Effect of the combined oral contraceptive pill and/or metformin in the management of polycystic ovary syndrome: A systematic review with meta-analyses

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Abstract

Background: Polycystic ovary syndrome (PCOS) has a prevalence of 8%-13%. Given the prevalence, diverse health impacts and variation in care, rigorous evidence-based guidelines are needed in PCOS management. This systematic review with meta-analyses aimed to investigate the effect of the combined oral contraceptive pill (COCP) and/or metformin in the management of hormonal and clinical features of PCOS, to inform international guidelines.

Methods: Electronic databases were searched systematically from inception until 11 January 2017 to inform the guideline process. Eligible studies were randomized controlled trials which investigated the effect of COCPs and/or metformin alone or combined on hormonal and clinical features in women with PCOS. Outcomes were prioritized as critical for informing a decision about an intervention or important or not important, according to GRADE. Articles were assessed by one author against selection criteria, in consultation with a second author. Data were double extracted independently by four authors, and data quality appraisal was completed. Meta-analyses were conducted, where appropriate.

Results: Fifty-six studies were eligible for inclusion. Outcomes prioritized by women and health professionals included the following: irregular cycles, insulin resistance, weight, BMI, thromboembolic events and gastrointestinal effects. In low-quality
evidence in adolescents, meta-analyses demonstrated that metformin was better than COCP for BMI (mean difference [MD] = −4.02 [−5.23, −2.81], \( P < 0.001 \)); COCP was better than metformin for menstrual regulation (MD = 0.19 [−0.25, −0.13], \( P < 0.00001 \)). In low-quality evidence in adults, meta-analyses demonstrated that metformin was better than placebo for BMI (MD = −0.48 [−0.94, −0.02], \( P = 0.04 \)); metformin was better than COCP for fasting insulin (MD = 4.00 [2.59, 5.41], \( P = 0.00001 \)), whereas COCP was better than metformin for irregular cycles (MD = 12.49 [1.34, 116.62], \( P = 0.03 \)). Combined oral contraceptive pill alone was better than the combination with an anti-androgen for BMI (MD = −3.04 [−5.45, −0.64], \( P = 0.01 \)). Metformin was associated with generally mild gastrointestinal adverse events. Differences in statistical significance were observed when outcomes were subgrouped by BMI.

**Conclusions:** This review identified that COCP therapy has benefits for management of hyperandrogenism and menstrual regulation. Metformin combined with the COCP may be useful for management of metabolic features. There is minimal evidence of benefits of adding an anti-androgen to COCP therapy. Metformin alone has benefits for adult women for management of weight, hormonal and metabolic outcomes, especially for women with BMI ≥ 25 kg/m². There is inadequate evidence to suggest the optimal COCP formulation, or dosing regimen and formulation of metformin.

**KEYWORDS**
contraceptive agents, guideline, management, meta-analysis, metformin, polycystic ovary syndrome, systematic review

# 1 INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, with a prevalence of 8%-13%. Many women remain undiagnosed, and delays in diagnosis are common. Indeed, an international study reported that it took over 2 years and seeing 3 or more healthcare professionals for over one-third of the women to receive the diagnosis. The most widely accepted diagnostic criteria internationally for PCOS, the Rotterdam criteria, require that women fulfil at least two of the following three criteria for diagnosis of PCOS: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovaries on ultrasound.

The aetiology of PCOS is largely unknown, though available information suggests that genetics, in addition to environmental and lifestyle factors, contribute to its development. The condition is heterogeneous, and women may present with a number of reproductive (menstrual dysfunction, infertility and pregnancy complications), endocrine (hyperandrogenism, hirsutism and acne), metabolic (insulin resistance, diabetes, weight gain and obesity) and psychosocial (anxiety, depression and poor quality of life) symptoms.

Whilst lifestyle management is recommended as the first-line intervention for women with PCOS, medical management including the combined oral contraceptive pill (COCP), insulin sensitizers, anti-androgens and/or anti-obesity medications may be required. Combined oral contraceptive pills are often prescribed for adolescents and adults with PCOS to ameliorate clinical symptoms related to hormonal disturbances. Their effect on clinically important outcomes such as menstrual cycles, hirsutism, anthropometry, androgen levels and metabolic outcomes is variably reported. Additionally, metformin is an extensively used insulin sensitizer, which has been evaluated alone or in combination with COCPs, anti-androgens and/or lifestyle interventions in randomized controlled trials (RCTs) in adult women and adolescent girls with PCOS. The role of metformin in clinical care, however, remains uncertain with small, short-term studies and variable end-points. Metformin is not approved for use in PCOS; however, it is not restricted from use in PCOS either. There is variability in the use of metformin for PCOS adolescents and women according to the treating clinician specialty.

Given the prevalence of PCOS, the impact it has on multiple aspects of a woman’s health, the long-term complications, and the current gap and inconsistencies in diagnosis and care, rigorous, evidence-based guidelines have been developed to guide health care. In this process, medical management of PCOS with the COCP and metformin were prioritized. The Australian Centre for Research Excellence in PCOS partnered with leading international societies European Society of Human Reproduction and Embryology (ESHRE) and American Society of Reproductive
Medicine (ASRM) and collaborated with 37 organizations including the US Endocrine Society to create the first International Evidence-based Guideline for Assessment and Management in PCOS. This brought together representatives of an international network across six continents, with widespread engagement and international partnership to drive awareness, patient self-management, improved, evidence-based practices and better health outcomes in PCOS.

This extensive systematic review directly informed the evidence-based guidelines, aiming to investigate the effect of the COCP and/or metformin, alone or in combination, in the management of consumer and health professional prioritized hormonal and clinical outcomes in PCOS.

2 | METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement checklist and was prepared to inform clinical practice recommendations in the updated and expanded evidence-based guideline for the assessment and diagnosis of PCOS. The rigorous methodology used for the development of the guideline is aligned with the National Health and Medical Research Council (NHMRC), ESHRE and GRADE methods and has been described in detail in the resulting final guideline. Seven hundred clinical and academic opinion leaders and consumers worldwide participated in a five-round Delphi exercise to identify and prioritize key clinical questions in PCOS care.

Here, we present the evidence for two clinical questions which were included in the international guideline:

1. Is the oral contraceptive pill alone or in combination effective for management of hormonal and clinical PCOS features in adolescents and adults with PCOS?
2. Is metformin alone or in combination effective for management of hormonal and clinical PCOS features and weight in adolescents and adults with PCOS?

For these two questions, comparisons (as determined through the Delphi question development and prioritization process) and “in combination” include any of the following: lifestyle, anti-androgens or anti-obesity agents.

2.1 | Selection criteria

The Population, Intervention, Comparison, Outcome (PICO) framework was used to guide the selection criteria for each clinical question, and these were developed a priori by the multi-disciplinary guideline development group (see Appendix S1). Briefly, the population of interest was all females with PCOS (diagnosed by Rotterdam, NIH or AES) of any ethnicity, weight and age, incorporating a subgroup of adolescents (10-19 years); eligible interventions included oral contraceptive pill alone or in combination with metformin, lifestyle, anti-androgens and anti-obesity agents to address the first question, and for the second question, metformin alone or in combination with lifestyle, OCP, anti-androgens and anti-obesity agents. Eligible comparisons included placebo or any other eligible intervention (listed above) or combinations of those. Using the GRADE prescribed method and scale, outcomes were prioritized as follows: critical for making a decision about the intervention (score 7-9), important (score 4-6) or of limited importance for making a decision (score 1-3; see Appendix S1). Briefly, the outcomes deemed critically important included irregular cycles, insulin resistance, weight, BMI, thromboembolic events and gastrointestinal effects.

2.2 | Systematic search for evidence

A systematic search strategy was designed to identify the best available evidence to answer a suite of clinical questions developed by the team for the section of the guideline regarding medical treatment options for the features of PCOS (additional clinical questions for which the search applies can be found in the technical report for the guideline). Consequently, the PRISMA flow diagram represents the search results across the suite of clinical questions included in the medical treatments section of the guideline, which was broader than the topics reported in this manuscript. A broad-ranging systematic search string for terms related to PCOS was developed to retrieve articles addressing women with PCOS in all cultural, geographical and socio-economic backgrounds, settings and life stage. This PCOS search string was combined with search terms relevant to the medical therapies outlined in the clinical questions and corresponding PICO. The search strategy was limited to English language systematic reviews and randomized controlled trials, and there were no limits on year of publication (See Appendix S1). Crossover RCT data were included if the study conducted a washout period of ≥8 weeks. For the first clinical question, reviewed studies were limited to those published in the last 20 years, based on consensus decision, given changes in doses and formulations over time.

2.3 | Databases

The following electronic databases were searched on 11 January 2017:

- Ovid MEDLINE(R) 1946 to Present with Daily Update
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <January 10, 2017>
- Ovid MEDLINE(R) Epub Ahead of Print <January 10, 2017>
- Embase Classic + Embase <1947 to 2017 January 10>
- EBM Reviews, incorporating:
  - Cochrane Database of Systematic Reviews <2005 to January 10, 2017>
  - ACP Journal Club <1991 to December 2016>
  - Database of Abstracts of Reviews of Effects <1st Quarter 2015>
2.4 Inclusion of evidence

To determine the literature to be assessed further, a reviewer (MM) scanned the titles, abstract sections and keywords of every record retrieved by the search strategy using the selection criteria described in the technical report of the guideline. Full articles were retrieved for further assessment if the information given suggested that the study met the inclusion criteria. Studies were selected and appraised by a reviewer (MM) in consultation with a second author (HT), using the selection criteria established a priori. Where there was any doubt regarding these criteria from the information given in the title and abstract, the full article was retrieved for clarification.

Where existing systematic reviews were identified, the most current (within 5 years), comprehensive (with the most outcomes relevant to PICO) and high-quality systematic review that met the inclusion criteria was used. Additional systematic reviews that met benchmark criteria and PICO were used if it reported additional outcomes relevant to the PICO that were not addressed in the first, most comprehensive systematic review. Additional RCTs that met the PICO and were not included in the existing systematic review(s) were also used.

2.5 Assessment of methodological quality

Methodological quality, in terms of risk of bias, of each of the included studies was assessed twice, independently by two of four reviewers (ECT, EB, AW and MM,) using criteria developed a priori for systematic reviews and RCTs. Individual quality items were investigated using a descriptive component approach that assessed selection bias, reporting bias, performance bias, potential confounding, attrition bias and appropriateness of the statistical analysis. Any disagreement or uncertainty was resolved by a discussion among the evidence reviewers to reach a consensus. Using this approach, each study was allocated a risk of bias rating of either low, moderate or high. Where there was more than one published article describing a study, all articles were used to complete one risk of bias assessment on the study.

2.6 Data extraction

Data, according to the a priori selection criteria and outcome prioritization process, were double extracted from included studies, independently by two of four reviewers (ECT, EB, AW and MM). Information was collected on general study details (title, authors, reference/source, country, year of publication, setting), participants (age, sex, inclusion/exclusion criteria, withdrawals/losses to follow-up, subgroups), interventions, outcomes, results (point estimates and measures of variability, frequency counts for dichotomous variables, number of participants, intention-to-treat analysis) and validity results. Where data were reported across multiple articles for the same study, data were extracted to one form.

2.7 Data synthesis

Meta-analyses were performed using Review Manager 5 by one author (MM). Due to clinical heterogeneity from differences in dose and timing of treatment, a random effects model was used for meta-analyses of the data. Mean differences were used to present the effect estimates for all meta-analyses with the exception of side effects presented as event rates; therefore, odds ratios were used. Subgroup analysis was conducted according to body mass index (BMI) since it is considered to cause variations in the outcomes in response to the therapies addressed here. Heterogeneity $I^2 > 50\%$ was considered to be high and results interpreted with caution. Forest plots and funnel plots are presented here for outcomes which were rated as critical during consensus discussions for this guideline development group. A complete set of forest plots and funnel plots can be found in the technical report for the International guideline. Where it was not appropriate to conduct meta-analyses, study data are presented narratively.

3 RESULTS

A systematic search of electronic databases was conducted on 11 January 2017, with a total of 3205 studies relevant to medical treatments for PCOS identified (MEDLINE = 2266, MEDLINE Epub = 16, MEDLINE IP = 72, all EBM = 181, PsycINFO = 18, EMBASE = 439, CINAHL = 213), of which 470 duplicates were excluded. A title and abstract review was performed on the remaining 2735 studies, with 2492 excluded at this first pass stage. A total of 243 articles relevant to medical treatments for PCOS were eligible for full-text screening; however, one full text could not be retrieved. Of the 242 full-text articles screened, 56 studies met the inclusion criteria for the Metformin and/or OCP comparisons presented in this review, whilst 120 full-text articles were excluded for not meeting the PICO criteria for the Metformin and/or OCP question. A table of the excluded studies with reasons for their exclusion can be found in the guideline technical report. Of the 56 studies which met the inclusion criteria for the Metformin and/or OCP comparisons investigated in this review, 46 studies are presented here in meta-analyses, and 10 studies are presented narratively (Figure 1).

3.1 Characteristics and quality of included RCTs

Key characteristics and detailed data of all 56 included studies are presented in Appendix S2. Treatment duration varied between 3 months and 24 months across the included studies. Sample sizes ranged from
10 participants (in a crossover study) to 253 participants. The majority of included studies were in adults (n = 6 in adolescents, n = 2 did not report age, n = 48 in adults), and the mean BMI of participants varied across studies from the normal range (18.50-24.99 kg/m²) to obese class III (≥40.00 kg/m²). In general, side effects were not adequately reported.

Detailed critical appraisals, including risk of bias and GRADE components, are presented in the technical report of the guideline. Studies presented in this systematic review were found to be at low, moderate or high risk of bias. Common reasons for these ratings included the following: not reporting whether participants, investigators and/or outcome assessors were blinded to the treatment group; not reporting whether allocation to the intervention group was concealed; not reporting whether there was a published study protocol, thus rendering it impossible to know whether the paper was free of selective outcome reporting; not reporting whether the study was sufficiently powered; not reporting whether the groups were similar at baseline; not reporting whether the study was funded; and not declaring whether there were any conflicts of interest.

### 3.2 | COCP vs placebo—adolescents with PCOS

One 6-month RCT21 with 20 participants with moderate risk of bias was identified to address this comparison in adolescents (it was also included in a systematic review22 which has been used here for the risk of bias appraisal). A statistically significant difference between groups in favour of the COCP was found for high-density lipoprotein cholesterol (HDL-C; $P < 0.05$), whilst no statistically significant differences were found for BMI, waist circumference (WC), total testosterone, sex hormone binding globulin (SHBG), free androgen index (FAI), hirsutism, total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, fasting insulin, fasting glucose, C-reactive protein (CRP) and plasminogen activator inhibitor 1 (PAI-1). Side effects were not reported.

### 3.3 | COCP vs lifestyle—adolescents with PCOS

One 6-month RCT21 with 18 participants at moderate risk of bias was identified to address this comparison in adolescents (it was also included in a systematic review22 which has been used here for the risk of bias appraisal). A statistically significant difference between groups in favour of the lifestyle intervention was found for LDL-C ($P < 0.05$), whilst no statistically significant differences were found for BMI, total testosterone, SHBG, FAI, hirsutism, total cholesterol, HDL, triglycerides, fasting insulin, fasting glucose, CRP and PAI-1. Side effects were not reported.

### 3.4 | COCP vs COCP—adults with PCOS

Eight RCTs comparing different COCPs ranged in duration from 3 to 12 months, had sample sizes between 20 and 150 participants and were rated as low-to-high risk of bias (Table S2). Due to the heterogeneity across studies in regard to the type, dose and duration of COCP use, the results could not be combined in meta-analyses and are thus presented individually.
3.5 | COCP vs metformin—adolescents with PCOS

One systematic review including four small RCTs of 6-24 months of duration that address this comparison in adolescents was identified (Table S3). Metformin doses ranged from 1700 to 2000 mg a day. Additional analysis of outcomes (weight and fasting insulin) not addressed in the systematic review was conducted by our evidence team. Whilst a statistically significant improvement was found in BMI (−4.02 [−5.23, −2.81], P < 0.001), dysglycaemia (oral glucose tolerance test [OGTT] 0.41 [0.19, 0.66], P = 0.02) and LDL-C (−35.50 [−57.45, −13.55], P = 0.002) with use of metformin over COCP, and a statistically significant improvement found in menstrual regulation (−0.19 [−0.25, −0.13], P < 0.00001) with use of COCP over metformin, we advise caution when interpreting results due to the low quality of evidence. No statistically significant differences were found for hirsutism, total testosterone, triglyceride, total cholesterol, HDL-C, weight, fasting insulin, SHBG, FAI, fasting blood glucose, CRP and PAI-1 (Table S3). Side effects included weight gain with COCP and gastrointestinal side effects with metformin. Side effects were not consistently reported.

3.6 | COCP vs Metformin—adults with PCOS

A Cochrane systematic review was published by Costello et al in 2007 which addressed this comparison (Table S4). Four of the studies included in Costello et al 2007 were identified by our search, but were excluded due to insufficient information in the full text (marked with #). Costello 2007 obtained additional information from the authors of the RCTs. This additional information, which was not listed in the full text of the RCTs, was shared with the evidence team and allowed them to be included here. Risk of bias and data extraction were not performed on these four studies and instead were adopted from Costello 2007, whilst risk of bias and data extraction were performed on all RCTs identified by our search that were published since Costello et al 2007.

There were statistically significant improvements with metformin (compared with COCP) for fasting insulin (4.00 [2.59, 5.41], P = 0.00001), including for both BMI subgroups (≥25 kg/m² and ≥25 kg/m²). There were minor differences in impact on lipids between BMI subgroups (Table S4).

There were statistically significant improvements with COCP (compared with metformin) for SHBG (118.25 [89.65, 146.85], P = 0.00001), FAI (−6.61 [−9.75, −3.48], P = 0.0001), total testosterone (−0.38 [−0.64, −0.12], P = 0.004) and irregular cycles (12.49 [1.34, 116.62], P = 0.03), including all BMI subgroups. No statistically significant differences were found for clamp, HOMA (change from baseline), BMI, waist-to-hip ratio (WHR), hirsutism, fasting glucose and total cholesterol, whilst a P value was not reported in the one study which measured weight²³ (Table S4). Gastrointestinal (GI)-related side effects were reported by both metformin and COCP groups, along with other adverse events. The majority of included studies for this comparison were of moderate quality, and therefore, findings should be interpreted with some degree of caution.

3.7 | COCP vs COCP + metformin—adults with PCOS

Six RCTs of moderate quality were identified to address this comparison (Table S5). The only parameter which had a statistically significant difference in favour of COCP alone was triglycerides (−0.20 [−0.39, −0.01], P = 0.04).

There were statistically significant improvements with COCP plus metformin (compared with COCP alone) for FAI (0.60 [0.35, 0.85], P = 0.00001), total testosterone (0.23 [0.01, 0.44], P = 0.04) and fasting glucose (0.38 [0.22, 0.54], P = 0.00001) when all participants were combined, whilst there were only small differences in outcomes between treatment groups for BMI subgroups (Table S5).

No statistically significant differences were found for weight, BMI, WHR, HOMA, HDL or LDL when all participants were combined (Table S5); however, sample sizes were small, and thus, results should be interpreted with caution.

GI-related events were reported by two studies, with minor GI-related events reported by 20% of participants in the combined COCP and metformin group in one study, and severe GI-related events reported by one participant in the combined COCP and metformin group in another study. No GI-related events were reported for the COCP alone group in any of the six RCTs identified.

3.8 | COCP vs COCP + anti-androgen—adults with PCOS

Four RCTs were identified to address this comparison in adults (Table S6). There was a statistically significant improvement with COCP alone (compared with COCP plus anti-androgen) for BMI (−3.04 [−5.45, −0.64], P = 0.01) and LDL (−13.76 [−27.66, 0.14], P = 0.05). No statistically significant differences were found in meta-analyses for weight, SHBG, fasting glucose, total cholesterol and HDL, and there were no extractable data for hirsutism. There were also no differences for side effects, including headache, breast-related side effects and nausea/vomiting between the two intervention groups (Table S6). P values were not reported for single RCTs reporting on WHR, FAI or testosterone. The studies in these meta-analyses were either at moderate or high risk of bias, and therefore, all findings should be interpreted with caution.

3.9 | Metformin vs placebo—adults and adolescents with PCOS

Twenty RCTs that address outcomes for this comparison were identified, of which 19 RCTs were in adults and 1 was in adolescents (Table S7). Metformin doses ranged from 1500 to 1700 mg a day. As per Table S7, clinically important differences include that metformin was better than placebo for BMI (−0.48 [−0.94, −0.02], P = 0.04), testosterone (−13.87 [−27.91, 0.17], P = 0.05), total cholesterol (−10.93 [−20.53, −1.33], P = 0.03) and triglycerides (−11.85 [−21.87, −1.83], P = 0.02) when all participants were combined. In BMI ≥ 25 kg/m² subgroup analyses, it was found that metformin offered additive
benefits for weight, BMI, total cholesterol and LDL, whilst there were differences in WHR in favour of metformin in the BMI < 25 kg/m² subgroup (Table S7).

Gastrointestinal side effects were more prevalent in the metformin groups, but only 4 out of 20 studies including in total 330 women and metformin doses of 1500-1700 mg/d reported on side effects without specific details. Ten to 62% of women taking metformin reported side effects. The majority of gastrointestinal side effects were mild to moderate and were self-limiting. The side effects reported included nausea, vomiting, diarrhoea, abdominal pain or nonspecific gastrointestinal disturbance. Only one study reported higher dropout in the metformin treated due to unacceptable gastrointestinal side effects and suggested using a lower initial metformin dose (500 mg/d). There were no reports on vitamin B12 levels (Table S7).

The majority of studies included for this comparison were at moderate risk of bias; thus, it is important to remain cautious in effect estimates and the quality of evidence across all outcomes.

3.10 | Metformin vs metformin (dose)

One study was identified to address this comparison. Age was not reported. There was no difference in weight between the two interventions in this very low-quality study (P = 0.35).19 Other relevant outcomes were mentioned in this study; however, no useable data were reported. The highest metformin dose used was 850 mg three times per day.

3.11 | Metformin vs metformin + COCP—adults with PCOS

Three RCTs that address this comparison in adults were identified (Table S8). When all participants were combined, no statistically significant differences were found for weight, BMI, FAI, testosterone, fasting insulin, fasting glucose-insulin ratio, total cholesterol, HDL and LDL. P values were not reported for fasting glucose, HOMA or OGTT. Side effects were not reported. Whilst a statistically significant improvement was found in WHR (−0.03 [−0.06, −0.01], P = 0.002) and triglycerides (−26.30 [−42.99, −9.60], P = 0.002) with use of metformin over metformin plus COCP, regardless of BMI, we advise caution when interpreting results due to moderate risk of bias across all studies.

3.12 | Metformin + lifestyle vs lifestyle ± placebo—BMI ≥ 25—adolescents and adults with PCOS

A systematic review including seven relevant RCTs that address this comparison in adults and adolescents was identified (Table S9). The evidence team conducted additional analysis of outcomes not addressed in the systematic review. No statistically significant differences were found for any of the outcomes in this body of evidence which was at low-to-moderate risk of bias. Side effects were not reported.

4 | DISCUSSION

This systematic review with meta-analyses is the most up to date, rigorous synthesis of peer-reviewed literature which has investigated the effect of the COCP and metformin on clinical, hormonal and metabolic features of PCOS, in both adolescents and adults. The 56 studies included here which met rigorous inclusion criteria and addressed clinically important comparisons were rated as low, moderate or high risk of bias. Some comparisons were limited by small sample sizes. Overall, COCP offers effective PCOS treatment ameliorating hyperandrogenism and cycle irregularity with no advantage of specific subtypes of COCP. Metformin improves metabolic, weight and other clinical features with mild side effects alone and in combination with COCP.

This systematic review was completed to directly inform recommendations in the recently launched international PCOS evidenced-based guideline, adopted across 38 societies and 71 countries. The systematic review presented here and the guideline address key gaps in the management of PCOS, and the guideline provides clear, rigorous and robust evidence-based recommendations which can be used internationally. In this review, we addressed specific clinical controversies on the type of COCP and the role of metformin in this common condition.

Here in this systematic review to inform the guideline, we confirm the role of COCP alone for the management of hyperandrogenism and menstrual regulation. Specific recommendations on dose and constituents of the COCP cannot be made based on studies in PCOS alone, due to a high degree of heterogeneity across studies on COCP in PCOS. We therefore defer to general population literature on COCP, highlighting that lower dose COCP and second-generation progestins offer a better safety profile.24

We highlight that in combination with metformin, COCP is useful for the management of metabolic features of PCOS in adults. We note that mild GI-related side effects were reported with the addition of metformin, which in practice could lead to reduced compliance with therapy. Like all medications, side effects and their potential impact on a woman's quality of life and day-to-day activities should be considered when recommending metformin; however, side effects are usually mild, self-limiting and may be minimized with a lower starting dose.7 Extended release preparations and taking metformin with food might also decrease GI-related side effects.25

Moving forward, we recommend that international evidence-based recommendations for COCP use should be followed in practice (Box 1 and Box 2).

With metformin compared with placebo for adults with PCOS, our meta-analyses demonstrate that there is a statistically significant difference post-treatment in favour of metformin for BMI, testosterone, total cholesterol and triglycerides, for participants across all BMI categories. For participants with a BMI > 25 kg/m², results indicate that there may be additive benefits for weight, BMI, total cholesterol and LDL. Weight is the primary concern for women with PCOS,2 and they are more likely to have rapid weight gain and obesity.26 In line with the previous comparisons,
GI-related side effects were more prevalent in the metformin groups, and thus, this should be taken into account by clinicians. We would therefore recommend metformin for adult women with PCOS for the prevention of weight gain, hormonal (testosterone) and metabolic outcomes (cholesterol and triglycerides), and for prevention of weight gain and metabolic outcomes (cholesterol and LDL), in women with PCOS with BMI ≥ 25. It has also been identified in this review that there is inadequate evidence to suggest whether one dosing regimen of metformin is superior to another. Additionally, the longest study duration was 24 months. We recommend that metformin use in practice should follow international evidence-based guideline recommendations (Box 3).

We recommend that future RCT research includes more detailed reporting of randomization methods, funding of research and...
 conflict of interest statements, allocation concealment and blinding of participants, investigators and outcome assessors, conducts sample size calculations and publishes study protocols prior to the commencement of a trial. We also recommend future RCTs investigate whether there is an optimum dosing regimen for metformin, in which combination of the pill may be superior for managing features of PCOS, and further RCTs investigating combinations of these medications. Side effects need to be more accurately documented and key impacts on quality of life assessed.

4.1 | Limitations
We did not contact study authors for missing information or data conversions; thus, if outcome data were presented in a form not usable in a meta-analysis (eg as a median and interquartile range), or where studies stated that they had conducted a RCT but then did not describe the method of randomization, or used an inadequate method of randomization, they were excluded. Additionally, in cases where data were obtained from an existing high-quality systematic review which reported risk of bias using an appropriate method, the systematic review’s appraisal was adopted. We acknowledge that critical appraisal is individual judgement based, and therefore, those conducted by other systematic reviewers may not be aligned with the judgements of this evidence review team, thus limiting the confidence in the effect estimates of some of results. Furthermore, our systematic review is at risk of language bias, as studies conducted in languages other than English were not considered. Overall, the primary weakness was the quality of existing studies, which underpin this review.

5 | CONCLUSION
This extensive systematic review with meta-analyses advances the literature as the most up to date, rigorous synthesis of peer-reviewed literature, which has investigated the effect of the COCP and metformin on clinical, hormonal and metabolic features of PCOS, in both adolescents and adults. It addresses key gaps on the role of these agents in PCOS and the role of metformin. We confirm that COCP therapy for women with PCOS improves hyperandrogenism and menstrual regulation. No type of COCP is adequately proven as superior, and aligned with general population recommendations and side effect profiles, higher dose oestrogen preparations should not be first line and lower dose preparations are recommended. We clarify the role of metformin alone or in combination with COCP showing it is useful for the management of metabolic features of PCOS specifically weight, hormonal and metabolic outcomes, especially in women with PCOS with a BMI ≥ 25 kg/m². We have directly informed international guideline recommendations and identified research gaps, including the need for additional high-quality RCTs to define optimal type and dose of both COCPs and metformin and to assess their impact on quality of life in PCOS.

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CONFLICT OF INTEREST

Eliza C Tassone, Tehri Piltonen, Jaideep Malhotra, Alexia Peña, Selma F Witchel, Anju Joham, Veryan McAllister, Daniela Romualdi, Mala Thondan and Marie Misso declared no conflicts of interest.

AUTHORS’ CONTRIBUTION

All authors contributed to developing the questions and corresponding PICO, and prioritized the outcomes. M.M designed the search strategy (with input from HT), ran the database searches, screened articles, performed data extraction and critically appraising, including risk of bias and GRADE, completed the statistical analyses and contributed to the write up of the manuscript. E.C.T performed data extractions, critically appraised articles and contributed to the write up of the manuscript. H.T designed the guideline project, obtained funding, chaired the evidence review workshop and guideline development group and contributed to the write up of the manuscript. T.P critically revised the manuscript. All authors assisted in interpretation of the synthesized literature and all approved the final version for submission.

DATA ACCESSIBILITY

The authors confirm that the data supporting the findings of this study are available within the article and the technical report of the international PCOS guideline, available at https://www.monash.edu/__data/assets/pdf_file/0020/1412282/PCOS-Guideline_Technical-report.pdf.

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REFERENCES

23. Dardzińska J, Rachor D, Kuligowska-Jakubowska M, et al. Effects of metformin or an oral contraceptive containing cyproterone...
acetate on serum c-reactive protein, interleukin-6 and soluble vascular cell adhesion molecule-1 concentrations in women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes. 2014;122(2):118-125.


SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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