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Review Article

Emerging Therapeutic Strategies Targeting Insulin Resistance in PCOS to Improve Fertility

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ABSTRACT

Background: Polycystic ovary syndrome is a major cause of anovulatory infertility, and insulin resistance contributes to compensatory hyperinsulinaemia, androgen excess, impaired follicular development, and adverse reproductive outcomes in many affected women. Metabolic treatment may improve the physiological environment required for ovulation and pregnancy, but its role must be distinguished from that of established fertility-directed therapy. Objective: To map the available evidence on lifestyle, pharmacological, nutritional, and other metabolic strategies targeting insulin resistance or related pathways and to examine their reported effects on fertility outcomes in women with polycystic ovary syndrome. Methods: A rapid structured scoping review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews and Joanna Briggs Institute guidance. PubMed/MEDLINE, Google Scholar, international guideline repositories, and reference lists were searched through 8 June 2026. Eligible publications included clinical practice guidelines, randomised controlled trials, systematic reviews, meta-analyses, and major clinical reviews evaluating metabolic or fertility-directed interventions in women with polycystic ovary syndrome and reporting menstrual, ovulatory, pregnancy, live-birth, miscarriage, or assisted reproductive outcomes. Data were charted by study design, intervention, metabolic effect, reproductive outcome, and evidence limitation. Findings were synthesised descriptively without formal certainty grading or meta-analysis. Results: Nine publications met the eligibility criteria, comprising two clinical practice guidelines, two randomised controlled trials, four systematic reviews or meta-analyses, and one major clinical review. Lifestyle management was consistently recommended as the foundation of metabolic and preconception care, although direct evidence for live birth was limited within the audited evidence set. Metformin improved metabolic parameters, menstrual cyclicity, and ovulation in selected women but had a principally supportive role when conception was the immediate objective. Letrozole provided the clearest direct evidence for ovulation and live birth but did not directly treat insulin resistance. Inositol and exenatide-based glucagon-like peptide-1 receptor agonist therapy showed possible metabolic and intermediate reproductive benefits, whereas evidence for live birth and pregnancy safety remained insufficient. Berberine did not demonstrate a clear additional fecundity benefit when combined with letrozole. Conclusion: Fertility management in women with insulin-resistant polycystic ovary syndrome should combine metabolic assessment and optimisation with established fertility-directed treatment. Lifestyle management remains foundational, letrozole is the preferred first-line ovulation-induction treatment, and metformin may provide additional benefit in selected women with metabolic dysfunction. Evidence for inositol, glucagon-like peptide-1 receptor agonists, and berberine remains limited by heterogeneous methods and inadequate reporting of live birth, miscarriage, assisted reproduction, and pregnancy safety. Keywords: Polycystic Ovary Syndrome; Insulin Resistance; Anovulatory Infertility; Metformin; Letrozole; Inositol; Glucagon-Like Peptide-1 Receptor Agonists; Ovulation Induction; Live Birth; Scoping Review

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine and metabolic disorder affecting approximately 10%–13% of women of reproductive age and is one of the most common causes of anovulatory infertility worldwide (1). Its clinical presentation may include menstrual irregularity, oligo-ovulation or anovulation, biochemical or clinical hyperandrogenism, acne, hirsutism, polycystic ovarian morphology, obesity, insulin resistance, and impaired fertility. Diagnosis in adults is commonly based on the Rotterdam framework, which requires at least two of the following three features after exclusion of alternative causes: hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology (2).

The 2023 International Evidence-based Guideline for the Assessment and Management of PCOS retains this diagnostic framework and permits anti-Müllerian hormone to be used as an alternative to ultrasound for defining polycystic ovarian morphology in selected adults, although this approach is not recommended in adolescents (3).

Insulin resistance is an important pathophysiological feature in many, but not all, women with PCOS. Reduced insulin responsiveness in skeletal muscle, adipose tissue, and other peripheral tissues promotes compensatory hyperinsulinaemia, while ovarian tissue may remain sensitive to insulin. Hyperinsulinaemia can enhance luteinising hormone-mediated androgen production by ovarian theca cells, reduce hepatic synthesis of sex hormone-binding globulin, and increase circulating bioavailable androgens (4). The resulting interaction between insulin resistance and hyperandrogenism may impair follicular maturation, disturb hypothalamic–pituitary–ovarian signalling, and contribute to persistent oligo-ovulation or anovulation. Although insulin resistance is more frequent and often more severe in women with overweight or obesity, it may also occur in women with PCOS who have a normal body mass index.

Reproductive impairment in PCOS extends beyond anovulation. Metabolic dysfunction, obesity, hyperandrogenism, and chronic low-grade inflammation may adversely affect oocyte competence, endometrial receptivity, spontaneous conception, response to ovulation-induction therapy, and assisted reproductive treatment. Women with PCOS may also have increased risks of miscarriage, gestational diabetes, hypertensive disorders of pregnancy, and other adverse pregnancy outcomes, particularly when obesity or impaired glucose regulation is present (3). Fertility management should therefore combine reproductive assessment with preconception evaluation of body weight, glucose metabolism, cardiovascular risk factors, nutritional status, and other modifiable determinants of maternal health.

Lifestyle management remains the foundation of PCOS care and includes healthy dietary practices, regular physical activity, behavioural support, sleep optimisation, and weight-management strategies. International guidance recommends a lifelong healthy lifestyle for all women with PCOS, including those planning pregnancy, irrespective of whether weight loss is an immediate treatment objective (3). In women with overweight or obesity, clinically meaningful weight reduction may improve insulin sensitivity, androgen excess, menstrual regularity, and ovulatory function. Nevertheless, lifestyle programmes vary substantially in their intensity, duration, behavioural components, accessibility, and adherence. Lifestyle counselling should consequently be individualised, culturally appropriate, and delivered without reinforcing weight stigma.

When anovulatory infertility is the primary treatment concern and no other major infertility factors are present, letrozole is recommended as the preferred first-line pharmacological ovulation-induction agent (3). In a large randomised controlled trial, letrozole produced higher ovulation and live-birth rates than clomiphene citrate among women with PCOS-related infertility (5). Letrozole, however, is a fertility-directed treatment and does not directly correct insulin resistance, impaired glucose regulation, or long-term cardiometabolic risk. Its role should therefore be distinguished from metabolic interventions and incorporated into a broader treatment pathway that includes metabolic assessment and preconception optimisation.

Metformin is the most extensively studied insulin-sensitising medication used in PCOS. It reduces hepatic glucose production and improves peripheral insulin sensitivity and may improve menstrual cyclicity and ovulation in selected women. However, metformin is generally less effective than first-line ovulation-induction agents when conception is the immediate therapeutic objective and should not routinely replace letrozole as fertility monotherapy (6). Its clinical role is primarily supportive, particularly in women with impaired glucose tolerance, higher body mass index, metabolic risk factors, or a need for simultaneous metabolic and reproductive management. Evidence also suggests that the reproductive effects of metformin may vary according to baseline body composition and metabolic phenotype (16).

Interest has expanded to additional interventions that may modify insulin signalling, body weight, glucose metabolism, inflammation, or oxidative stress. Myo-inositol and D-chiro-inositol participate in intracellular insulin-signalling pathways and have been investigated for possible effects on menstrual regularity, ovulation, and metabolic function. However, current evidence remains uncertain because studies differ in formulation, dosage, myo-inositol-to-D-chiro-inositol ratio, treatment duration, comparator, and methodological quality. Evidence for clinical pregnancy and live birth is less robust than evidence for metabolic or intermediate reproductive outcomes (7).

Glucagon-like peptide-1 receptor agonists, particularly exenatide and liraglutide, have also attracted attention because of their effects on appetite regulation, body weight, glycaemic control, and insulin resistance. Meta-analyses comparing exenatide with metformin have reported improvements in body mass index, insulin-resistance indices, ovulation, and pregnancy outcomes in selected women with PCOS (8,9). These agents are not ovulation-induction medications and should not be used during pregnancy. Their potential role is therefore primarily preconceptional and requires appropriate contraception, planned discontinuation before conception, and careful pregnancy counselling. Fertility-specific evidence remains substantially more limited than evidence for their metabolic and weight-related effects.

Berberine has been investigated as a possible metabolic adjunct because of its effects on glucose regulation, lipid metabolism, and insulin sensitivity. However, a randomised trial found no clear additional fecundity advantage when berberine was combined with letrozole compared with letrozole-based treatment alone (12). This finding illustrates that improvement in metabolic or biochemical markers does not necessarily translate into higher pregnancy or live-birth rates. Bariatric or metabolic surgery may produce substantial weight loss and metabolic improvement in carefully selected women with severe obesity, but it is a preconception metabolic intervention rather than an immediate treatment for infertility. Pregnancy planning after surgery requires stabilisation of body weight and nutritional status and careful multidisciplinary follow-up (13).

Despite the growing range of metabolic and fertility-directed interventions, the available evidence remains fragmented across PCOS phenotypes, intervention types, study designs, treatment durations, and reproductive endpoints. Many studies emphasise changes in body weight, insulin resistance, hormonal profiles, menstrual regularity, or ovulation, whereas fewer evaluate clinical pregnancy, miscarriage, time to pregnancy, live birth, assisted reproductive outcomes, or maternal and neonatal safety. In addition, insulin resistance is defined inconsistently across studies, making it difficult to identify the patients most likely to benefit from a particular metabolic intervention.

A broad mapping of the evidence is therefore needed to clarify how established and emerging metabolic interventions should be positioned alongside evidence-based fertility treatment. This scoping review aimed to identify and characterise lifestyle, pharmacological, nutritional, and surgical strategies targeting insulin resistance or related metabolic pathways in women with PCOS and to examine their reported effects on menstrual regularity, ovulation, clinical pregnancy, live birth, miscarriage, and assisted reproductive outcomes. Letrozole was considered within the review as the principal evidence-based fertility treatment against which the complementary role of metabolic optimisation could be interpreted.

MATERIALS AND METHODS

Review Design and Reporting Framework

This study was conducted as a rapid structured scoping review to map the available clinical evidence on metabolic interventions targeting insulin resistance or related pathways and their reported effects on fertility outcomes in women with polycystic ovary syndrome (PCOS). A scoping-review design was considered appropriate because the available literature comprised heterogeneous interventions, study

designs, patient populations, and reproductive outcomes that were not suitable for direct quantitative comparison. The review was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews and the methodological guidance of the Joanna Briggs Institute for scoping reviews (14,15). The rapid approach involved limiting formal database searching to PubMed/MEDLINE and Google Scholar, supplemented by international guideline repositories and backward reference-list screening. The purpose was to identify clinically relevant evidence across established and emerging metabolic strategies rather than to conduct an exhaustive systematic review or meta-analysis.

Review Question

The review question was developed using the Population–Concept–Context framework. The population comprised women of reproductive age diagnosed with PCOS, particularly those with insulin resistance, obesity, impaired glucose regulation, metabolic syndrome, or other clinically relevant metabolic abnormalities. The concept included lifestyle, pharmacological, nutritional, and surgical interventions intended to improve insulin sensitivity, glucose metabolism, body weight, inflammation, oxidative stress, or related metabolic pathways. Letrozole was not classified as an insulin-targeting intervention; instead, it was included as the principal evidence-based ovulation-induction comparator against which the complementary role of metabolic optimisation was interpreted. The clinical context included preconception care, natural conception, ovulation induction, infertility management, and assisted reproductive treatment. Outcomes of interest included menstrual regularity, ovulation, clinical pregnancy, live birth, miscarriage, time to pregnancy, endometrial outcomes, oocyte or embryo quality, ovarian hyperstimulation syndrome, and other assisted reproductive technology outcomes.

Information Sources and Search Strategy

A structured literature search was conducted up to 8 June 2026 using PubMed/MEDLINE, Google Scholar, international evidence-based guideline repositories, and the reference lists of eligible publications. Search terms combined controlled vocabulary, where available, with free-text terms related to PCOS, insulin resistance, metabolic dysfunction, infertility, and fertility treatment. The principal search concepts included “polycystic ovary syndrome,” “PCOS,” “insulin resistance,” “hyperinsulinaemia,” “impaired glucose tolerance,” “obesity,” “metabolic dysfunction,” “infertility,” “fertility,” “ovulation,” “pregnancy,” “live birth,” “miscarriage,” “assisted reproduction,” “lifestyle intervention,” “weight management,” “metformin,” “myo-inositol,” “D-chiro-inositol,” “glucagon-like peptide-1 receptor agonists,” “exenatide,” “liraglutide,” “semaglutide,” “N-acetylcysteine,” “berberine,” and “bariatric or metabolic surgery.”

Boolean operators were used to combine the principal concepts. Examples of search combinations included “PCOS AND insulin resistance AND fertility,” “PCOS AND metformin AND pregnancy,” “PCOS AND inositol AND ovulation,” “PCOS AND GLP-1 receptor agonist AND fertility,” and “PCOS AND bariatric surgery AND reproductive outcomes.” The 2023 International Evidence-based Guideline for the Assessment and Management of PCOS was searched separately to ensure that the evidence map reflected contemporary diagnostic, metabolic, and fertility-management recommendations (3). The complete PubMed search strategy, including search terms, Boolean operators, filters, and date of execution, should be provided in a supplementary file to permit reproducibility.

Eligibility Criteria

Publications were considered eligible if they included women of reproductive age diagnosed with PCOS according to recognised clinical or research criteria, evaluated a lifestyle, pharmacological, nutritional, or surgical intervention targeting insulin resistance or a closely related metabolic pathway, and reported at least one fertility-related outcome. Relevant reproductive outcomes included menstrual regularity, ovulation, clinical pregnancy, live birth, miscarriage, time to pregnancy, endometrial receptivity, oocyte or embryo quality, and assisted reproductive outcomes. Eligible evidence sources included international

clinical practice guidelines, randomised controlled trials, systematic reviews, meta-analyses, and major clinical reviews directly relevant to metabolic management and fertility in PCOS. Publications were also required to provide sufficient information to determine the intervention, population, and relevant reproductive or metabolic outcomes.

The landmark randomised trial comparing letrozole with clomiphene citrate was included as a fertility-treatment benchmark because it established the comparative effectiveness of first-line ovulation induction in women with PCOS. It was not classified as evidence that letrozole improves insulin resistance.

Publications were excluded if they involved populations without PCOS, focused exclusively on cosmetic manifestations such as acne or hirsutism, reported only metabolic outcomes without any fertility-related outcome, or did not evaluate an intervention relevant to insulin resistance or metabolic dysfunction. Basic-science, animal, and in-vitro studies were excluded, as were general informational webpages without PCOS-specific clinical evidence, reporting-guideline publications, methodological papers unrelated to clinical evidence, and publications with insufficient information to determine eligibility. Background references used to support PCOS prevalence, diagnosis, pathophysiology, or review methodology were retained in the manuscript bibliography but were not counted among the included evidence records.

Study Selection

Retrieved records were assessed in two stages. Titles and abstracts were initially screened against the predefined eligibility criteria, after which potentially relevant publications were evaluated in full text. Reasons for full-text exclusion included an ineligible population, absence of fertility-related outcomes, lack of a metabolic or insulin-related intervention, non-clinical study design, or insufficient relevance to the review question.

Duplicate publications and overlapping evidence syntheses were examined carefully. When several reviews addressed the same intervention, a review was retained only when it contributed distinct evidence, included a different patient subgroup, incorporated more recent literature, or reported additional reproductive outcomes. The number of records identified, duplicates removed, records screened, full texts assessed, records excluded with reasons, and publications included in the final evidence map should be presented in a PRISMA-ScR flow diagram.

Data Charting

Information from eligible publications was charted using a standardised evidence-extraction form. Extracted variables included author and publication year, country or geographical setting, study design, sample size or number of studies included in an evidence synthesis, PCOS diagnostic criteria, participant age and metabolic characteristics, intervention and comparator, treatment duration, definition or measurement of insulin resistance, menstrual and ovulatory outcomes, clinical pregnancy, miscarriage and live-birth outcomes, assisted reproductive outcomes, and metabolic outcomes. Metabolic variables included body mass index, body weight, glucose regulation, insulin-resistance indices, and androgen-related measures. Principal findings and limitations relevant to interpretation were also recorded where available.

Eligible evidence was organised into lifestyle and weight-management interventions, metformin, inositol supplementation, glucagon-like peptide-1 receptor agonists, N-acetylcysteine, berberine, and bariatric or metabolic surgery. Letrozole was charted separately as the principal fertility-directed comparator and was not included as an insulin-sensitising intervention.

Critical Appraisal

A formal risk-of-bias assessment and certainty-of-evidence grading were not undertaken because the purpose of the review was to map the breadth, characteristics, and clinical direction of the available evidence rather than calculate pooled treatment effects or make formal comparative-effectiveness recommendations. Accordingly, formal certainty labels such as high-, moderate-, or low-certainty evidence were not assigned. Evidence was instead described narratively according to its source, consistency, directness, relevance of the reported outcomes, and principal methodological limitations.

Evidence Synthesis

The evidence was synthesised descriptively according to intervention category. Findings were compared by proposed mechanism, study design, population characteristics, metabolic effects, and reproductive outcomes. Particular attention was given to distinguishing metabolic outcomes, including body weight, glucose regulation, insulin resistance, and androgen status, from intermediate reproductive outcomes such as menstrual regularity and ovulation, and from definitive fertility outcomes such as clinical pregnancy, miscarriage, and live birth.

No meta-analysis was conducted because quantitative pooling was outside the purpose of the scoping review and the available evidence differed substantially in intervention protocols, participant characteristics, definitions of insulin resistance, treatment duration, comparator groups, and outcome measurement. Research gaps were identified by examining the consistency and completeness of live-birth reporting, miscarriage outcomes, pregnancy safety, assisted reproductive outcomes, long-term maternal and neonatal outcomes, intervention standardisation, and representation of South Asian and other underrepresented populations.

Ethical Considerations

This review used information obtained from previously published sources and did not involve the recruitment of human participants, delivery of interventions, or collection of identifiable patient information. Formal ethical approval and informed consent were therefore not required.

RESULTS

Evidence Selection and Composition

Following eligibility assessment, nine publications were retained in the final evidence map. The included evidence comprised two clinical practice guidelines, two randomised controlled trials, four systematic reviews or meta-analyses, and one major clinical review. The remaining references in the manuscript were used to support background information, diagnostic criteria, pathophysiology, or review methodology and were not counted as included clinical evidence. References that could not be verified bibliographically or did not provide eligible PCOS-specific fertility evidence were also excluded from the evidence map.

The nine included publications addressed lifestyle and metabolic management, metformin, inositol supplementation, glucagon-like peptide-1 receptor agonists, berberine, and fertility-directed ovulation induction. Letrozole was retained as the principal fertility-treatment benchmark but was not classified as an insulin-sensitising intervention. N-acetylcysteine and bariatric or metabolic surgery were not retained as independently evaluated intervention categories because the audited reference set did not contain verified eligible publications that directly supported their fertility-related effects in women with PCOS.

Characteristics of the Included Evidence

The included publications varied substantially in design, clinical purpose, intervention type, and reported outcomes. Clinical guidelines provided broad recommendations regarding lifestyle management, metabolic assessment, metformin, inositol, and fertility treatment. Randomised trials provided direct comparative evidence for letrozole and berberine-based fertility treatment. Systematic

reviews and meta-analyses addressed metformin, inositol, and exenatide-based interventions, while the major clinical review provided a broader synthesis of fertility-treatment options in women with PCOS.

Table 1. Composition of the Evidence Included in the Scoping Review

Evidence type	Number of publications	Included references
International or professional clinical guidelines	2	3, 6
Randomised controlled trials	2	5, 12
Systematic reviews and meta-analyses	4	7, 8, 9, 16
Major clinical review	1	17
Total	9	3, 5–9, 12, 16, 17

The included sources were not mutually exclusive by intervention category because guidelines and broad clinical reviews addressed more than one treatment. Consequently, the number of sources contributing to individual intervention categories exceeded the total number of unique publications when counted across categories.

Lifestyle and Preconception Metabolic Management

Lifestyle management was consistently positioned as the foundation of PCOS care in the international guideline and the broader clinical review (3,17). The reported benefits primarily concerned improvement in body weight, metabolic health, menstrual cyclicity, and readiness for fertility treatment. Lifestyle optimisation was also recommended as part of preconception care because metabolic risk factors may influence treatment response and pregnancy-related health.

However, the audited evidence set did not include a dedicated randomised trial or systematic review specifically quantifying the effects of lifestyle intervention on clinical pregnancy or live birth. The fertility-related evidence for lifestyle management within the present evidence map was therefore mainly guideline-based and indirect. Variation in the intensity, duration, content, and adherence requirements of lifestyle interventions further limited comparative interpretation.

Metformin

Metformin was evaluated in one professional guideline, one systematic review and meta-analysis, the international PCOS guideline, and the major clinical review (3,6,16,17). Across these sources, metformin was associated with improvement in insulin sensitivity, glucose regulation, menstrual cyclicity, and ovulation in selected women with PCOS. Its potential reproductive benefit appeared most relevant among women with metabolic dysfunction, impaired glucose regulation, higher body mass index, or an indication for simultaneous metabolic management.

The evidence did not support metformin as a replacement for first-line ovulation induction when conception was the immediate treatment objective. Compared with fertility-directed ovulation-induction agents, metformin generally had a supportive rather than primary role. Live-birth findings were less consistent than findings for ovulation or metabolic improvement, and the magnitude of reproductive benefit appeared to vary according to body composition, baseline metabolic status, comparator treatment, and clinical context.

Letrozole as a Fertility-Treatment Benchmark

Letrozole was evaluated as the principal fertility-directed comparator rather than as an insulin-targeting intervention. The international guideline recommended letrozole as the preferred first-line pharmacological treatment for anovulatory infertility in women with PCOS when no other major infertility factors were present (3). The landmark randomised trial comparing letrozole with clomiphene citrate demonstrated superior ovulation and live-birth outcomes with letrozole (5).

These findings established letrozole as the intervention with the clearest direct evidence for ovulation induction and live birth within the included evidence set. However, letrozole did not directly address insulin resistance or metabolic risk. The evidence therefore supported a treatment model in which

metabolic assessment and optimisation accompanied, rather than replaced, effective fertility-directed ovulation induction.

Inositol Supplementation

Evidence for myo-inositol and D-chiro-inositol was derived principally from the international guideline and one systematic review and meta-analysis developed to inform its recommendations (3,7). Inositol supplementation was associated with possible improvements in insulin signalling, selected metabolic measures, menstrual regularity, and ovulation.

Interpretation was limited by substantial heterogeneity in inositol formulation, dose, myo-inositol-to-D-chiro-inositol ratio, treatment duration, participant characteristics, and comparator groups. Evidence was more frequently reported for metabolic measures and intermediate reproductive outcomes than for clinical pregnancy or live birth. The findings therefore supported inositol as a possible adjunctive option but did not establish equivalence or superiority to standard fertility treatment.

Glucagon-Like Peptide-1 Receptor Agonists

Evidence concerning glucagon-like peptide-1 receptor agonists was derived from two systematic reviews and meta-analyses comparing exenatide alone or in combination with metformin against metformin-based treatment (8,9). These reviews reported improvements in body weight, body mass index, indices of insulin resistance, and selected reproductive outcomes, including ovulation and pregnancy.

The reproductive evidence was primarily based on exenatide and could not be generalised directly to newer glucagon-like peptide-1 receptor agonists. Live-birth outcomes were inadequately reported, and the studies varied in treatment duration, comparator regimens, baseline body weight, and reproductive endpoints. The findings therefore indicated potential preconception metabolic and reproductive benefit but did not establish these agents as fertility medications.

Berberine

Berberine was represented by one randomised controlled trial comparing letrozole, berberine, and their combination in women with PCOS-related infertility (12). Although berberine was investigated for its potential metabolic effects, the addition of berberine to letrozole did not demonstrate a clear additional fecundity benefit over letrozole-based treatment.

This finding indicated that improvement in metabolic or biochemical measures could not be assumed to result in improved pregnancy or live-birth outcomes. Evidence for berberine was limited to a small number of eligible sources within the present map, preventing firm conclusions regarding its independent reproductive effectiveness or routine clinical use.

Comparative Evidence Across Intervention Categories

The included publications more frequently reported metabolic outcomes, menstrual regularity, and ovulation than definitive fertility outcomes. Letrozole had the most direct evidence for ovulation and live birth, while metformin, inositol, and exenatide-based interventions were supported more consistently by metabolic measures and intermediate reproductive outcomes. Clinical pregnancy was reported in several treatment categories, but live birth, miscarriage, time to pregnancy, and assisted reproductive outcomes were evaluated less consistently.

Table 2. Audited Evidence by Intervention Category

Intervention category	Included references	Evidence represented	Principal outcomes reported
Lifestyle and preconception management	3, 17	Guideline and clinical review	Metabolic health, weight management, menstrual function, preconception optimisation
Metformin	3, 6, 16, 17	Guidelines, systematic review/meta-analysis, and clinical review	Insulin sensitivity, menstrual regularity, ovulation, pregnancy, live birth

Intervention category	Included references	Evidence represented	Principal outcomes reported
Letrozole	3, 5, 17	Guideline, randomised trial, and clinical review	Ovulation, clinical pregnancy, live birth
Inositol	3, 7	Guideline and systematic review/meta-analysis	Metabolic measures, menstrual regularity, ovulation, pregnancy
GLP-1 receptor agonists, principally exenatide	8, 9	Systematic reviews and meta-analyses	Weight, BMI, insulin resistance, ovulation, pregnancy
Berberine	12	Randomised controlled trial	Ovulation and fecundity-related outcomes
N-acetylcysteine	None verified	—	—
Bariatric or metabolic surgery	None verified	—	—

Distribution of Reported Outcomes

Outcome reporting differed substantially between intervention categories. Metabolic improvement was addressed across most insulin-targeting therapies, whereas definitive reproductive outcomes were concentrated in the fertility-directed letrozole evidence. A reported outcome did not necessarily indicate a statistically significant or clinically meaningful treatment benefit.

Table 3. Outcome Coverage Across the Audited Evidence Base

Intervention	Metabolic outcomes	Menstrual regularity	Ovulation	Clinical pregnancy	Live birth	Miscarriage or pregnancy safety
Lifestyle management	Reported broadly	Reported	Reported	Limited direct evidence	Not adequately established	Limited
Metformin	Frequently reported	Reported	Reported	Evaluated with variable findings	Inconsistent or limited	Limited
Letrozole	Not a principal outcome	Not a principal outcome	Directly evaluated	Directly evaluated	Directly evaluated	Evaluated less consistently
Inositol	Frequently reported	Reported	Reported	Limited	Insufficient	Insufficient
Exenatide-based GLP-1 therapy	Frequently reported	Variably reported	Reported	Reported in selected studies	Insufficient	Insufficient
Berberine	Reported	Limited	Evaluated	Evaluated	Insufficient	Insufficient

Reported indicates that the outcome was assessed in the included evidence and does not by itself indicate treatment effectiveness. Limited indicates that few eligible sources or inconsistent findings were available. Insufficient indicates that the audited evidence did not permit a reliable conclusion.

Research Gaps

The principal limitation of the evidence map was the imbalance between surrogate or intermediate outcomes and definitive fertility outcomes. Insulin resistance indices, body weight, menstrual regularity, and ovulation were reported more frequently than live birth, miscarriage, pregnancy safety, or neonatal outcomes. Definitions of insulin resistance and metabolic dysfunction were also inconsistent, limiting comparison across populations and interventions.

Evidence for assisted reproductive treatment was inadequately represented in the audited reference set. Few sources provided consistent information on ovarian stimulation response, oocyte yield, embryo quality, ovarian hyperstimulation syndrome, clinical pregnancy after assisted reproduction, or live birth following in-vitro fertilisation or intracytoplasmic sperm injection. The evidence was also insufficient to determine whether treatment effects differed according to PCOS phenotype, ethnicity, body mass index, baseline insulin resistance, or glucose-tolerance status.

Table 4. Research Gaps Identified From the Audited Evidence

Research gap	Priority for future research
Limited live-birth reporting	High
Inconsistent definitions of insulin resistance	High
Limited miscarriage and pregnancy-safety data	High
Heterogeneous supplement formulations and doses	High
Limited evidence for newer GLP-1 receptor agonists	High
Inadequate ART-specific reporting	Moderate to high

Research gap	Priority for future research
Limited phenotype- and BMI-stratified analyses	Moderate
Underrepresentation of South Asian populations	Moderate
Limited long-term maternal and neonatal follow-up	High

Overall Evidence Map

The audited evidence supported a staged and individualised approach to fertility management in women with PCOS. Lifestyle and metabolic risk assessment formed the foundation of care, while letrozole remained the fertility-directed intervention with the clearest evidence for ovulation and live birth. Metformin had a supportive role in women with metabolic dysfunction, and inositol or exenatide-based therapy showed possible benefits that were more consistently demonstrated for metabolic or intermediate reproductive outcomes than for live birth. Evidence for berberine did not demonstrate a clear additional fecundity benefit when combined with letrozole.

Overall, the available evidence indicated that metabolic optimisation may improve the biological and clinical conditions associated with fertility, but it should not be interpreted as a substitute for established ovulation-induction treatment. The limited and inconsistent reporting of live birth, miscarriage, assisted reproductive outcomes, and pregnancy safety prevented definitive comparative conclusions for most emerging metabolic interventions.

DISCUSSION

This rapid scoping review mapped the available clinical evidence on metabolic and fertility-directed interventions relevant to insulin resistance and reproductive outcomes in women with polycystic ovary syndrome. The audited evidence comprised nine eligible publications and demonstrated an important distinction between interventions that improve the metabolic environment associated with reproductive dysfunction and treatments that directly induce ovulation. Lifestyle management was consistently recommended as the foundation of care, metformin had a supportive role in selected women with metabolic dysfunction, and letrozole provided the clearest direct evidence for ovulation and live birth. Inositol and exenatide-based glucagon-like peptide-1 receptor agonist therapy showed potential metabolic and intermediate reproductive benefits, whereas evidence for definitive fertility outcomes remained limited.

The findings were consistent with the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome, which recommends healthy lifestyle behaviours throughout the reproductive lifespan and identifies letrozole as the preferred first-line pharmacological treatment for anovulatory infertility when no other major infertility factors are present (3). Lifestyle management may improve insulin sensitivity, weight-related risk, androgen excess, menstrual cyclicity, and preconception health. These benefits are clinically important because obesity, impaired glucose regulation, and other metabolic abnormalities may influence fertility-treatment response and pregnancy-related risk. Nevertheless, the audited evidence set did not contain a dedicated systematic review or randomised trial that allowed the independent effect of lifestyle intervention on live birth to be quantified. Lifestyle management should therefore be described as foundational metabolic and preconception care rather than as a proven substitute for ovulation-induction treatment.

The evidence also reinforced the need to distinguish metabolic optimisation from direct fertility treatment. Letrozole inhibits aromatase and promotes follicular development through a temporary reduction in oestrogen-mediated hypothalamic feedback. In the landmark randomised trial by Legro et al., letrozole produced higher cumulative ovulation and live-birth rates than clomiphene citrate among women with polycystic ovary syndrome-related infertility (5). This evidence supports its position as the fertility-directed intervention with the most clinically meaningful reproductive outcomes in the present evidence map. However, letrozole does not directly improve insulin sensitivity, impaired glucose tolerance, or long-term cardiometabolic risk. It should therefore be used within a broader clinical

pathway that includes metabolic assessment and preconception optimisation rather than being classified as an insulin-targeting therapy.

Metformin remained the most extensively established insulin-sensitising medication represented in the included evidence. Its principal actions include suppression of hepatic glucose production and improvement of peripheral insulin sensitivity. These effects may reduce compensatory hyperinsulinaemia and indirectly improve androgen excess, menstrual cyclicity, and ovulation. Professional guidance and systematic-review evidence indicate that metformin may improve reproductive outcomes in selected women, particularly when metabolic dysfunction, impaired glucose regulation, or higher body mass index is present (6,13). However, its effectiveness as fertility monotherapy is generally inferior to that of established ovulation-induction agents. Metformin should therefore be considered an adjunct or an individually indicated metabolic treatment rather than the preferred first-line drug when immediate conception is the principal objective.

The clinical relevance of metformin may also vary according to patient phenotype and treatment context. Women with more pronounced insulin resistance or glucose intolerance may derive greater metabolic benefit than metabolically lower-risk patients, while reproductive outcomes may depend on whether metformin is used alone, combined with ovulation induction, or administered in an assisted reproductive setting. The audited evidence did not permit reliable subgroup comparisons according to phenotype, body mass index, ethnicity, or baseline insulin resistance. Consequently, broad statements that metformin improves fertility in all women with polycystic ovary syndrome would exceed the available evidence.

Inositol supplementation was associated with possible improvements in insulin signalling, metabolic parameters, menstrual regularity, and ovulation. The systematic review informing the international guideline nevertheless identified considerable heterogeneity in formulation, dose, myo-inositol-to-D-chiro-inositol ratio, treatment duration, comparator selection, and study quality (7). These differences limit comparison across studies and make it difficult to identify an optimal formulation or treatment regimen. Furthermore, improvements in menstrual cyclicity or ovulation do not necessarily establish benefit for clinical pregnancy or live birth. Inositol may therefore be considered a possible adjunct for selected patients, but the current evidence does not justify its use as an alternative to established ovulation-induction treatment.

Exenatide-based glucagon-like peptide-1 receptor agonist therapy represented an emerging preconception metabolic strategy. The included meta-analyses reported improvements in body weight, body mass index, insulin-resistance indices, ovulation, and selected pregnancy outcomes compared with metformin-based treatment (8,9). These findings support the hypothesis that substantial metabolic improvement before conception may enhance reproductive function in some women. However, several limitations restrict clinical interpretation. The reproductive evidence was derived principally from exenatide studies, treatment protocols differed, live-birth reporting was inadequate, and pregnancy-safety outcomes were not sufficiently evaluated. Evidence from exenatide cannot automatically be extrapolated to liraglutide, semaglutide, tirzepatide, or other newer agents.

Glucagon-like peptide-1 receptor agonists should consequently be regarded as preconception metabolic therapies rather than fertility medications. Their use requires individualised counselling regarding contraception, treatment discontinuation before planned conception, and avoidance during pregnancy. Apparent improvement in pregnancy rates may be mediated by weight reduction, improved insulin sensitivity, restoration of ovulation, or a combination of these mechanisms. Trials designed specifically around live birth and pregnancy safety are required before these agents can be incorporated into routine fertility pathways for polycystic ovary syndrome.

Berberine was supported by substantially less reproductive evidence. The eligible randomised trial comparing letrozole, berberine, and their combination did not demonstrate a clear additional fecundity

advantage from adding berberine to letrozole (10). This finding is clinically important because improvement in glucose, lipid, or other biochemical markers should not be interpreted automatically as improvement in fertility. Evidence concerning berberine was also limited by uncertainty regarding product standardisation, dose consistency, drug interactions, and safety around conception. Its routine use for fertility enhancement cannot therefore be recommended from the current evidence map.

A major finding of the review was the imbalance between intermediate and definitive outcomes. Most metabolic interventions were evaluated using body weight, fasting insulin, insulin-resistance indices, androgen concentrations, menstrual regularity, or ovulation. These outcomes are clinically informative but do not directly establish successful fertility treatment. Clinical pregnancy, miscarriage, time to pregnancy, healthy live birth, maternal complications, and neonatal outcomes are more meaningful endpoints but were reported less frequently. Future trials should prioritise live birth as the principal reproductive outcome and should report pregnancy loss and maternal–neonatal safety systematically.

The literature was also characterised by inconsistent definitions of insulin resistance. Studies used fasting insulin, homeostatic model assessment indices, oral glucose tolerance testing, body mass index, or other indirect indicators. This variation limits comparison between studies and may result in clinically heterogeneous populations being grouped together. Future research should use prespecified and standardised metabolic definitions and should stratify findings by body mass index, glucose-tolerance status, polycystic ovary syndrome phenotype, ethnicity, and baseline severity of insulin resistance.

Assisted reproductive outcomes were insufficiently represented in the audited evidence. The available sources did not provide consistent data concerning gonadotropin requirement, ovarian response, oocyte yield, embryo quality, ovarian hyperstimulation syndrome, implantation, clinical pregnancy, miscarriage, or live birth following in-vitro fertilisation or intracytoplasmic sperm injection. This limits conclusions regarding whether metabolic treatment improves assisted reproductive outcomes beyond its effects on weight, glucose metabolism, or ovulation. Future studies should distinguish spontaneous conception, pharmacological ovulation induction, and assisted reproductive treatment as separate clinical contexts.

The review had several strengths. It applied a clinically focused Population–Concept–Context framework, distinguished insulin-targeting therapies from fertility-directed treatment, separated intermediate reproductive outcomes from definitive fertility endpoints, and audited the included evidence against explicit eligibility criteria. The revised synthesis also avoided assigning formal evidence-certainty grades in the absence of a structured risk-of-bias assessment.

Several limitations must nevertheless be recognised. The search was rapid and targeted rather than exhaustive and was limited principally to PubMed/MEDLINE and Google Scholar, supplemented by guideline repositories and reference-list screening. Relevant studies indexed in other bibliographic databases may therefore have been missed. The small and heterogeneous evidence base prevented quantitative synthesis and direct comparison between interventions. A formal risk-of-bias assessment was not conducted, and the conclusions should consequently be interpreted as an evidence map rather than a comparative-effectiveness hierarchy. The inclusion of guidelines and systematic reviews also introduced potential overlap in the primary studies represented across evidence sources. Finally, limited evidence from South Asian and other underrepresented populations restricted the regional generalisability of the findings.

From a clinical perspective, the findings support an individualised and staged treatment pathway. Women with polycystic ovary syndrome-related infertility should undergo simultaneous reproductive and metabolic assessment, including evaluation of ovulatory dysfunction, other infertility factors, body weight, glucose regulation, cardiovascular risk, and preconception health. Lifestyle management should remain foundational, letrozole should be used as the preferred first-line ovulation-induction treatment when clinically appropriate, and metformin should be considered selectively for women with relevant

metabolic indications. Inositol and glucagon-like peptide-1 receptor agonists may have adjunctive or preconception roles, but their use should reflect the limitations of the fertility-specific evidence. Berberine should not be assumed to improve fecundity on the basis of metabolic effects alone.

CONCLUSION

Insulin resistance and related metabolic abnormalities are important components of reproductive dysfunction in many women with polycystic ovary syndrome, but metabolic improvement and direct fertility treatment are not interchangeable. Lifestyle management remains the foundation of metabolic and preconception care, while letrozole provides the clearest evidence for first-line ovulation induction and live birth. Metformin has a supportive role in selected women with impaired glucose regulation or increased metabolic risk. Inositol and exenatide-based glucagon-like peptide-1 receptor agonist therapy show possible benefits for metabolic health and intermediate reproductive outcomes, but evidence for live birth, miscarriage reduction, assisted reproduction, and pregnancy safety remains insufficient. Berberine has not demonstrated a clear additional fecundity benefit when added to letrozole. Future research should use standardised definitions of insulin resistance, stratify findings by clinical phenotype and metabolic risk, and prioritise healthy live birth, pregnancy loss, assisted reproductive outcomes, and long-term maternal and neonatal safety.

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