to align to the other studies.[27] A 6-month study, Kriplani (2010), compared EE/DSG ($n = 29$) with EE/DRSP ($n = 29$), with a high RoB.[34] A further 6-month study, Amiri (2021), had four arms with four different progestins, with the two arms of EE/DSG ($n = 20$) and EE/DRSP ($n = 17$) relevant to this comparison; the study had a high RoB.[32]

Meta-analysis showed that body mass index (BMI) was lower after treatment with fourth-generation compared with third-generation progestins (MD 1.17 kg/m^2 [95% CI 0.33; 2.02]). Total testosterone (MD 0.60 nmol/L [95% CI 0.13; 1.07]) and low-density lipoprotein (LDL) levels (MD 0.26 mmol/L [95% CI 0.07; 0.46]) were lower, and high-density lipoprotein (HDL) levels were higher (MD −0.15 [95% CI −0.22; −0.08]) after treatment with a fourth-generation progestin. For other outcomes, including hirsutism, no differences were seen. Cycle regularity was not reported in any of the included studies.

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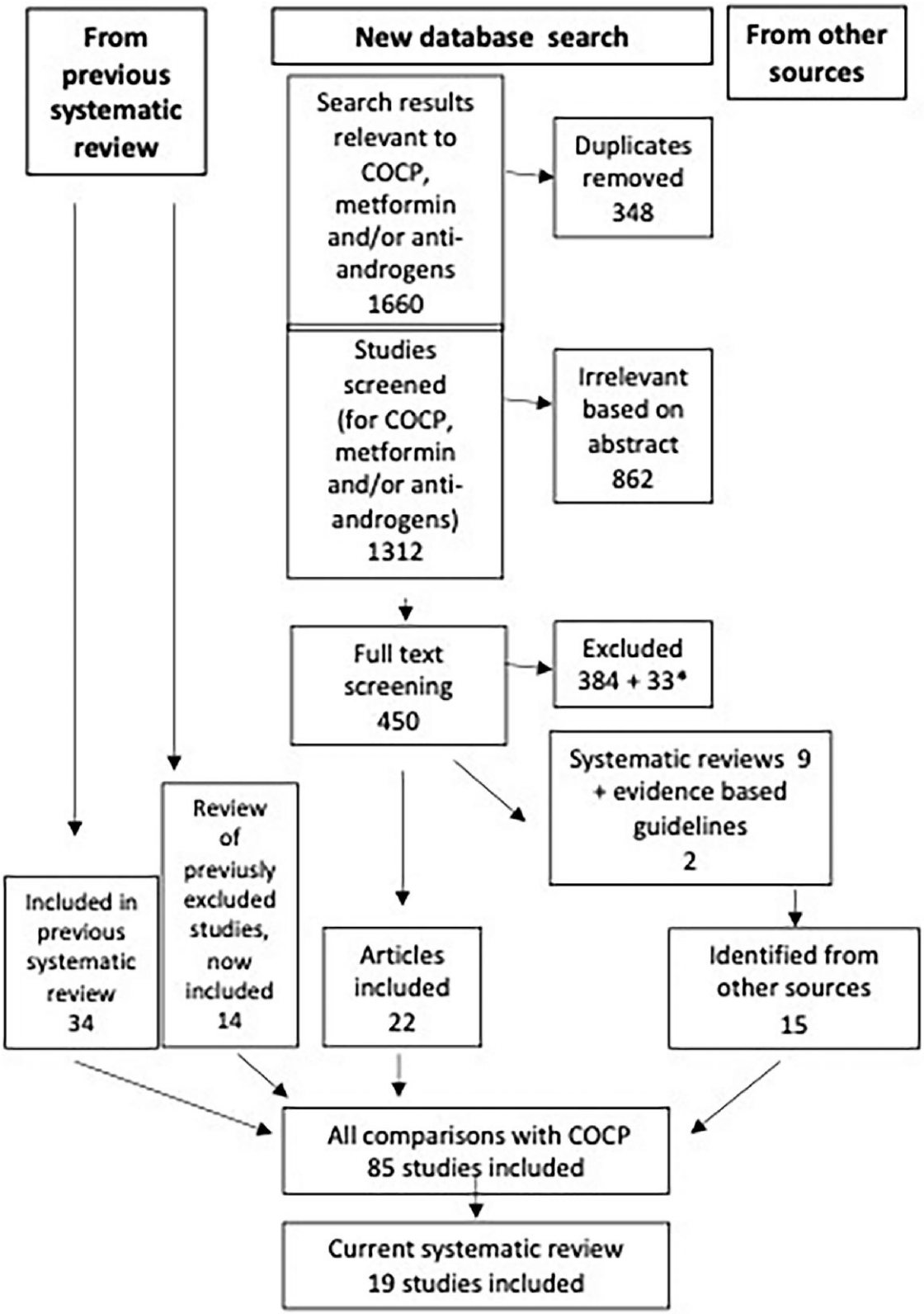

Figure 1. PRISMA flowchart over included studies. The search was performed for three questions (treatment with COCP, metformin, and antiandrogens) related to the update of the PCOS guidelines. In this systematic review, results comparing COCP with different levels of EE, different progestins, the combination EE/CPA, and progestin alone are included. *Included in metformin and/or antiandrogen questions, but not in COCP. COCP, combined oral contraceptive pills; EE, estrogen; and CPA, cyproterone acetate.

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Table 2. Characteristics of included studies.

Study ID	ROB	Interventions	Setting Duration	*N*	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Outcomes
Amiri (2020)	High	1) EE 30 µg + LNG 0.15 mg, then EE 30 µg + DSG 150 µg 2) EE 30 µg + LNG 0.15 mg, then EE 30 µg + CPA 2 mg 3) EE 30 µg + LNG 0.15 mg, then EE 30 µg + DRSP 3 mg 4) EE 30 µg + DSG 150 µg, then EE 30 µg + LNG 0.15 mg 5) EE 30 µg + CPA 2 mg, then EE 30 µg + LNG 0.15 mg 6) EE 30 µg + DRSP 3 mg, then EE 30 µg + LNG 0.15 mg	Iran 6 m	1) 9 2) 9 3) 8 4) 26 5) 20 6) 16	NR, aged 18–45	NR	Androgen Excess Society	NR	NR	FAI, m-FG, weight, BMI, WHR, SHBG, DHEAS, glucose, insulin, HOMA, TG, chol, LDL, and HDL
Amiri (2021)	High	1) OCs containing ethinyl estradiol (EE) 30 µg + LNG 0.15 mg 2) OCs containing EE 30 µg + DSG 150 µg 3) OCs containing EE 35 µg + CPA 2 mg 4) OCs containing EE 30 µg + DRSP 3 mg.	Iran 6 m	1) 23 2) 20 3) 28 4) 17	1) 28.5 ± 5.6 2) 27.6 ± 4.5 3) 30.7 ± 6.0 4) 30.0 ± 6.1	1) 25.5 ± 4.0 2) 25.7 ± 3.9 3) 26.0 ± 5.4 4) 25.8 ± 5.3	Androgen Excess Society	NR	Excluded	BMI, WHR, TG, Chol, LDL, and HDL
Bhattacharya (2012)	Low	1) 30 µg EE + 150 µg DSG 21/7 2) 35 µg EE + 2000 µg CPA 21/7 3) 30 µg EE + 3000 µg DRSP 21/7	India 12 months	1) 49 2) 51 3) 50	1) 22.24 ± 4.47 2) 22.32 ± 4.17 3) 22.33 ± 4.76	1) 25.41 ± 4.49 2) 26.41 ± 3.81 3) 26.47 ± 4.65	Androgen Excess Society	NR	NR	BMI, WHR, FG score, TT, SHBG, FAI, glucose, insulin, and HOMA
Bhattacharya (2016)	Low	1) 30 µg EE + 3 mg DRSP 21/7 2) 20 µg EE + 3 mg DRSP 24/4	India 12 months	1) 46 2) 48	1) 21.47 ± 4.27 2) 22.28 ± 3.91	1) 26.21 ± 5.15 2) 26.38 ± 5.70	Rott		Nonsmokers	BMI, WHR, FG score, TT, SHBG, and FAI
Cagnacci (2006)	High	1) Biphasic—40 µg EE + 25 µg DSG first 7 days, then 14 days 30 µg EE + 125 µg DSG 2) Monophasic—35 µg EE + 2 mg CPA	Italy 6 months	1) 10 2) 10	1) 22.7 ± SE 0.7 2) 21.8 ± SE 0.8	1) 23.5 ± SE 1.9 2) 22.6 ± SE 0.9	Author determined criteria (similar to Rotterdam)	NR	NR	BMI, WHR, glucose, and insulin
Christakou (2014)	Mod	1) 35 µg EE +2 mg CPA 2) 30 µg EE + 3 mg DRSP 3) Met 1700mg/day	Greece 6 months	1) 38 2) 36 3) 35	1) 22 ± 0.6 2) 23.2 ± 0.6 3) 21.5 ± 0.5	1) 21.80 ± 0.35 2) 22.37 ± 0.48 3) 23.03 ± 0.67	NIH	NR	All nonsmokers	BMI, HOMA, TT, SHBG, FAI, and CRP
Chung (2014) (crossover)	Mod	1) 10 mg MPA/d for 10 d/m first 4 m, then 4 m washout, then 35 µg EE + 2 mg CPA/d 21/7 for 4 m 2) As above in reverse	Hong Kong 4 m/phase (12 m)	1) 38 2) 36	1) 16.7 ± 1.6 2) 17.5 ± 1.3	1) 23.7 ± 5.3 2) 23.6 ± 5.1	Rotterdam	1) 12.1 ± 1.4 2) 12.1 ± 1.3	NR	Weight, BMI, WHR, hirsutism score, TT, and SF-36
DeLeo (2010)	High	1) 30 µg EE + DRSP 2) 30 µg EE + CMA 3) 30 µg EE + GSD 4) 30 µg EE + DSG	Italy 3 months	10/group	Age 16–35 years. Mean not reported	All lean, mean not reported	Rott	NR	NR	Free T, TT, A4, SHBG, DHEAS, and adverse effects
Fonseka (2020)	Low	1) 35 µg EE + 2 mg CPA (Diane-35)	Sri Lanka 12 months	1) 20 2) 23	1) 23.35 ± 5.10 2) 22.39 ± 6.45	1) 28.27 ± 6.94 2) 26.74 ± 4.88	Rott	NR	NR	mFG score

(*continued*)

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Table 2. Continued

Study ID	ROB	Interventions	Setting Duration	*N*	Mean age	Mean BMI	PCOS	Age at menarche	Smokers	Outcomes
		2) 20 μg EE + 0.15 mg DSG (Fermion) 3) Metformin + EE/CPA 4) Metformin + EE/DSG		3) 26 6) 30	3) 24.81 ± 6.24 4) 27.90 ± 6.89	3) 27.93 ± 4.89 4) 27.20 ± 4.28				
Kahraman (2014)	High	35 μg EE + 2 mg CPA 30 μg EE + 3 mg DRSP	Turkey 12 months	1) 19 2) 20	Median age 21 vs. 21.5 years	Median/IQR: 1) 22.8/19.5–34.9 2) 22.0/18.0–43.4	Androgen Excess Society	NR	NR	BMI, hirsutism score, SHBG, TT, FAI, androstenedione, DHEAS, insulin, glucose, HOMA, TG, LDL, HDL, CRP, and OGTT
Kriplani (2010)	High	1) 30mcg EE + 3 mg DRSP 21/7 2) 30 μg EE + 150 μg DSG 21/7	India 6 months	1) 29 2) 29	22.5 ± 4.7 (all participants)	1) 27.6 ± 5.4 2) 26.1 ± 3.6	Rotterdam ESHRE/ASRM Workshop criteria	NR	Excluded	TG, LDL, HDL, chol, glucose, insulin, HOMA, TT, SHBG, FAI, bioavailable testo, and side effects
Mastorakos (2002)	High	1) EE 30 μg + 0.15 mg DSG 2) EE 35 μg + 2 mg CPA	Greece 12 months	1) 14 2) 14	1) 17.5 ± 0.5 2) 17.5 ± 0.4	1) 25.5 ± 1.8 2) 24.8 ± 1.1	NIH	NR	NR	TT, fT, A4, DHEAS, SHBG, chol, HDL, and LDL
Mastorakos (2006)	Low	1) 0.15 mg DSG + 0.030 mg EE 21/7 2) 2 mg CPA + 0.035 mg EE 21/7	Greece 12 months	1) 18 2) 18	1) 17.01 ± 0.73 2) 17.16 ± 0.63 (SE)	1) 25.8 ± 1.81 2) 0.73 ± 0.06 (SE)	NIH criteria	NR	NR	Glucose, insulin, HOMA, and OGTT
Morgante (2020)	High	1) EE 30 mg/DRSP 3 mg, 2) EE 30 mg/CMA 2 mg, 3) EE 30 mg/DNG 2 mg	Italy 3 months	1) 20 2) 20 3) 20	Mean age NR, aged 16–35	Mean BMI NR, stated to be < 25	Rott	NR	NR	DHEAS, TT, SHBG, and androstenedione
Ozdemir (2008)	Mod	1) 10 mg MPA 10 d/month 2) 30 μg of EE + 3 mg DRSP 21/7	Turkey 6 months	1) 31 2) 32	1) 23.4 ± 3.9 2) 22.7 ± 3.8	1) 23.6 ± 4.4 2) 24.3 ± 4.8	Rott	NR	Excluded	BMI, WHR, insulin, glucose, HOMA, chol LDL, HDL, TG, TT, SHBG, FAI, DHEAS, and FG score
Panidis (2011)	High	1) 35 μg EE + 2 mg CPA 2) 3 mg DRSP/30 mcg EE 3) Met 1700mg/day	Greece 6 months	1) 15 2) 15 3) 15	1) 20.67 ± 4.13 2) 22.00 ± 2.07 3) 20.53 ± 3.09	1) 21.04 ± 1.97 2) 21.69 ± 2.33 3) 21.83 ± 1.73	NIH	NR	NR	BMI, HOMA, glucose, insulin, TT, A4, DHEAS, SHBG, and FAI
Podfigurna (2020)	High	1) 3 mg DRSP/30 mcg EE 2) 2 mg CMA/30 mcg EE	Poland 6 months	1) 60 2) 60	26.92 ± 4.72 for all	28.13 ± 5.79 for all	Rott	NR	NR	FG score, BMI, T, DHEA-S, GLU, INS, and HOMA
Taheripanah (2010)	High	1) OCP—no details 2) EE + CPA (Diane)—no details	Iran 3 months	1) 30 2) 30	1) 22.9 ± 0.5 2) 23.97 ± 0.61	1) 21.17 ± 2.06 2) 21.73 ± 2.76	Rott	NR	NR	FG score, fT, and DHEAS
Yildizhan (2015)	High	1) 3 mg DRSP/30 μg EE 2) 2 mg CMA/30 μg EE	Turkey 6, 12, and 24 months	At 12 months: 1) 57 2) 55	1) 25.36 ± 2.91 2) 24.82 ± 3.20	1) 24.82 ± 3.32 2) 23.56 ± 3.32	Rott	NR	NR	BMI, WHR, HDL, LDL, TG, chol, HOMA, DHEAS, FG score, SHBG, CRP, TT, and FAI

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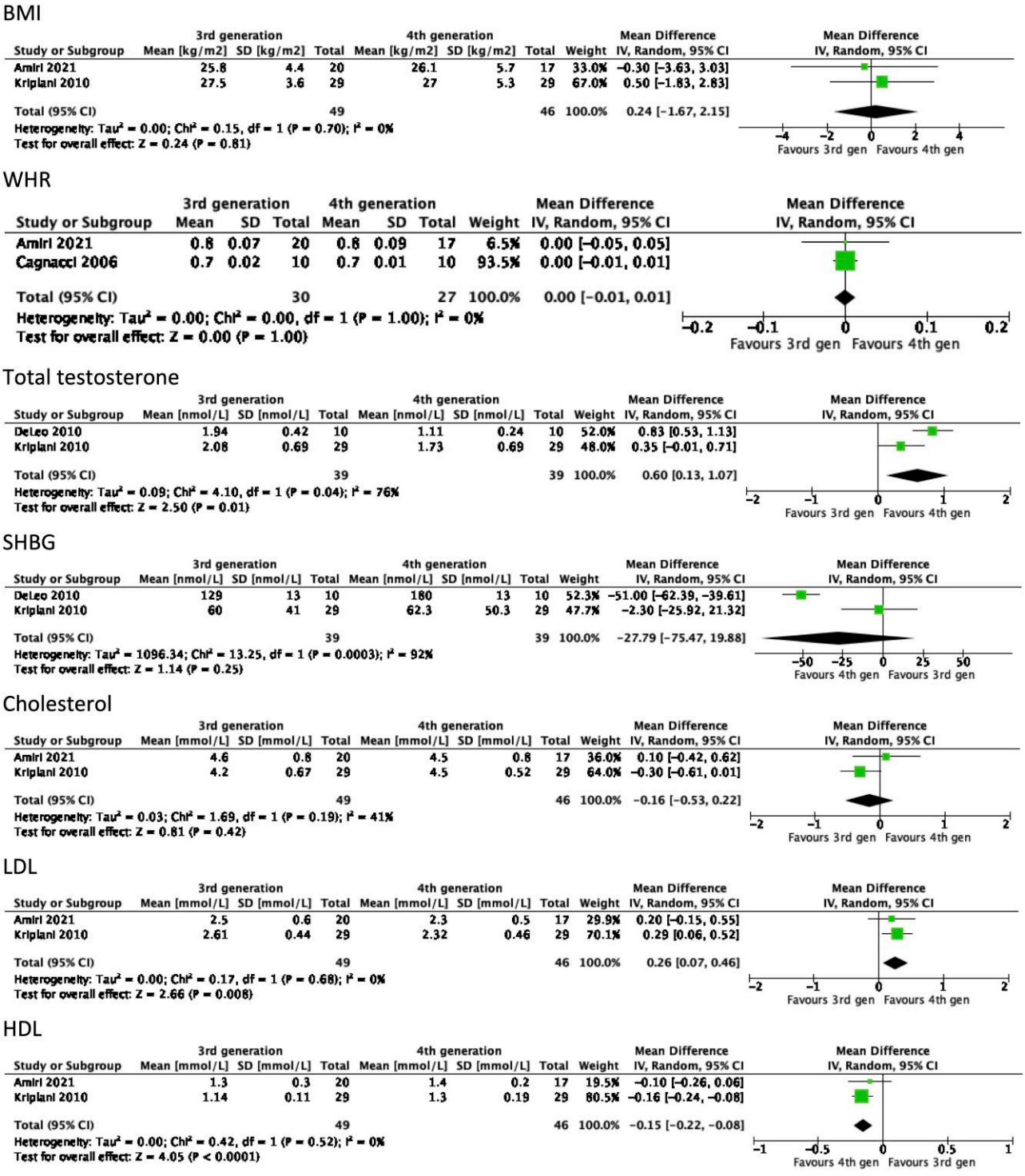

Figure 2. Comparison of combined oral contraceptive pills (COCPs) with third-generation vs. COCP with fourth-generation progestins in women with PCOS.

Results are shown summarized in Table S4. Results from meta-analyses are shown in Figure 2 and narrative results from the systematic review (where a meta-analysis could not be performed) in Table S5.

COCP vs. EE/CPA

Eleven studies, of 3–12-month duration, were identified comparing COCPs containing CPA with COCPs with other progestins. Seven had a high RoB,[31,32,35–39] one moderate,[40] and three a low RoB.[26,33,41] Two[37,41] were conducted in an adolescent population. Details on study characteristics are shown in Table 2, summary results in Table 3, meta-analysis in Figure 3, and narrative results (when a meta-analysis could not be performed) in Table S6.

Regarding BMI, seven studies were identified, with four included in the meta-analysis, showing EE/CPA had a lower BMI compared with COCPs without CPA (MD 0.62 kg/m^2 [95%

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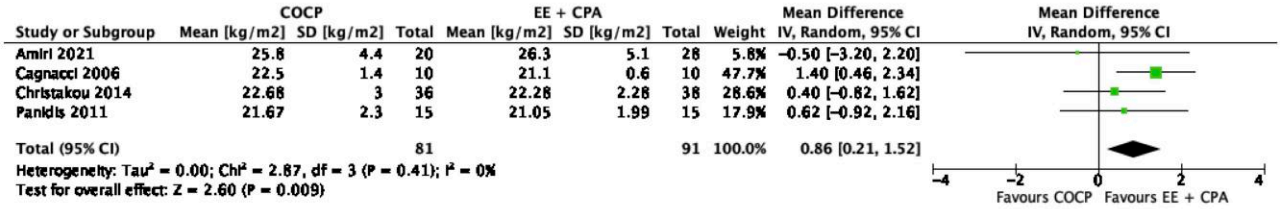
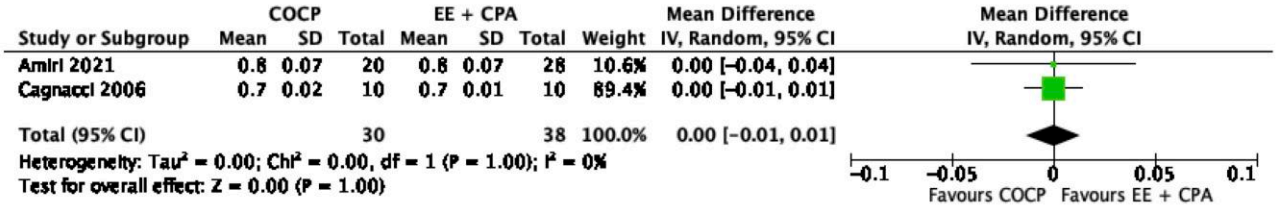
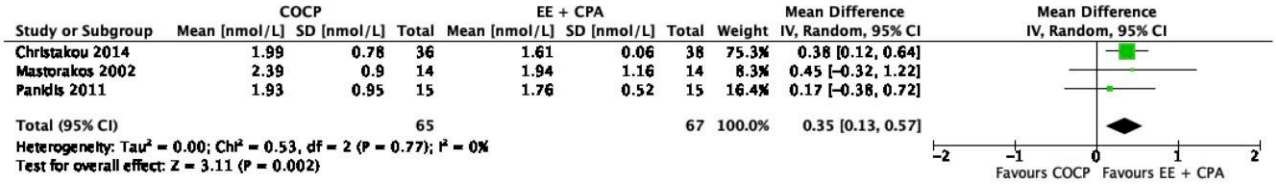
BMI



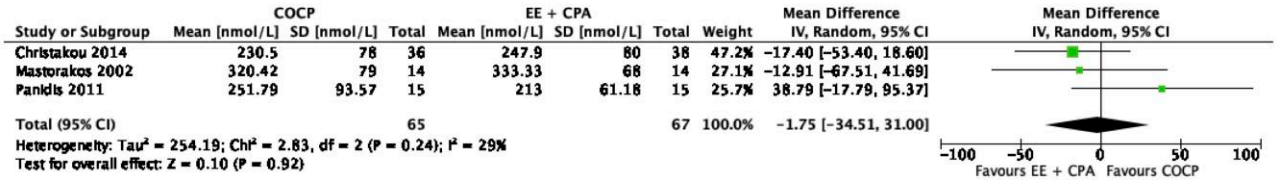
WHR



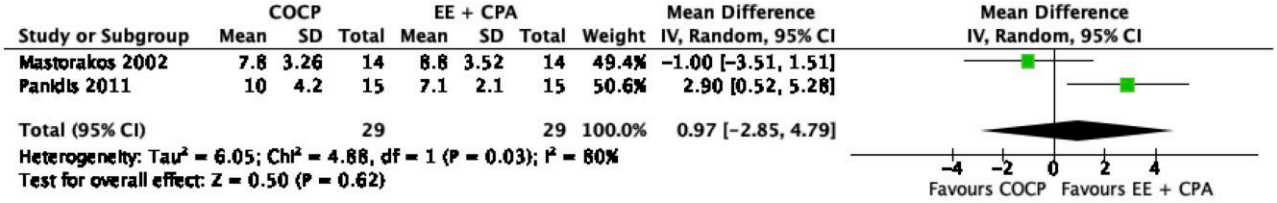
Testosterone



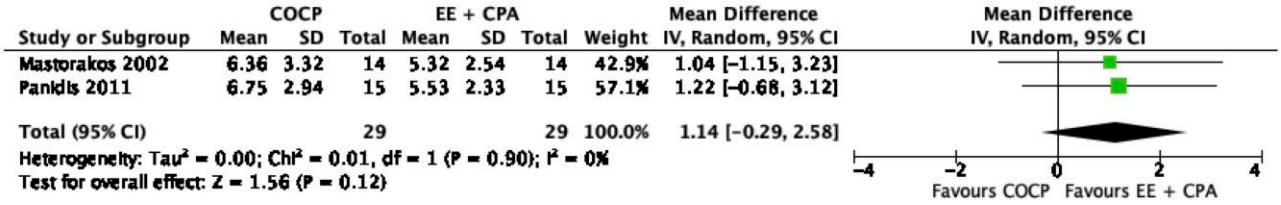
SHBG



Androstenedione



DHEAS



Insulin

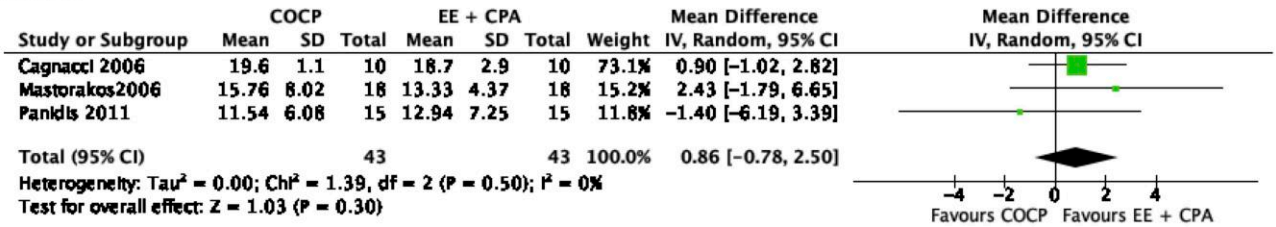


Figure 2. Continued

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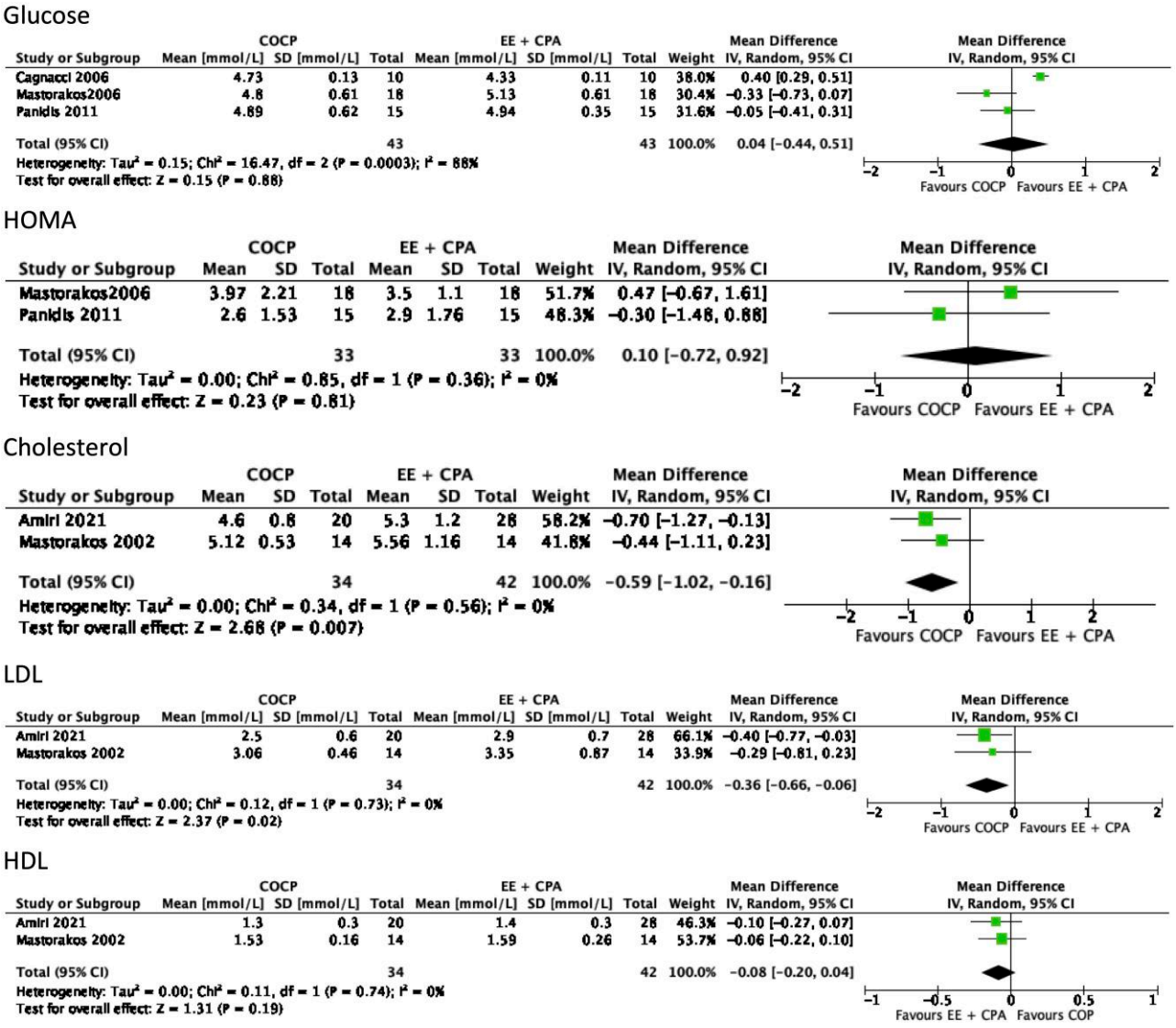

Figure 3. Comparison of combined oral contraceptive pills vs. ethinyl estradiol (EE)/cyproterone acetate (CPA) in women with PCOS.

CI 0.05–1.20]). At baseline, there was a trend for a difference in BMI, 23.24 vs. 23.05 kg/m^2 for COCP without CPA compared with EE/CPA, respectively. For WHR, no difference was apparent. Treatment with EE/CPA improved hirsutism and FAI levels, as shown in the narrative summary. On meta-analysis, total testosterone levels were lower after EE/CPA treatment (MD 0.38 nmol/L [95%CI 0.33_0.43]). Sex hormone binding globulins, DHEAS, or androstenedione levels did not differ.

Regarding metabolic parameters, EE/CPA treatment resulted in higher LDL and cholesterol. No differences were seen in glucose, insulin, HOMA-IR, HDL, or cholesterol or CRP levels. Cycle regularity was not reported in any of the included studies. Regarding adverse effects, this was not assessed systematically in the included papers, but no major adverse effects were reported (Table S6).

Any COCP vs. progestin alone

Two studies, both with a moderate RoB, were identified, one in adolescents[42] and one in adults.[43] Both used medroxyprogesterone acetate alone. Chung et al. compared it with EE/CPA over 4 months, and Ozdemir et al. compared it with EE/DRSP over 6 months (Table S7). Meta-analysis on BMI, WHR, and total testosterone showed no differences in any of these outcomes (Figure S3).

Other outcomes, with results from only one study, showed lower FAI and higher SHBG after conventional COCP treatment and lower triglyceride levels after progestin alone. Hirsutism and HRQoL did not differ (Tables S7 and S8).

Discussion

This systematic review and meta-analysis directly compares the efficacy of different COCPs in the treatment of PCOS. These results will inform the 2023 update of the International Evidence-Based Guidelines on the Assessment and Treatment of PCOS and advance evidence from the 2018 guidelines.[1,5] The use of COCP specifically as a treatment in PCOS is off label, and the benefits as well as risks must be considered. According to our systematic review, EE/CPA had a better effect on hirsutism and biochemical hyperandrogenism compared with COCPs with other progestins. However, it is associated with more adverse events like VTE

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Table 3. Combined oral contraceptive pills (COCPs) compared with ethinyl estradiol (EE) + cyproterone acetate (CPA) treatment. Outcomes that could not be included in the meta-analysis, including reported adverse effects, are reported narratively in Table S6.

Comparison: COCP vs. EE/CPA											
Population	No. studies	Quality assessment						No. participants		Effect, random [95% CI]	Favors	Certainty
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP	EE/CPA			
Outcome: BMI												
Adults	4[a]	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	81	89	MD 0.62 kg/m^2 (0.05; 1.20)	**Lower after EE/CPA**	⊕⊕◯◯ Low
Outcome: WHR												
Adults	2[c]	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Serious[m]	None	30	38	MD 0.00 (−0.01; 0.01)	No difference	⊕◯◯◯ Very low
Outcome: FAI												
Adults	3	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	100	104	Not applicable—see narrative summary	**Lower after EE/CPA**	⊕⊕◯◯ Low
Outcome: Total testosterone												
Overall	3[d]	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	65	67	MD 0.38 nmol/L (0.33; 0.43)	**EE/CPA**	⊕⊕◯◯ Low
Adults	2	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	51	53	MD 0.38 nmol/L (0.33; 0.43)	**EE/CPA**	⊕⊕◯◯ Low
Adolescents	1	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	14	14	MD 0.45 nmol/L (−0.32; 1.22)	No difference	⊕◯◯◯ Very low
Outcome: SHBG												
Overall	3[e]	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	65	67	MD −5.86 nmol/L (−35.34; 23.63)	No difference	⊕⊕◯◯ Low
Adults	2	RCT	Very serious[b]	Serious[s]	No serious indirectness	Serious imprecision[t]	None	51	53	MD 3.36 nmol/L (−49.79; 56.52)	No difference	⊕◯◯◯ Very low
Adolescents	1	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	14	14	MD −12.91 nmol/L (−67.51; 41.69)	No difference	⊕◯◯◯ Very low
Outcome: Androstenedione												
Overall	2[g]	RCT	Very serious[b]	Very serious[h]	No serious indirectness	Very serious[i]	None	35	35	MD 0.78 nmol/L (−3.03; 4.58)	No difference	⊕◯◯◯ Very low
Adults	1	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	15	15	MD 2.90 nmol/L 0.52; 5.28)	**EE/CPA**	⊕◯◯◯ Very low
Adolescents	1	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	14	14	MD 0.97 nmol/L (−2.85; 4.79)	No difference	⊕◯◯◯ Very low
Outcome: DHEAS												
Overall	2[j]	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	29	29	MD 1.14 nmol/L (−0.29; 2.58)	No difference	⊕◯◯◯ Very low
Adults	1	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	15	15	MD 1.22 nmol/L (−0.68; 3.12)	No difference	⊕◯◯◯ Very low
Adolescents	1	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	14	14	MD 1.04 nmol/L (−1.15; 2.58)	No difference	⊕◯◯◯ Very low
Outcome: Insulin												
Overall	3[l]	RCT	Serious[f]	No serious inconsistency	No serious indirectness	Serious imprecision[m]	None	43	43	MD 0.86 µU/mL (−0.78; 2.50)	No difference	⊕⊕◯◯ Low
Adults	2	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	25	25	MD 0.58 µU/mL (−1.20; 2.53)	No difference	⊕◯◯◯ Very low

(*continued*)

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Table 3. Continued

Comparison: COCP vs. EE/CPA											
Population	**No. studies**	**Quality assessment**						**No. participants**		**Effect, random [95% CI]**	**Favors**	**Certainty**
		Design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**COCP**	**EE/CPA**			
Adolescents	1	RCT	Serious[f]	No serious inconsistency	No serious indirectness	Very serious[k]	None	18	18	MD 2.43 μU/mL (−1.79; 6.65)	No difference	⊕◯◯◯ Very low
Outcome: Glucose												
Overall	3[n]	RCT	Very serious[b]	Very serious[h]	No serious indirectness	No serious imprecision	None	43	43	MD 0.04 mmol/L (−0.44; 0.51)	No difference	⊕◯◯◯ Very low
Adults	2	RCT	Very serious[b]	Very serious[h]	No serious indirectness	Very serious[k]	None	25	25	MD 0.21 mmol/L (−0.23; 0.65)	No difference	⊕◯◯◯ Very low
Adolescents	1	RCT	Serious[f]	No serious inconsistency	No serious indirectness	Very serious[k]	None	18	18	MD −0.33 mmol/L (−0.73; 0.07)	No difference	⊕◯◯◯ Very low
Outcome: HOMA												
Overall	2[o]	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Serious[m]	None	33	33	MD 0.10 (−0.72; 0.92),	No difference	⊕◯◯◯ Very low
Adults	1[o]	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	15	15	MD −0.30 (−1.48; 0.88),	No difference	⊕◯◯◯ Very low
Adolescents	1	RCT	Serious[f]	No serious inconsistency	No serious indirectness	Very serious[k]	None	18	18	MD 0.47 (−0.67; 1.61),	No difference	⊕◯◯◯ Very low
Outcome: Cholesterol												
Overall	2[p]	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Serious[m]	None	34	42	MD −0.59 mmol/L (−1.02; −0.16)	**COCP**	⊕◯◯◯ Very low
Adults	1	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	20	28	MD −0.70 (−1.27; −0.13)	**COCP**	⊕◯◯◯ Very low
Adolescents	1	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	14	14	MD −0.44 (−1.11; 0.23)	No difference	⊕◯◯◯ Very low
Outcome: LDL												
Overall	2[q]	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Serious[m]	None	34	42	MD −0.36 mmol/L (−0.66; −0.06)	**COCP**	⊕◯◯◯ Very low
Adults	1	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	20	28	MD −0.40 mmol/L (−0.77; −0.03)	**COCP**	⊕◯◯◯ Very low
Adolescents	1	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	14	14	MD −0.29 mmol/L (−0.81; 0.23)	No difference	⊕◯◯◯ Very low
Outcome: HDL												
Overall	2[r]	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Serious[m]	None	34	42	MD −0.08 mmol/L (−0.20; 0.04)	No difference	⊕◯◯◯ Very low
Adults	1	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	20	20	MD −0.10 mmol/L (−0.27; 0.07)	No difference	⊕◯◯◯ Very low
Adolescents	1	RCT	Very serious[b]	No serious inconsistency	No serious indirectness	Very serious[k]	None	14	14	MD −0.06 mmol/L (−0.22; 0.10)	No difference	⊕◯◯◯ Very low
Outcome: Hirsutism												
Adults	3	RCT	Serious	No serious inconsistency	Serious indirectness	No serious	None	92	90	Not applicable—see narrative summary	**EE/CPA**	⊕⊕◯◯ Low

(*continued*)

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Table 3. Continued

Comparison: COCP vs. EE/CPA												
Population	No. studies	Quality assessment						No. participants		Effect, random [95% CI]	Favors	Certainty
		Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	COCP	EE/CPA			
Outcome: Free testosterone												
Adults	2	RCT	Very serious[b]	No serious inconsistency	Serious indirectness	Serious[m]	None	34	33	Not applicable—see narrative summary	No difference	⊕◯◯◯ Very low
Outcome: OGTT												
Adults	2	RCT	Very serious[b]	No serious inconsistency	Serious	Serious[m]	None	38	37	Not applicable—see narrative summary	No difference	⊕◯◯◯ Very low
Outcome: Triglycerides												
Adults	2	RCT	Very serious[b]	No serious inconsistency	Serious	Serious[m]	None	37	47	Not applicable—see narrative summary	No difference	⊕◯◯◯ Very low
Outcome: CRP												
Adults	2	RCT	Very serious[b]	No serious inconsistency	Serious	Serious[m]	None	56	57	Not applicable—see narrative summary	No difference	⊕◯◯◯ Very low

[a]Two additional studies, not included in the meta-analysis: Bhattacharya (2012) reported mean change, −0.45 ± 6.75 for a third-generation COCP vs. −0.59 ± 4.76 kg/m^2 for EE/CPA, *P* value not reported; Kahraman (2014) reported median change, −1 (−9 to 17) for a fourth-generation COCP vs. −1 (−12 to 6), *P* = .789.
[b]Downgraded twice since majority of studies had a high risk of bias.
[c]Two additional studies, not included in the meta-analysis: Bhattacharya (2012) reported mean change, 0.00 ± 0.08 for a third-generation COCP vs. −0.02 ± 0.08 for EE/CPA, *P* value not reported; Kahraman (2014) reported median change, −4 (−31 to 35) for a fourth-generation COCP vs. 0 (−11 to 14), *P* = .03.
[d]Two studies not included in the meta-analysis: Bhattacharya (2012) reported mean change in TT, −0.10 ± 0.39 ng/mL for a third-generation COCP vs. −0.03 ± 0.42 for EE/CPA, *P* value not reported; Kahraman (2014) reported median % change, −39 (−84 to 43) for a fourth-generation COCP vs. −16 (−78 to 125) for EE/CPA, *P* = .087.
[e]Two additional studies not included in the meta-analysis: Bhattacharya (2012) reported mean change, 99.53 ± 67.52 nmol/L for a third-generation COCP vs. −142.91 ± 60.71 for EE/CPA, *P* = .02; Kahraman (2014) reported median % change (range) 178 (−57 to 897) vs. 270 (31 to 1062) nmol/L, *P* = .238.
[f]Downgraded once since some studies had moderate or high risk of bias.
[g]One additional study, not included in the meta-analysis: Kahraman (2014) reported median % change (range) −29 (−100 to 25) for COCP vs. −18 (−47 to 52) for EE/CPA, *P* = .052.
[h]Downgraded twice since $I^2 > 50\%$ and CIs not overlapping.
[i]Downgraded twice due to wide CI and few patients.
[j]One additional study, not included in the meta-analysis: Kahraman (2014) reported median % change (range) −32 (−53 to 15) for COCP vs. −10 (−49 to 63) for EE/CPA, *P* = .046.
[k]Downgraded twice due to very few patients.
[l]Two additional studies, not included in the meta-analysis: Bhattacharya (2012) reported mean change, −0.02 ± 17.35 for a third-generation COCP vs. 6.38 ± 15.22 for EE/CPA, *P* value not reported; Kahraman (2014) reported median % change (range) 7 (−85 to 223) vs. 0 (−82 to 128), *P* = .603.
[m]Downgraded once due to few participants.
[n]Two additional studies not included in the meta-analysis: Bhattacharya (2012) reported mean change, −4.28 ± 11.66 for a third-generation COCP vs. −2.46 ± 16.86 for EE/CPA, *P* value not reported; Kahraman (2014) reported median % change (range) 0 (−15 to 6) vs. 0 (−10 to 18), *P* = .397.
[o]Three additional studies, not included in the meta-analysis. Bhattacharya (2012) reported mean change, −0.28 ± 3.98 for a third-generation COCP vs. 1.21 ± 4.03 for EE/CPA, *P* value not reported; Kahraman (2014) reported median % change (range) 2 (−71 to 216) vs. −18 (−80 to 462), *P* = .227. Christakou reported medians (IQR) 2.25 (1.65) vs. 2.42 (1.44).
[p]One additional study, not included in the meta-analysis. Kahraman (2014) reported median % change (range) 7 (−13 to 59) for COCP vs. 11 (−17 to 79) for EE/CPA, *P* = .673.
[q]One additional study, not included in the meta-analysis. Kahraman (2014) reported median % change (range) 2 (−30 to 68) vs. 5 (−16 to 63) *P* = .555.
[r]Two additional studies not included in the meta-analysis. Kahraman (2014) reported median % change (range) + 5 (−42 to 45) after COCP treatment vs. + 16 (−45 to 46) after EE/CPA, *P* = .070. Wang 2016 reported medians, 1.67 (1.45, 1.98) mmol/L after COCP and 1.59 (1.36, 1.89) mmol/L after EE/CPA, *P* = .322.
[s]Downgraded once due to $I^2 > 50\%$.
[t]Downgraded once due to wide CI.

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in the general population. For comparisons of generational progestins, evidence regarding the effect on clinical hyperandrogenism did not show a difference between different generations. However, the newer nonandrogenic progestins may be more beneficial on blood lipids compared with older generations.

The estrogen component

Higher EE doses are associated with higher SHBG, the most important binding protein for testosterone which directly influences the bioavailable testosterone.[44] Here, different doses of EE were compared, and as expected, the higher (30 µg) dose was associated with higher SHBG levels compared with lower EE (20 µg). However, despite this, no changes in hirsutism, carbohydrate, or lipid parameters were evident after 12 months. During the last decades, newer natural estrogens have been introduced in COCPs: 17β-estradiol, its valeric acid ester (estradiol valerate), and esterol (17α-hydroxy-estriol). In women without PCOS, these natural estrogens do not appear to negatively affect carbohydrate metabolism at all and have a more beneficial effect on lipid metabolism.[16] Thus, these kinds of COCPs are of particular interest in women with PCOS, since they have increased metabolic risk factors.[45] Here, no studies were identified comparing EE with other kinds of estrogens.

The progestin component

With current evidence, as presented in this review, EE/CPA were better than conventional COCPs in reducing hirsutism. However, the use of EE/CPA might be associated with an increased metabolic risk (higher cholesterol and LDL). All EE/CPA combination had a higher dose of EE, 35 µg, which may influence both results and risk profile, including risk of VTE. A possible treatment option that might be appealing in PCOS in the future could be a combination of CPA with a lower dose of EE or a natural estrogen compound, but to our knowledge, no such preparations are available to date. The comparisons regarding COCPs according to progestin generations had overall low-quality evidence; however, there are indications favoring the latest fourth-generational COCPs in terms of their metabolic profile.

Irregular menstrual cycles

Combined oral contraceptive pills improve irregular cycles, with either continuous preparations or timed withdrawal bleeding to protect the endometrium from unopposed estrogen exposure. In the included studies here, improvement of irregular cycles was not reported, and potential differences cannot be assessed. However, as shown in a previous study in women with PCOS, comparing COCP treatment normally results in regular bleedings compared with no treatment.[46]

Hyperandrogenism

Effects on hyperandrogenism may differ, with later-generation progestins theoretically offering advantages. The efficacy of COCP on hyperandrogenism is primarily related to the estrogen effect on SHBG production, reducing circulating free androgen levels. The progestins antagonize the estrogen-induced SHBG increase to varying degrees, making the choice of progestin in COCP relevant, where third- and fourth-generation progestins result in more than 3–4 times higher SHBG increase compared with second-generation COCP.[15]

Overall, there is as yet inadequate evidence to influence conventional COCP choice based on clinical hyperandrogenism, but here, we report less hirsutism after EE/CPA treatment compared with conventional COCP. The combination EE/CPA is used second line in the treatment of severe acne and in hirsutism as per the World Health Organization (WHO) recommendations, both in women with and without PCOS.[11,47] A previous systematic review on COCPs and the effect on hyperandrogenism in women with PCOS included both RCTs and non-RCTs, but only compared the difference between before and after treatments.[44] These results suggested, based on larger mean differences between before and after treatment, that EE/CPA would be more favorable in the treatment of hirsutism and also indicated that a longer duration of treatment resulted in a greater improvement (both for conventional COCPs and EE/CPA), but as that systematic review and meta-analysis included no direct comparisons between the treatments, these conclusions must be considered with great caution.[44]

Effects on metabolism

Fourth-generation COCPs could be more beneficial in effects on metabolism, as LDL was lower, but HDL higher, after fourth-generation compared with third-generation COCP treatment. These effects on lipid metabolism are in line with findings from the general population, where the newer nonandrogenic progestins are more beneficial on lipids compared with older generations.[16] In addition, BMI was lower after treatment with the fourth-generation COCPs, most likely related to mineralocorticoid effects of DRSP. However, all these findings were low-quality evidence.

The newer natural estrogens do not appear to negatively affect carbohydrate metabolism and have a more beneficial effect on lipid metabolism.[48,49] No RCTs in PCOS using these agents were identified.

Mental health and HRQoL

Women with PCOS have decreased HRQoL and increased prevalence of depression compared with women in general.[50,51] Mental health and HRQoL were reported as an outcome only for the comparison COCP vs. progestin alone. Based on findings in the general population, some data suggest an increased risk of depression and suicidal behavior associated with COCP treatment.[52,53] The risk of effects on mood appears higher if the patient had an ongoing or previous mental health disorder prior to starting COCP treatment.[54]

In contrast, COCP treatment resulted in slightly improved HRQoL and decreased depressive symptoms when used as part of a preconception intervention in infertile women with PCOS; however, this is a distinct cohort of women.[55] Importantly, available data regarding associations between specific COCP composition and mental health in women with PCOS are limited. Psychosocial and mental health outcomes are important and should be included in future studies on COCP in PCOS.

VTE risk

Combined oral contraceptive pills with second-generation progestins, especially those containing LNG, are generally

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considered the first-line COCP due to lower risk of VTE.[56] In the included RCTs, there were no reports on VTEs. However, such adverse effects are rare and can be better studied in large epidemiological settings. A recent cohort study including almost 600 000 women from the general population showed an increased VTE incidence rate ratio of 1.4 of hormonal contraception users compared with nonusers,[12] the risk varying depending on type of progestin and estrogen. The risk of VTE with EE/CPA compared with other COCPs is increased, with the risk more than doubled compared with EE/LNG in the general population.[12,56] In the last guideline, EE/CPA was specifically *not* recommended as first-line COCP treatment, due to the risk profile in the general population.[1]

Key knowledge gaps

In the previous guidelines, no recommendations regarding specific types of COCPs could be made. Here, evidence has advanced but remains mainly of low quality. This is largely due to few and small studies with a high RoB, and studies moving forward need to have appropriate methodology and sample size to overcome these concerns. There is a need for more RCTs with a low RoB for all comparisons reported here. Some of the most important gaps are prioritized for future research, including high-quality studies with comparisons between COCPs with second- and fourth-generation progestins and with lower dose EE, natural estrogens, and CPA. In addition, there is a need to systematically studying the impact on mental health, HRQoL, sexual function, and adverse effects, including severe events like VTE.

Strengths and limitations

These data provide up-to-date information regarding the effects of different COCPs in PCOS; this information will directly inform the 2023 update of PCOS guidelines. It identifies what is currently known about differences between different COCPs and also helps guide future research by identifying key gaps.

Relevant limitations of the studies included here were poor description of randomization process, no blinding, and a high drop-out rate. Regarding biochemical hyperandrogenism, different methods were used by different studies, limiting the comparisons. Another limitation is that only oral combined hormonal treatments were included; hence, our results are inapplicable to other administrative routes. Due to lack of studies, subgroup analysis regarding adolescents could not be done.

Conclusions

We report available data regarding different COCPs in the treatment of PCOS. With current evidence, EE/CPA may be better compared with conventional COCPs in reducing clinical as well as biochemical hyperandrogenism but is currently not recommended as a first-line treatment in PCOS due to higher VTE risk in the general population. Cyproterone acetate in combination with lower dose EE or with natural estrogens could be an interesting option in the future. Later-generation progestins offer theoretical benefits, but more and better evidence on clinical outcomes is needed in women with PCOS. There is no difference in improvement of hirsutism between low and high doses of EE, supporting the increased use of COCP with low EE doses also in women with PCOS.

Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Conflict of interest: Coauthor T.P. is on the editorial board of EJE. She was not involved in the review or editorial process for this paper, on which she are listed as authors. None of the authors declare any conflicts of interest.

Data availability

All data used in this manuscript is secondary and can be found in the online versions of the published studies. Our own data synthesis of these manuscripts is available upon reasonable request to the corresponding author.

References

1. Teede HJ, Misso ML, Costello MF, *et al.* Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Fertil Steril.* 2018;110(3):364-379. https://doi.org/10.1016/j.fertnstert.2018.05.004
2. Bazarganipour F, Taghavi SA, Montazeri A, Ahmadi F, Chaman R, Khosravi A. The impact of polycystic ovary syndrome on the health-related quality of life: a systematic review and meta-analysis. *Iran J Reprod Med.* 2015;13(2):61-70. https://pubmed.ncbi.nlm.nih.gov/25999994/
3. Hahn S, Janssen OE, Tan S, *et al.* Clinical and psychological correlates of quality-of-life in polycystic ovary syndrome. *Eur J Endocrinol.* 2005;153(6):853-860. https://doi.org/10.1530/eje.1.02024
4. Karjula S, Morin-Papunen L, Franks S, *et al.* Population-based data at ages 31 and 46 show decreased HRQoL and life satisfaction in women with PCOS symptoms. *J Clin Endocrinol Metab.* 2020;105(6):1814-1826. https://doi.org/10.1210/clinem/dgz256
5. Teede H, Tassone EC, Piltonen T, *et al.* Effect of the combined oral contraceptive pill and/or metformin in the management of polycystic ovary syndrome: a systematic review with meta-analyses. *Clin Endocrinol (Oxf).* 2019;91(4):479-489. https://doi.org/10.1111/cen.14013
6. Teal S, Edelman A. Contraception selection, effectiveness, and adverse effects: a review. *JAMA.* 2021;326(24):2507-2518. https://doi.org/10.1001/jama.2021.21392
7. Darney PD. The androgenicity of progestins. *Am J Med.* 1995;98(1):S104-S110. https://doi.org/10.1016/S0002-9343(99)80067-9
8. Venous thromboembolism in women: a specific reproductive health risk. *Hum Reprod Update.* 2013;19(5):471-482. https://doi.org/10.1093/humupd/dmt028
9. de Bastos M, Stegeman BH, Rosendaal FR, *et al.* Combined oral contraceptives: venous thrombosis. *Cochrane Database Syst Rev.* 2014;3(2):Cd010813. https://doi.org/10.1002/14651858.CD010813.pub2
10. Weill A, Dalichampt M, Raguideau F, *et al.* Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. *BMJ.* 2016;353:i2002. https://doi.org/10.1136/bmj.i2002

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11. De Leo V, Musacchio MC, Cappelli V, Piomboni P, Morgante G. Hormonal contraceptives: pharmacology tailored to women's health. *Hum Reprod Update*. 2016;22(5):634-646. https://doi.org/10.1093/humupd/dmw016
12. Heikinheimo O, Toffol E, Partonen T, But A, Latvala A, Haukka J. Systemic hormonal contraception and risk of venous thromboembolism. *Acta Obstet Gynecol Scand*. 2022;101(8):846-855. https://doi.org/10.1111/aogs.14384
13. Stanczyk FZ, Hapgood JP, Winer S, Mishell DR Jr. Progestogens used in postmenopausal hormone therapy: differences in their pharmacological properties, intracellular actions, and clinical effects. *Endocr Rev*. 2013;34(2):171-208. https://doi.org/10.1210/er.2012-1008
14. Edwards M, Can AS. Progestin. *StatPearls*. 2022. https://www.ncbi.nlm.nih.gov/books/NBK563211/
15. Zimmerman Y, Eijkemans MJ, Coelingh Bennink HJ, Blankenstein MA, Fauser BC. The effect of combined oral contraception on testosterone levels in healthy women: a systematic review and meta-analysis. *Hum Reprod Update*. 2014;20(1):76-105. https://doi.org/10.1093/humupd/dmt038
16. Bastianelli C, Farris M, Rosato E, Brosens I, Benagiano G. Pharmacodynamics of combined estrogen-progestin oral contraceptives: 1. Effects on metabolism. *Expert Rev Clin Pharmacol*. 2017;10(3):315-326. https://doi.org/10.1080/17512433.2017.1271708
17. Joham AE, Norman RJ, Stener-Victorin E, *et al*. Polycystic ovary syndrome. *Lancet Diabetes Endocrinol*. 2022;10(9):668-680. https://doi.org/10.1016/S2213-8587(22)00163-2
18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8(5):336-341. https://doi.org/10.1016/j.ijsu.2010.02.007
19. Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. https://doi.org/10.1136/bmj.n71
20. Forslund M, Melin J, Alesi S, *et al*. Combined oral contraceptive pill compared with no medical treatment in the management of polycystic ovary syndrome: a systematic review. *Clin Endocrinol (Oxf)*. 2023;99(1):79-91. https://doi.org/10.1111/cen.14913
21. Covidence. In: Veritas health innovation M, Australia., editor. Accessed July–November 2022. www.covidence.org
22. Sterne JAC, Savović J, Page MJ, *et al*. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
23. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and shiny web app for visualizing risk-of-bias assessments. *Res Synth Methods*. 2020;12(1):55-61. https://doi.org/10.1002/jrsm.1411
24. Schünemann H BJ, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group, Updated October, 2013, Accessed December 12, 2022, guidelinedevelopment.org/handbook
25. Bhattacharya SM, Jha A, DasMukhopadhyay L. Comparison of two contraceptive pills containing drospirenone and 20 µg or 30 µg ethinyl estradiol for polycystic ovary syndrome. *Int J Gynaecol Obstet*. 2016;132(2):210-213. https://doi.org/10.1016/j.ijgo.2015.06.065
26. Fonseka S, Wijeyaratne CN, Gawarammana IB, *et al*. Effectiveness of low-dose ethinylestradiol/cyproterone acetate and ethinylestradiol/desogestrel with and without metformin on hirsutism in polycystic ovary syndrome: a randomized, double-blind, triple-dummy study. *J Clin Aesthet Dermatol*. 2020;13(7):18-23.
27. De Leo V, Di Sabatino A, Musacchio MC, *et al*. Effect of oral contraceptives on markers of hyperandrogenism and SHBG in women with polycystic ovary syndrome. *Contraception* 2010;82(3):276-280. https://doi.org/10.1016/j.contraception.2010.04.002
28. Morgante G, Cappelli V, Troìa L, De Leo V. Evaluation of different antiandrogenic progestins on clinical and biochemical variables in polycystic ovary syndrome. *Eur J Contracept Reprod Health Care*. 2020;25(3):176-181. https://doi.org/10.1080/13625187.2020.1736546
29. Podfigurna A, Meczekalski B, Petraglia F, Luisi S. Clinical, hormonal and metabolic parameters in women with PCOS with different combined oral contraceptives (containing chlormadinone acetate versus drospirenone). *J Endocrinol Invest*. 2020;43(4):483-492. https://doi.org/10.1007/s40618-019-01133-3
30. Yildizhan R, Gokce AI, Yildizhan B, Cim N. Comparison of the effects of chlormadinone acetate versus drospirenone containing oral contraceptives on metabolic and hormonal parameters in women with PCOS for a period of two-year follow-up. *Gynecol Endocrinol*. 2015;31(5):396-400. https://doi.org/10.3109/09513590.2015.1006187
31. Amiri M, Nahidi F, Bidhendi-Yarandi R, Khalili D, Tohidi M, Ramezani Tehrani F. A comparison of the effects of oral contraceptives on the clinical and biochemical manifestations of polycystic ovary syndrome: a crossover randomized controlled trial. *Hum Reprod*. 2020;35(1):175-186. https://doi.org/10.1093/humrep/dez255
32. Amiri M, Rahmati M, Hedayati M, Nahidi F, Ramezani Tehrani F. Effects of oral contraceptives on serum concentrations of adipokines and adiposity indices of women with polycystic ovary syndrome: a randomized controlled trial. *J Endocrinol Invest*. 2021;44(3):567-580. https://doi.org/10.1007/s40618-020-01349-8
33. Bhattacharya SM, Jha A. Comparative study of the therapeutic effects of oral contraceptive pills containing desogestrel, cyproterone acetate, and drospirenone in patients with polycystic ovary syndrome. *Fertil Steril*. 2012;98(4):1053-1059. https://doi.org/10.1016/j.fertnstert.2012.06.035
34. Kriplani A, Periyasamy AJ, Agarwal N, Kulshrestha V, Kumar A, Ammini AC. Effect of oral contraceptive containing ethinyl estradiol combined with drospirenone vs. desogestrel on clinical and biochemical parameters in patients with polycystic ovary syndrome. *Contraception* 2010;82(2):139-146. https://doi.org/10.1016/j.contraception.2010.02.009
35. Cagnacci A, Tirelli A, Renzi A, Paoletti AM, Volpe A. Effects of two different oral contraceptives on homocysteine metabolism in women with polycystic ovary syndrome. *Contraception* 2006;73(4):348-351. https://doi.org/10.1016/j.contraception.2005.09.011
36. Kahraman K, Sükür YE, Atabekoğlu CS, *et al*. Comparison of two oral contraceptive forms containing cyproterone acetate and drospirenone in the treatment of patients with polycystic ovary syndrome: a randomized clinical trial. *Arch Gynecol Obstet*. 2014;290(2):321-328. https://doi.org/10.1007/s00404-014-3217-5
37. Mastorakos G, Koliopoulos C, Creatsas G. Androgen and lipid profiles in adolescents with polycystic ovary syndrome who were treated with two forms of combined oral contraceptives. *Fertil Steril*. 2002;77(5):919-927. https://doi.org/10.1016/S0015-0282(02)02993-X
38. Panidis D, Georgopoulos NA, Piouka A, *et al*. The impact of oral contraceptives and metformin on anti-Müllerian hormone serum levels in women with polycystic ovary syndrome and biochemical hyperandrogenemia. *Gynecol Endocrinol*. 2011;27(8):587-592. https://doi.org/10.3109/09513590.2010.507283
39. Taheripanah R, Sepahvandi M, Entezari A, Amiri Z, Samani EN. Evaluation of serum PSA after cyproterone compound treatment compared with oral contraceptive pill in hirsute polycystic ovary syndrome patients. *Middle East Fertil Soc J*. 2010;15(3):159-162. https://doi.org/10.1016/j.mefs.2010.06.007
40. Christakou C, Kollias A, Piperi C, Katsikis I, Panidis D, Diamanti-Kandarakis E. The benefit-to-risk ratio of common treatments in PCOS: effect of oral contraceptives versus metformin on atherogenic markers. *Hormones (Athens)* 2014;13(4):488-497. https://doi.org/10.14310/horm.2002.1553
41. Mastorakos G, Koliopoulos C, Deligeoroglou E, Diamanti-Kandarakis E, Creatsas G. Effects of two forms of combined oral contraceptives on carbohydrate metabolism in adolescents with polycystic ovary syndrome. *Fertil Steril*. 2006;85(2):420-427. https://doi.org/10.1016/j.fertnstert.2005.07.1306

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42. Chung JP, Yiu AK, Chung TK, Chan SS. A randomized crossover study of medroxyprogesterone acetate and Diane-35 in adolescent girls with polycystic ovarian syndrome. *J Pediatr Adolesc Gynecol*. 2014;27(3):166-171. https://doi.org/10.1016/j.jpag.2013.09.011
43. Ozdemir S, Görkemli H, Gezginç K, Ozdemir M, Kiyici A. Clinical and metabolic effects of medroxyprogesterone acetate and ethinyl estradiol plus drospirenone in women with polycystic ovary syndrome. *Int J Gynaecol Obstet*. 2008;103(1):44-49. https://doi.org/10.1016/j.ijgo.2008.05.017
44. Amiri M, Kabir A, Nahidi F, Shekofteh M, Ramezani Tehrani F. Effects of combined oral contraceptives on the clinical and biochemical parameters of hyperandrogenism in patients with polycystic ovary syndrome: a systematic review and meta-analysis. *Eur J Contracept Reprod Health Care*. 2018;23(1):64-77. https://doi.org/10.1080/13625187.2018.1435779
45. Lim SS, Kakoly NS, Tan JWJ, *et al*. Metabolic syndrome in polycystic ovary syndrome: a systematic review, meta-analysis and meta-regression. *Obes Rev*. 2019;20(2):339-352. https://doi.org/10.1111/obr.12762
46. El Maghraby HA, Nafee T, Guiziry D, Elnashar A. Randomized controlled trial of the effects of metformin versus combined oral contraceptives in adolescent PCOS women through a 24 month follow up period. *Middle East Fertil Soc J*. 2015;20(3):131-137. https://doi.org/10.1016/j.mefs.2014.10.003
47. Falsetti L, Galbignani E. Long-term treatment with the combination ethinylestradiol and cyproterone acetate in polycystic ovary syndrome. *Contraception* 1990;42(6):611-619. https://doi.org/10.1016/0010-7824(90)90002-D
48. Gemzell-Danielsson K, Cagnacci A, Chabbert-Buffet N, *et al*. A novel estetrol-containing combined oral contraceptive: European expert panel review. *Eur J Contracept Reprod Health Care*. 2022;27(5):373-383. https://doi.org/10.1080/13625187.2022.2093850
49. Kangasniemi MH, Haverinen A, Luiro K, *et al*. Estradiol valerate in COC has more favorable inflammatory profile than synthetic ethinyl estradiol: a randomized trial. *J Clin Endocrinol Metab*. 2020;105(7):e2483-e2490. https://doi.org/10.1210/clinem/dgaa186
50. Jones GL, Hall JM, Balen AH, Ledger WL. Health-related quality of life measurement in women with polycystic ovary syndrome: a systematic review. *Hum Reprod Update*. 2008;14(1):15-25. https://doi.org/10.1093/humupd/dmm030
51. Cooney LG, Lee I, Sammel MD, Dokras A. High prevalence of moderate and severe depressive and anxiety symptoms in polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Rep*. 2017;32(5):1075-1091. https://doi.org/10.1093/humrep/dex044
52. Skovlund CW, Mørch LS, Kessing LV, Lidegaard Ø. Association of hormonal contraception with depression. *JAMA Psychiatry*. 2016;73(11):1154-1162. https://doi.org/10.1001/jamapsychiatry.2016.2387
53. Edwards AC, Lönn SL, Crump C, *et al*. Oral contraceptive use and risk of suicidal behavior among young women. *Psychol Med*. 2022;52(9):1710-1717. https://doi.org/10.1017/S0033291720003475
54. Bengtsdotter H, Lundin C, Gemzell Danielsson K, *et al*. Ongoing or previous mental disorders predispose to adverse mood reporting during combined oral contraceptive use. *Eur J Contracept Reprod Health Care*. 2018;23(1):45-51. https://doi.org/10.1080/13625187.2017.1422239
55. Dokras A, Sarwer DB, Allison KC, *et al*. Weight loss and lowering androgens predict improvements in health-related quality of life in women with PCOS. *J Clin Endocrinol Metab*. 2016;101(8):2966-2974. https://doi.org/10.1210/jc.2016-1896
56. Dragoman MV, Tepper NK, Fu R, Curtis KM, Chou R, Gaffield ME. A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception. *Int J Gynaecol Obstet*. 2018;141(3):287-294. https://doi.org/10.1002/ijgo.12455

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