



Polycystic Ovary Syndrome, Insulin Resistance and Weight: Sequencing Treatment When Goals Conflict

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Abstract

Polycystic ovary syndrome affects more than one woman in ten and presents with reproductive, dermatological and metabolic features that do not respond to the same treatment. A meta-analysis of 36 randomised trials, conducted to inform the 2023 international guideline, found the combined oral contraceptive superior for cycle regularity and metformin superior for metabolic outcomes, with metformin lowering insulin by 27.12 pmol/L and triglycerides by 0.15 mmol/L relative to the pill. For hirsutism there was no difference between them. Combining the two improved biochemical hyperandrogenism, insulin and insulin resistance beyond the pill alone, yet produced no difference in clinical outcomes. Body mass index modified the comparison, with metformin favoured metabolically above 25 kg/m² and the pill favoured for hirsutism below it. Underlying all of this is an awkward fact: insulin resistance is described as a key feature of the syndrome while routine clinical measurement of it is not recommended, because available measures are inaccurate.

Keywords: Polycystic ovary syndrome; Metformin; Combined oral contraceptive; Insulin resistance; Treatment sequencing

Introduction

Polycystic ovary syndrome affects more than one in ten women of reproductive age and is diagnosed on reproductive and endocrine criteria [1,2,3]. Its manifestations span menstrual irregularity, hyperandrogenism, subfertility, metabolic disturbance and psychological burden, and few patients present with all of them [4,5,29]. Depression and anxiety are substantially more common than in the general population and are the subject of a dedicated position statement [24,25].

Treatment is therefore not a single decision. The features respond to different agents, and a choice that helps one may leave another untouched or worsen it [6,7,32]. Comparisons between contraceptive preparations and between insulin sensitisers and anti-androgens have been synthesised separately [21,32]. The 2023 international guideline organises its recommendations around the feature being treated rather than around the diagnosis [1,8].

This review examines what the comparative evidence shows about the two principal pharmacological options, how the choice between them depends on which goal is prioritised, and what the guideline says about the metabolic feature that underlies much of the syndrome.

Material and Methods

Search strategy: PubMed and the archives of the major endocrinology, reproductive medicine and metabolic journals were searched for comparative studies of pharmacological treatment in polycystic ovary syndrome. Search terms combined polycystic ovary syndrome with metformin, combined oral contraceptive, insulin resistance, hirsutism and guideline. Reference lists of the guideline [1] and its informing meta-analysis [9] were screened by hand for primary sources.

Eligibility: Studies were included if they compared pharmacological treatments head to head in defined populations

with the syndrome, or synthesised such comparisons. Guideline documents are cited for the recommendations they contain and are identified as such.

Data extraction and handling: Design, population, comparison and the reported estimate were extracted as published. Whether an outcome is biochemical or clinical is stated in each case, because the two diverge in this literature and the distinction carries the central argument. This review reports published findings and the content of guidance; it makes no dietary, caloric or exercise recommendations and offers no advice on the choice of contraception or fertility treatment for any individual. No pooling or re-analysis was performed. Figures 1 to 6 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The comparison: A systematic review and meta-analysis performed to inform the 2023 guideline searched five databases, identified 1,660 publications and included 36 randomised controlled trials comparing the combined oral contraceptive, metformin and the two in combination (Figure 5) [9]. Quality was assessed using a formal grading framework.

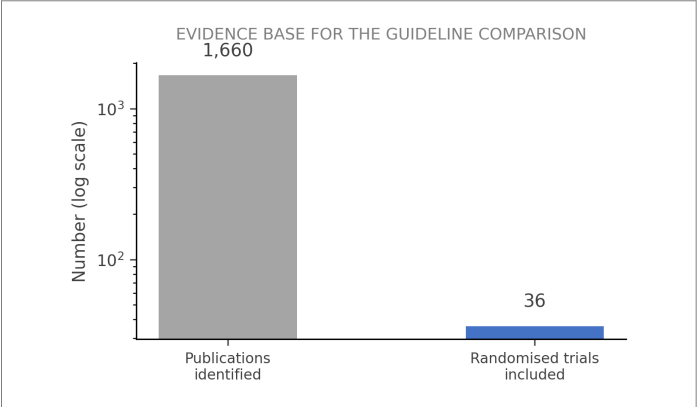


Figure 5: Evidence base for the guideline comparison [9]

Where each agent performed better: Metformin was superior to the contraceptive for metabolic outcomes, particularly in women with a body mass index of 25 kg/m2 or above, while the contraceptive was superior for cycle regularity and, in women with a body mass index below 25, for hirsutism (Figure 1) [9]. Metformin lowered insulin by 27.12 pmol/L (95% CI 13.59 to 40.65) and triglycerides by 0.15 mmol/L (0.01 to 0.29) relative to the contraceptive (Figure 2) [9].

Hirsutism showed no difference: Comparing metformin with the contraceptive, and comparing the contraceptive with combination treatment, no differences in hirsutism were observed [9]. This is notable because hirsutism is among the features women most often present with and is frequently the reason treatment is sought [4,10].

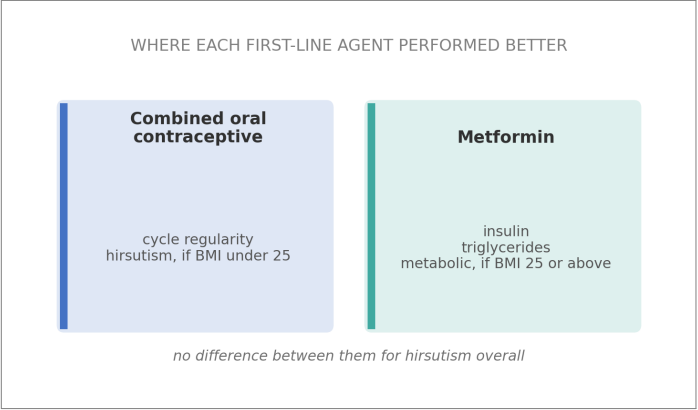


Figure 1: Where each first-line agent performed better [9]



Figure 2: Metformin against the contraceptive pill on metabolic measures [9]

What combination added: Relative to the contraceptive alone, combination treatment was superior for insulin, by 17.03 pmol/L (95% CI 7.79 to 26.26), for insulin resistance, by 0.44 (0.17 to 0.70), and for free androgen index, by 0.58 (0.36 to 0.80), with sex hormone binding globulin also differing by 16.61 nmol/L; testosterone did not differ (Figure 3) [9]. The meta-analysis reported that although combination treatment improved biochemical hyperandrogenism, insulin levels and insulin resistance more than the contraceptive alone, no difference was seen in clinical outcomes (Figure 4) [9].

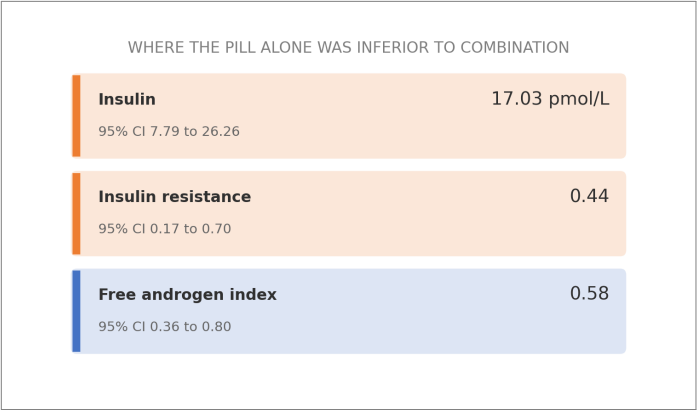


Figure 3: Where the contraceptive alone was inferior to combination treatment [9]

Table 1: Head-to-head comparisons as reported by the original investigators [9]

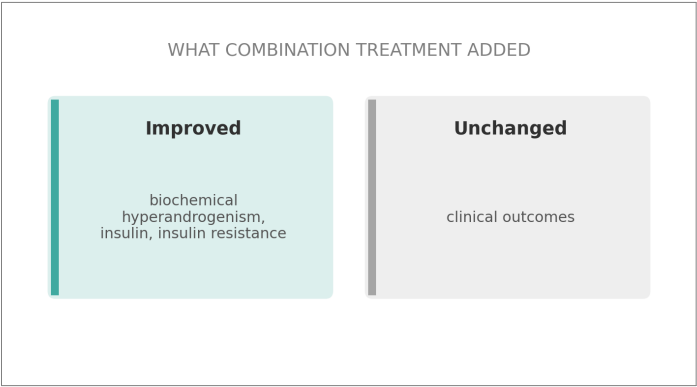


Figure 4: What combination treatment added, and what it did not [9]

Outcome	Better agent	Reported estimate
Insulin	Metformin	-27.12 pmol/L [9]
Triglycerides	Metformin	-0.15 mmol/L [9]
Cycle regularity	Contraceptive	Superior [9]
Hirsutism, overall	Neither	No difference [9]
Hirsutism, body mass index under 25	Contraceptive	Superior [9]

What the guideline recommends: The 2023 guideline makes the combined oral contraceptive first-line pharmacological treatment for menstrual irregularity and hyperandrogenism, with no specific preparation recommended and a preference for lower ethinyl estradiol doses and preparations with fewer side effects. Metformin is recommended primarily for metabolic features and has greater efficacy than inositol. Letrozole is the preferred first-line pharmacological treatment for infertility, on the basis of randomised comparison against clomiphene and against clomiphene with metformin [16,17,18] (Figure 6) [1,8]. Anti-androgens have a limited role where other therapies are ineffective or contraindicated, and anti-obesity agents and metabolic surgery may be considered on the basis of general population guidance [1,22]. Lifestyle intervention has been assessed in Cochrane review and alongside metformin [15,23,28].

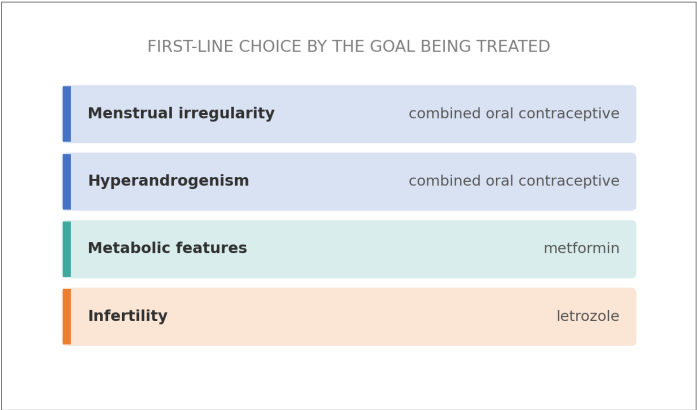


Figure 6: First-line choice by the goal being treated [1,8]

Feature being treated	Recommended first-line option
Menstrual irregularity	Combined oral contraceptive [1]
Hyperandrogenism	Combined oral contraceptive [1]
Metabolic features	Metformin [1]

Feature being treated	Recommended first-line option
Infertility	Letrozole [1]
Hirsutism, some subgroups	Mechanical laser therapy [1]

Table 2: Guideline recommendations organised by the feature being treated [1,8]

The measurement problem: The guideline states that insulin resistance is recognised as a key feature of the syndrome, yet that routinely available measures of insulin resistance are inaccurate and clinical measurement is not currently recommended [1,11]. Management is therefore directed at features that can be observed rather than at the physiological abnormality believed to underlie them. Clamp studies confirm intrinsic insulin resistance in this population, but they are research tools rather than clinic tests [11,26,27].

In adolescents: A systematic review of randomised trials in adolescents reported that contraceptives were effective in reducing hyperandrogenic symptoms and regulating cycles but were often associated with adverse metabolic effects, including raised hepatic enzymes and insulin resistance, while insulin-sensitising regimens showed better outcomes for ovulation, insulin sensitivity and body composition with fewer metabolic side effects [12]. Combination therapy showed a balanced improvement across reproductive and metabolic measures, and the overall quality of included studies was rated as having some concerns [12].

Consideration	What the evidence indicates
Which agent to start	Depends on the feature prioritised [9]
Combination therapy	Biochemical gain, no clinical difference [9]
Body mass index	Modifies which agent performs better [9]
Insulin resistance	Central to the syndrome, not measurable in clinic [1]
Adolescents	Contraceptives may worsen metabolic markers [12]

Table 3: Factors bearing on the sequencing decision

Where the metabolic risk actually sits: The reason metabolic features matter is long-term risk. Systematic review reports increased risk of type 2 diabetes and cardiovascular disease in this population, and pregnancy complications appear raised independently of obesity [5,13,34]. None of the treatment trials reviewed here measures those outcomes, so the metabolic arm of the decision rests on surrogates throughout [9,33].

Psychological features are part of the picture: Depressive and anxiety symptoms are substantially more common in this population than in comparable women without the syndrome, and a position statement addresses their assessment alongside quality of life and disordered eating [24,25]. The guideline recommends screening for them, which places a third domain alongside the reproductive and metabolic ones and further complicates any single treatment sequence [1,29].

Discussion

The structure of this problem is unusual and worth naming. Most treatment decisions involve choosing the better of two options for a single outcome. Here the two first-line agents are each better for a different outcome, and the outcomes belong to the same patient [9]. A woman presenting with irregular cycles, hirsutism and raised insulin has no single best drug, and the guideline reflects that by organising its recommendations around the feature rather than the diagnosis [1].

That makes the sequencing question genuine rather than rhetorical. It also makes the consultation the decisive step, because which feature matters most is a judgement the patient is better placed to make than the clinician. A woman seeking regular cycles and a woman concerned about long-term metabolic risk are asking for different treatments, and both are asking correctly.

Combination therapy looks like the obvious resolution and the data do not support it as one. Adding metformin to the contraceptive improved insulin, insulin resistance and biochemical hyperandrogenism, and produced no difference in clinical outcomes [9]. That is a clean example of biochemical benefit without demonstrated clinical benefit, and it should be described that way rather than presented as combined advantage. Whether the biochemical difference would translate into clinical difference over longer follow-up than these trials provided is unknown.

The measurement problem underneath deserves more attention than it receives. Insulin resistance is described as a key feature of the syndrome, and clinical measurement of it is not recommended because the available assays are inaccurate [1,11]. So the abnormality thought to drive much of the condition cannot be quantified in the patient in front of you, which means it cannot be used to select treatment, to monitor response or to define who has the metabolic phenotype. Body mass index is being used as a proxy, and the meta-analysis found it modified which agent performed better [9]. That is pragmatic and it is not the same thing.

A final observation concerns adolescents, where the evidence points somewhat against the adult recommendation. Contraceptives were effective for hyperandrogenic symptoms but were associated with adverse metabolic effects in this age group, while insulin-sensitising regimens performed better metabolically [12]. The studies were rated as having some concerns and the finding should not be over-read, but it suggests the sequencing question may resolve differently at different ages [19,20].

A practical consequence follows from the structure of the evidence. Because each agent was compared against the other on a panel of outcomes, and each won on some, the meta-analysis cannot produce a ranking and does not attempt one. Its own conclusion is that the choice should be based on symptoms [9]. That is an unusual thing for a synthesis of 36 trials to conclude,

and it is the correct conclusion rather than a failure to reach one.

What would change the position is outcome data over a longer horizon. If the biochemical advantage of combination treatment translated into fewer cases of type 2 diabetes or cardiovascular events over a decade, the calculus would shift and the combination would have a clinical claim it currently lacks [5,9,13]. No trial reviewed here was designed or powered to detect that, and the condition is lifelong while the trials run for months [23,28].

Study limitations

The limitations belong to the underlying literature. The meta-analysis pools 36 trials differing in preparation, dose, duration and population, and reported outcomes are predominantly biochemical and short-term rather than clinical and long-term [9]. Hirsutism assessment is subjective and slow to change, which limits what trials of conventional duration can detect [4,10]. Diagnostic criteria for the syndrome have changed over the period covered, so trial populations are not identical [2,3]. Insulin resistance is reported as an index derived from fasting measurements whose accuracy the guideline itself questions [1,11]. Adolescent evidence is limited and rated as having some concerns [12]. Long-term cardiometabolic outcomes, which are the reason the metabolic features matter, are not endpoints in these trials [5,13,33]. Pregnancy complications are raised in this population and appear independent of obesity [34]. And the guideline notes that weight bias and stigma should be minimised and that permission should be sought before weighing, which is a reminder that the metabolic conversation carries risks of its own [1,14,30,31].

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Conclusion

Polycystic ovary syndrome does not have a first-line treatment; it has first-line treatments, and which one applies depends on what the patient wants addressed. The combined oral contraceptive is better for cycle regularity, metformin is better for metabolic measures, and for hirsutism the trials found no difference between them. Combination therapy improves the biochemistry without a demonstrated difference in clinical outcomes, so it resolves the conflict on paper rather than in practice. Underneath sits a measurement gap that is rarely stated plainly: insulin resistance is held to be central to the syndrome and cannot be measured accurately in clinic, so body mass index stands in for it. Sequencing treatment here is a conversation about priorities, not an algorithm.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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