Brief description of patient problem/setting: A 26 year old woman presents to a family medicine clinic with concerns about irregular menstrual cycles for the past three years. She reports menses occurring every 2- 4 months and associated weight gain despite no major changes in diet. She denies pelvic pain, abnormal uterine bleeding, or galactorrhea. She is not currently attempting to conceive and is not using contraception. Her past medical history is unremarkable. On physical examination, her BMI is 31 kg/m². Laboratory evaluation reveals elevated fasting insulin levels and a hemoglobin A1c of 5.9%, suggestive of insulin resistance. Pelvic ultrasound demonstrates enlarged ovaries with multiple peripheral follicles. She is diagnosed with polycystic ovary syndrome (PCOS). The patient asks whether starting metformin or combined oral contraceptive pills would be more beneficial for improving her menstrual regularity and addressing her underlying metabolic concerns.

Search Question: In women with polycystic ovary syndrome, does metformin compared to combined oral contraceptive pills lead to greater improvement in menstrual regularity and insulin sensitivity?

Question Type: What kind of question is this?

Prevalence Screening Diagnosis Prognosis **Treatment** Harms

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)? Please explain your choices.

If meta-analyses or systematic reviews are not available, the next highest level of evidence to include would be randomized controlled trials (RCTs), as they minimize bias through randomization and allow for direct comparison of interventions. In addition, prospective cohort studies may be included if RCTs are limited or unavailable, as they can provide insight into long-term outcomes and real-world effectiveness, although they are more susceptible to confounding. Retrospective cohort studies or case-control studies may also be considered for generating additional evidence, especially when studying outcomes that are difficult to assess in controlled trials

PICO search terms:

P	I	C	O
Polycystic ovary syndrome	Metformin	Combined Oral contraceptive pills	Menstrual Regularity

PCOS	Insulin Sensitizing agents	OCP	Insulin Resistance
Young women with PCOS	Biguanides	Hormonal contraception	Glycemic control
Polycystic ovarian syndrome	Glucose lowering therapy	Estrogen-progestin contraceptives	Menstrual cycle
Reproductive aged women			Ovulation

Search tools and strategy used:

I used pubmed and Cochrane library

Search terms used in Pubmed: Polycystic Ovary Syndrome OR PCOS

AND Metformin OR Insulin Sensitizing agents

AND Combined Contraceptives oral OR oral contraceptive pills OR OCP

AND menstrual regularity OR ovulation OR insulin resistance OR insulin sensitivity

Filters applied: Publication within last 10 years, English language, Human subjects, Female population, Adult: 19+ years

Results returned: 7 articles

Search terms used in Cochrane library:

- Polycystic Ovary Syndrome AND Metformin AND Oral contraceptives

Filters applied:

- Trials and systematic reviews
- Published within last 10 years

Results returned: 6 articles

Explain how you narrowed your choices to the few selected articles. For example, if your search returned 25 articles among the several databases used, what was the process used to determine which four articles to use?

The initial search was conducted in PubMed and the Cochrane Library using the predefined PICO search terms. Filters were applied to include articles published within the last 10 years, English language, human subjects, and female populations. The search finally yielded approximately 13 articles across databases. After that Titles and abstracts were reviewed for relevance to the specific PICO question comparing metformin versus combined oral

contraceptive pills in women with PCOS. Articles were excluded if they: Did not compare metformin and OCPs at all, Focused solely on adolescent populations, Were narrative reviews or non-systematic commentary articles Preference was given to randomized controlled trials, systematic reviews, and meta-analyses, as these represent the highest levels of evidence for treatment questions. Ultimately, three articles were selected based on methodological quality, direct comparison of interventions, relevance to the defined outcomes, and recency of publication.

Results Found:

Article 1: Metformin and Combined Oral Contraceptive Pills in the Management of Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis

Melin, J., Forslund, M., Alesi, S., Piltonen, T., Romualdi, D., Spritzer, P. M., Tay, C. T., Pena, A., Witchel, S. F., Mousa, A., & Teede, H. (2024). Metformin and Combined Oral Contraceptive Pills in the Management of Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis. *The Journal of clinical endocrinology and metabolism*, *109*(2), e817–e836. https://doi.org/10.1210/clinem/dgad465

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

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

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

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

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

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

- This article is a systematic review and meta-analysis that synthesizes evidence from multiple randomized controlled trials.. It was selected because it directly addresses the PICO question by comparing metformin and combined oral contraceptive pills (COCPs) in women with polycystic ovary syndrome. The study evaluates clinically relevant outcomes including insulin levels, insulin resistance, androgen markers, and biochemical parameters, which align closely with the focus on menstrual regularity and insulin sensitivity. Additionally, it was published in 2023 and is MEDLINE-indexed, meeting the requirement for recent, high-quality evidence within the last 10 years.

Key Points:

- COCPs were superior to metformin in reducing androgen, including free androgen index (FAI) and total testosterone, and were more effective at increasing sex hormone-binding globulin (SHBG), supporting stronger control of hyperandrogenism and menstrual irregularity.
- Metformin demonstrated metabolic effects, significantly lowering fasting insulin levels, improving insulin resistance, and reducing triglycerides compared with COCPs alone.
- COCPs were more effective for menstrual cycle regulation, while metformin showed less consistent benefit for restoring regular cycles.
- Combination therapy (metformin + COCP) showed additive benefits, improving both androgen and metabolic parameters more than either therapy alone in several outcomes.
- Metformin was associated primarily with gastrointestinal side effects, while COCPs carried typical hormonal therapy risks, emphasizing the importance of tolerability and long-term adherence in treatment decisions.
- The authors emphasize that treatment should be individualized, with COCPs preferred when hyperandrogenism and menstrual irregularity predominate, and metformin favored when insulin resistance and metabolic risk are the primary concerns.
- Limitations included heterogeneity in trial design, dosing, duration, and PCOS phenotypes, as well as variable certainty of evidence across outcomes.
- Overall conclusion: COCPs are stronger for androgen suppression and menstrual regulation, whereas metformin is stronger for metabolic improvement, and combination therapy may offer the broadest benefit in selected patients.

Article 2: A randomized, controlled trial comparing the metformin, oral contraceptive pills and their combination in patients with polycystic ovarian syndrome

Kumar, Y., Kotwal, N., Singh, Y., Upreti, V., Somani, S., & Hari Kumar, K. V. S. (2018). A randomized, controlled trial comparing the metformin, oral contraceptive pills and their combination in patients with polycystic ovarian syndrome. *Journal of family medicine and primary care*, *7*(3), 551–556. https://doi.org/10.4103/jfmpc.jfmpc_83_17

Background: Polycystic ovarian syndrome (PCOS) is a condition characterized by insulin resistance (IR) and hormonal dysfunction. We conducted a randomized, controlled trial

comparing the effects of metformin, oral contraceptive pills (OCP) and their combination in PCOS.

Materials and Methods: We randomized 90 newly diagnosed PCOS (age 18–40 year, symptom duration >6 months) patients into three groups (Group 1–Metformin, Group 2–OCP, and Group 3– Metformin + OCP) in this prospective study. We excluded patients with past use of insulin sensitizers and hormone therapy. We evaluated for the hyperandrogenism (acne, acanthosis, hirsutism, and hormone panel), IR by homeostasis model assessment (HOMA-IR), inflammation (high-sensitivity C-reactive protein, fibrinogen, and ferritin), and body composition (% fat, android/gynoid ratio) markers at baseline and 6 months after therapy. The data were analyzed using appropriate statistical methods and $P < 0.05$ was considered statistically significant.

Results: The study population had a mean age 23.2 ± 4.4 years and body mass index of 28.4 ± 6.1 kg/m. The improvement in the clinical parameters was similar in all the groups. The combination therapy showed a better response in reducing inflammatory markers, IR, and body composition than either of the groups using a single drug. Metformin alone has resulted in a minor reduction of the androgens. None of the patients developed significant adverse effect to the given therapy.

Conclusion: PCOS is managed with either metformin or OCP in many patients. The combination improves the hyperandrogenism, body composition, and reduces the inflammatory markers.

- This article was selected because it directly compares metformin, oral contraceptive pills (OCP), and combination therapy in women with PCOS, aligning precisely with the PICO question. It is a randomized controlled trial, providing strong comparative treatment evidence. The study evaluates clinically relevant outcomes including insulin resistance (HOMA-IR), androgen levels, menstrual irregularity, inflammatory markers, lipid profile, and body composition. Additionally, it is a peer-reviewed journal.

Key Points :

- OCP significantly reduced hirsutism and androgen-related symptoms, whereas metformin alone produced only minor reductions in androgen levels. Combination therapy demonstrated greater improvement in acne and androgen markers compared to either monotherapy.
- Metformin significantly reduced fasting insulin levels and improved HOMA-IR, demonstrating clear benefits for insulin resistance. In contrast, OCP alone showed worsening of certain insulin resistance parameters. Combination therapy improved insulin resistance more effectively than OCP alone.
- Metformin improved lipid parameters, likely through improvement of insulin resistance. Metformin also reduced inflammatory markers such as high-sensitivity C-reactive protein and fibrinogen, with combination therapy showing the greatest reduction in inflammatory markers overall.

- In terms of body composition, metformin improved body fat percentage and overall body composition, whereas OCP was associated with worsening body composition parameters.
- No significant adverse effects were reported overall; two patients experienced mild gastrointestinal intolerance with metformin, and one patient developed a self-limited rash with OCP.

Article 3: Impact of combined hormonal contraceptives and metformin on metabolic syndrome in women with hyperandrogenic polycystic ovary syndrome and obesity: The COMET-PCOS randomized clinical trial

Dokras, A., Coutifaris, C., Remaley, A. T., Mehta, N. N., Playford, M. P., Kunselman, A. R., Stetter, C. C., Dodson, W. C., & Legro, R. S. (2025). Impact of combined hormonal contraceptives and metformin on metabolic syndrome in women with hyperandrogenic polycystic ovary syndrome and obesity: The COMET-PCOS randomized clinical trial. *PLoS medicine*, *22*(12), e1004662. https://doi.org/10.1371/journal.pmed.1004662

Background: The risk-to-benefit ratio of using combined oral contraceptive pills (COCPs) and/or metformin for comprehensive management of polycystic ovary syndrome (PCOS) in women with obesity is unclear. As there is a lack of robust evidence on the impact of these first-line medications on cardiovascular disease (CVD) risk, we compared the effect of COCPs, metformin or both on prevalence of metabolic syndrome (MetS) in participants with hyperandrogenic PCOS and hypothesized that COCPs would increase prevalence of MetS while metformin would decrease prevalence of MetS.

Methods and findings: We conducted a multicenter, double-blind, double-dummy, randomized trial (COMET-PCOS) in participants between ages ≥18 and ≤40 years and body mass index (BMI) ≥25 kg/m2 and ≤ 48 kg/m2 with hyperandrogenic PCOS (defined by the Rotterdam criteria). Participants were randomized 1:1:1 to 24 weeks of low-dose COCPs (20 μg ethinyl estradiol/0.15 mg desogestrol), metforminXR (2,000 mg), or both (Combined). The primary outcome, assessed by intention-to-treat analysis, was the effect of the different treatment groups on the prevalence of MetS at the end of study. The analytical model included site, race, and the presence or absence of MetS at the screening visit as covariates. The secondary outcomes included changes in each component of MetS (TG, HDL-C, BP, WC, and fasting glucose levels) over the study period. Of the 240 participants randomly assigned, 20 out of 79 in the COCP group, 16 out of 81 in the metformin group, and 17 out of 80 in the combined group dropped out of the study. A total of 169 participants (70.4%) completed the trial between January 2018 and June 2023 (mean age: 29.5 years; mean BMI: 35.6 kg/m2; 70% were White and 23% were Black). The overall prevalence of MetS was 31% at baseline and comparable across groups. At the end of the study, the prevalence of MetS was 26.2% (17/65) in the metformin group, 28.6% (17/59) in the Combined group, and 28.8% (17/59) in COCP group with no significant difference in trend of MetS prevalence between groups (adjusted $p = 0.26$). Waist circumference (mean change (MC) −2.23 cm; 95% CI [−3.98, −0.49]; $p = 0.01$), BMI (MC −0.49 kg/m2; 95% CI

[−0.88, −0.10]; $p = 0.01$), and android fat mass measured by DXA (MC −167 g; 95% CI [−264, −71[; $p < 0.001$) decreased in the COCP group over the study period whilst there was no statistically significant changes in these parameters in the metformin only group when compared to baseline.. In the metformin and Combined groups, the majority of participants (>64%) reported diarrhea, while 24.1% in the COCP group reported uterine bleeding. The main methodologic limitation of the study is the potential lack of power to detect differences in secondary outcomes.

Conclusions: In participants with hyperandrogenic PCOS and overweight/obesity, low-dose COCPs effectively managed PCOS symptoms without increasing prevalence of MetS. Our findings challenge the current practice of using metformin alone or with COCPs for lowering cardiometabolic risk.

- This article was selected because it is a recent (2025) randomized clinical trial directly comparing metformin, COCPs, and combination therapy in women with PCOS. As a multicenter, double-blind RCT, it provides high-level, contemporary evidence. It evaluates important metabolic and clinical outcomes including metabolic syndrome, body composition, and adverse effects, making it highly relevant to the PICO question.

Key Points:

- The primary outcome was prevalence of metabolic syndrome (MetS) after 24 weeks; there was no significant difference in MetS prevalence among the COCP, metformin, and combined groups at study end.
- Although metabolic syndrome prevalence did not differ, low-dose COCPs led to statistically significant reductions in waist circumference, BMI, and central body fat (android fat) compared to baseline, suggesting some metabolic benefit for anthropometric measures.
- Gastrointestinal side effects (primarily diarrhea) were common in both metformin and combination groups (>64%), whereas abnormal vaginal bleeding was more frequently reported in the COCP-only group, highlighting different tolerability profiles of these therapies.
- Menstrual frequency tended to increase in the metformin group compared with baseline, while COCP groups experienced continuous endometrial suppression, showing divergent effects on cycle outcomes related to mechanism of action.
- The trial challenges the assumption that metformin alone or with COCPs, necessarily decreases metabolic syndrome prevalence in overweight/obese women with PCOS, suggesting that COCPs alone may be sufficient for symptomatic management without worsening cardiometabolic risk over 24 weeks.

What is the clinical "bottom line" derived from these articles in answer to your question?

In women with polycystic ovary syndrome, combined oral contraceptive pills (COCPs) are generally more effective than metformin for improving hyperandrogenic symptoms and regulating menstrual cycles, while metformin provides greater benefit in improving insulin resistance and other metabolic parameters. Evidence from randomized controlled trials and meta-analyses suggests that neither therapy is universally superior, as each targets different aspects of PCOS pathophysiology. Combination therapy may offer additive benefits by addressing both hormonal and metabolic abnormalities. Therefore, for this 26-year-old woman with PCOS presenting with irregular menses and laboratory evidence of insulin resistance, combined oral contraceptive pills would likely provide greater improvement in menstrual cycle regulation and suppression of hyperandrogenic symptoms, especially since she is not currently attempting pregnancy. In addition to starting COCPs, lifestyle modification with diet and exercise would be strongly recommended to address her prediabetes (A1c 5.9%) and reduce overall metabolic risk factors.

The patient should be reevaluated in about 3 months to assess improvement in menstrual regularity and metabolic markers. If there is limited improvement with lifestyle modification or if insulin resistance remains a concern, metformin could then be considered as an adjunct therapy to target insulin resistance and help reduce long-term metabolic risk. At the end of the day, treatment should be individualized based on patient-specific goals, including menstrual regulation, metabolic risk reduction, and need for contraception, while also considering medication side effects and long-term adherence.