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PHARMACOLOGICAL MODULATION OF THE METABOLIC–REPRODUCTIVE AXIS IN POLYCYSTIC OVARY SYNDROME: A PHENOTYPE-ORIENTED REVIEW OF INSULIN SENSITIZATION, WEIGHT MANAGEMENT, AND OVULATION INDUCTION

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ABSTRACT

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine-metabolic disorder in which insulin resistance, hyperinsulinemia, hyperandrogenism, adiposity, dyslipidemia, abnormal folliculogenesis, and anovulation interact through multiple pathophysiological pathways. This heterogeneity limits the effectiveness of a uniform pharmacological approach and supports treatment selection according to the dominant metabolic and reproductive phenotype.

Objective: To critically review contemporary pharmacological strategies targeting the metabolic–reproductive axis in PCOS and to evaluate the roles of metformin, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), anti-obesity agents, inositols, letrozole, clomiphene citrate, and gonadotropin-based therapy in relation to insulin resistance, androgen excess, ovulatory dysfunction, and fertility outcomes.

Materials and Methods: A focused narrative review of contemporary international guidelines, systematic reviews, meta-analyses, randomized controlled trials, and major mechanistic studies was undertaken. Priority was given to evidence published or updated between 2023 and 2026, together with selected foundational studies describing the metabolic and reproductive pathophysiology of PCOS. The analysis focused on drug mechanism, metabolic effects, reproductive efficacy, safety, and clinical positioning according to PCOS phenotype.

Results: Metformin remains the best-established insulin-sensitizing pharmacological option for metabolic manifestations of PCOS and produces modest improvements in insulin resistance, fasting glucose, body mass index, and selected reproductive outcomes, particularly when metabolic dysfunction is prominent. Letrozole is the preferred first-line pharmacological agent for ovulation induction in women with anovulatory infertility and no additional infertility factors. Clomiphene citrate remains an effective alternative, while its combination with metformin may be advantageous in selected women. GLP-1 RAs demonstrate clinically relevant weight reduction in women with PCOS and overweight or obesity, but evidence for direct improvement in ovulation, pregnancy, and live birth remains insufficient. Inositol may improve selected metabolic parameters, but current evidence does not support its use as an established fertility therapy. Gonadotropins retain an important second-line role when oral ovulation-induction therapy is unsuccessful.

Conclusion: Pharmacotherapy of PCOS should be based on metabolic–reproductive phenotyping rather than on ovarian morphology alone. Metformin is most appropriately positioned as a

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metabolic modifier, letrozole as first-line ovulation induction, and GLP-1 RAs as emerging agents for weight-centred metabolic management in appropriately selected women. Future trials should determine whether correction of insulin resistance before conception translates into sustained improvements in ovulation, pregnancy, live birth, and long-term maternal metabolic outcomes.

Keywords: polycystic ovary syndrome, insulin resistance, metformin, GLP-1 receptor agonists, letrozole, clomiphene citrate, obesity, hyperandrogenism, ovulation, infertility, pharmacotherapy.

INTRODUCTION

Polycystic ovary syndrome is among the most common endocrine disorders affecting women of reproductive age and is characterized by a highly variable combination of ovulatory dysfunction, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology. Its clinical expression extends far beyond reproductive dysfunction because a substantial proportion of affected women also demonstrate insulin resistance, compensatory hyperinsulinemia, obesity or central adiposity, dyslipidemia, impaired glucose regulation, and increased long-term cardiometabolic risk [1–4]. The close interaction between metabolic and reproductive disturbances is central to contemporary understanding of PCOS. Insulin resistance is not merely a metabolic comorbidity but may participate directly in ovarian dysfunction. Hyperinsulinemia can stimulate ovarian theca-cell androgen production, enhance gonadotropin-dependent steroidogenesis, and reduce hepatic synthesis of sex hormone-binding globulin, thereby increasing the biologically active fraction of circulating androgens. The resulting endocrine environment may interfere with follicular selection, contribute to persistence of multiple small antral follicles, and promote chronic oligo-anovulation [4–6].

Adiposity can further amplify this process. Central fat accumulation is associated with altered adipokine signaling, chronic low-grade inflammation, increased free-fatty-acid flux, oxidative stress, and impaired insulin signaling. Consequently, women with apparently similar ovarian morphology may have substantially different metabolic risk profiles and different responses to pharmacological treatment. This heterogeneity argues against a single universal treatment algorithm based solely on the presence of polycystic ovaries.

The pharmacological management of PCOS therefore has several distinct goals. In a woman whose primary concern is metabolic dysfunction, the therapeutic priority may be improving insulin sensitivity, weight-related risk, or glucose metabolism. In a woman seeking pregnancy, restoration of ovulation and achievement of live birth become the central outcomes. In another patient, menstrual irregularity, hyperandrogenism, or long-term endometrial protection may dominate clinical decision-making. This distinction is particularly important for drug research because several agents used in PCOS act on different components of the syndrome. Metformin primarily modifies metabolic physiology. Letrozole and clomiphene citrate directly facilitate ovulation induction. GLP-1 receptor agonists predominantly reduce weight and improve metabolic parameters. Anti-androgens address hyperandrogenic manifestations but are inappropriate when pregnancy is possible without reliable contraception. Inositol compounds have insulin-sensitizing potential, yet their clinically meaningful benefits remain uncertain. Recent evidence has

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further strengthened the relevance of the metabolic-reproductive axis. A 2026 analysis of women with PCOS undergoing ovulation induction demonstrated that greater preconception insulin resistance was associated with less favorable ovulatory, pregnancy, and live-birth outcomes, suggesting that metabolic status before fertility therapy may have prognostic importance [7].

The purpose of the present review is therefore to synthesize current pharmacological evidence through a phenotype-oriented framework and to clarify how insulin sensitization, weight-management therapy, and ovulation-induction drugs can be positioned within an integrated treatment strategy for women with PCOS.

MATERIALS AND METHODS

The present study was designed as a focused narrative review. The conceptual framework was derived from contemporary evidence describing the relationships among insulin resistance, dyslipidemia, hyperandrogenism, anti-Müllerian hormone, ovarian morphology, follicular development, and ovulation in PCOS. Priority was given to the 2023 International Evidence-based Guideline for the Assessment and Management of PCOS, recent systematic reviews and meta-analyses evaluating metformin, anti-obesity medications, GLP-1 receptor agonists and inositols, the updated Cochrane evidence on aromatase inhibitors for ovulation induction, and recent reproductive-outcome studies. The pharmacological interventions were evaluated according to five principal domains: primary mechanism of action; effects on weight and glucose-insulin metabolism; effects on androgenic and hormonal parameters; influence on ovulation and fertility; and clinically relevant safety considerations. The review was narrative rather than systematic; therefore, no pooled meta-analysis was performed and no new effect estimates were generated. Quantitative findings mentioned in the text were derived from published studies rather than calculated from an original patient dataset.

RESULTS

PCOS encompasses several overlapping phenotypes. Some women have marked insulin resistance, abdominal obesity, hyperinsulinemia, and dyslipidemia, while others present predominantly with hyperandrogenism and ovulatory dysfunction despite normal body mass index. Pharmacological selection should therefore address the dominant clinical objective rather than simply the presence of PCOS. The metabolic evaluation may include body mass index, waist circumference, glycemic status, lipid profile, and, in a research context, fasting insulin and HOMA-IR. Although HOMA-IR is useful for research and metabolic phenotyping, it should not be interpreted as a universally standardized diagnostic criterion because assay methods and population-specific thresholds differ substantially. This distinction is important when evaluating therapeutic studies. A drug that reduces HOMA-IR may be biologically relevant without necessarily improving live-birth rates, while an ovulation-inducing medication may substantially improve fertility despite having little effect on insulin resistance. Consequently, metabolic and reproductive endpoints should be evaluated separately and then integrated clinically.

Metformin remains the most extensively studied insulin-sensitizing drug in PCOS. Its principal actions include inhibition of hepatic gluconeogenesis, improvement in peripheral insulin sensitivity, and reduction in compensatory hyperinsulinemia. These

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changes may indirectly reduce ovarian androgen production and improve the endocrine environment associated with follicular development. A contemporary systematic review and meta-analysis conducted to inform the international PCOS guideline found that metformin, compared with placebo, produced modest but significant improvements in BMI, HOMA-IR, and fasting glucose, while gastrointestinal adverse effects occurred more frequently [8]. These data reinforce the positioning of metformin primarily as a treatment for metabolic manifestations rather than as a universal reproductive medication. Current recommendations particularly support consideration of metformin in adults with PCOS and increased metabolic risk, especially in those with higher body mass index. It may also be considered in selected women with lower BMI, although the evidence is less robust [1]. The reproductive effects of metformin are more complex. Lower insulin concentrations may reduce hyperandrogenic stimulation of the ovary and may improve menstrual cyclicity and spontaneous ovulation in some women. Nevertheless, metformin is less effective as a dedicated first-line ovulation-induction agent than letrozole. In women with anovulatory infertility and no other infertility factors, metformin may improve pregnancy-related outcomes compared with no pharmacological treatment, but patients should be informed that more effective ovulation-induction agents are available [1]. Metformin may also have a role as adjunctive therapy. Combination with clomiphene citrate can improve ovulation and clinical pregnancy in selected women compared with clomiphene alone. Its use in assisted reproduction has additionally been investigated for reducing ovarian hyperstimulation risk in selected stimulation protocols. The tolerability of metformin is clinically relevant. Gastrointestinal symptoms such as nausea, abdominal discomfort, and diarrhea are the most frequent adverse effects. Gradual dose escalation and extended-release formulations may improve tolerability and adherence. Long-term treatment should be periodically reviewed according to metabolic indication and therapeutic response.

The increasing recognition of obesity as an important modifier of PCOS has stimulated interest in anti-obesity pharmacotherapy. GLP-1 receptor agonists such as liraglutide and semaglutide reduce appetite, delay gastric emptying, improve glycemic regulation, and produce clinically meaningful weight loss in general obesity populations. In PCOS, these agents are particularly attractive because weight loss may indirectly improve insulin resistance, androgen excess, menstrual function, and fertility potential. However, their metabolic benefits should not automatically be interpreted as proven reproductive benefits. A systematic review used to inform the 2023 international guideline concluded that available evidence on pharmacological anti-obesity therapy in PCOS remained limited, although several agents demonstrated favorable anthropometric effects [9]. More recently, a 2026 systematic review and meta-analysis of randomized controlled trials reported that GLP-1 receptor agonists produced modest short-term reductions in BMI in women with PCOS and overweight or obesity, while the evidence remained insufficient for firm conclusions regarding insulin-related outcomes, menstrual regularity, hirsutism, or other reproductive endpoints [10]. Thus, GLP-1 receptor agonists are currently better viewed as weight-management and metabolic-risk therapies rather than established fertility medications. International guidance allows their consideration for higher weight in adults with PCOS according to general obesity-treatment principles. An important limitation is reproductive safety. Women who can become pregnant require effective contraception

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during GLP-1 receptor agonist treatment because pregnancy safety data are insufficient. If pregnancy is being actively pursued, treatment planning must include appropriate discontinuation according to the relevant product information and specialist recommendations. Another consideration is weight regain after treatment discontinuation. PCOS is a chronic metabolic disorder, and pharmacological weight management may require long-term strategies. Shared decision-making should therefore address expected benefits, gastrointestinal adverse effects, cost, treatment duration, and the possibility of weight recurrence after drug withdrawal.

Letrozole represents a fundamentally different pharmacological strategy because its primary therapeutic target is ovulation rather than insulin resistance. By reversibly inhibiting aromatase, letrozole reduces estrogen synthesis, temporarily decreases estrogen-mediated hypothalamic-pituitary negative feedback, and promotes endogenous follicle-stimulating hormone secretion. Contemporary international guidance recommends letrozole as first-line pharmacological treatment for anovulatory infertility in women with PCOS when no other infertility factor is present [1]. Updated Cochrane evidence supports its efficacy in improving ovulation and fertility-related outcomes compared with older oral ovulation-induction approaches [11]. The distinction between letrozole and metformin illustrates the importance of phenotype-oriented treatment. A woman with marked insulin resistance but no immediate fertility goal may benefit primarily from metabolic intervention. A metabolically healthy woman with persistent anovulatory infertility requires direct ovulation induction. A woman with both significant insulin resistance and anovulation may require sequential or combined management of both domains. Letrozole is used off-label for ovulation induction in some jurisdictions, and pregnancy must be excluded before treatment. Clinical protocols vary according to starting dose, treatment duration, stair-step regimens, and response monitoring.

Clomiphene citrate is a selective estrogen receptor modulator that has historically served as a major oral ovulation-induction treatment in PCOS. Although letrozole is now generally preferred, clomiphene remains clinically useful where letrozole is unavailable, contraindicated, or unsuccessful. Clomiphene blocks estrogen-mediated negative feedback at hypothalamic estrogen receptors, resulting in increased gonadotropin secretion and follicular recruitment. Unlike letrozole, however, its anti-estrogenic activity may adversely influence cervical mucus and endometrial development in some patients. Combination of clomiphene citrate with metformin may be particularly relevant in women with a metabolic phenotype or previous inadequate response to clomiphene alone. Current guideline evidence indicates that clomiphene combined with metformin may improve ovulation and clinical pregnancy compared with clomiphene alone, while combination therapy can also provide advantages over metformin monotherapy for fertility outcomes [1]. Because clomiphene may recruit more than one dominant follicle, ultrasound monitoring may be appropriate to reduce the risk associated with multiple follicular development and multiple pregnancy.

Exogenous gonadotropins occupy an important second-line position in women with PCOS who do not respond adequately to oral ovulation-induction medications. Direct administration of follicle-stimulating hormone can promote follicular development independently of endogenous gonadotropin modulation. The major clinical challenge is the

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heightened ovarian sensitivity typical of PCOS. Excessive follicular recruitment may lead to multiple pregnancy or ovarian hyperstimulation syndrome. Consequently, low-dose step-up protocols, careful ultrasound monitoring, and individualized dose adjustment are essential. In women progressing to IVF or ICSI, PCOS-associated high ovarian reserve requires specific strategies to minimize ovarian hyperstimulation. GnRH antagonist protocols and agonist triggering in appropriate settings permit effective risk reduction.

Myo-inositol and D-chiro-inositol have gained popularity because of their proposed roles in intracellular insulin signaling. Their theoretical relevance is attractive in PCOS, where impaired insulin signaling is common. However, biological plausibility does not necessarily translate into clinically meaningful reproductive benefit. A 2024 systematic review and meta-analysis conducted to inform the international PCOS guideline concluded that evidence for inositol remained limited and uncertain, particularly for clinically important outcomes such as ovulation, pregnancy, and live birth [12]. Current guidance suggests that inositol may be considered according to individual preferences, with recognition of limited harms and possible metabolic benefits, but metformin has stronger evidence for central adiposity and selected metabolic manifestations. In women with PCOS-related infertility, inositol remains experimental rather than an established fertility therapy.

Variability in supplement composition, myo-inositol/D-chiro-inositol ratios, dose, manufacturing quality, and regulatory oversight further complicates interpretation of available studies.

Pharmacological strategy	Principal target	Main expected benefit	Reproductive role	Important limitation
Metformin	Insulin resistance, hepatic glucose production	Improved metabolic profile; modest effects on weight and cycles	Adjunctive or selected fertility role	GI adverse effects; not the most effective primary ovulation agent
GLP-1 receptor agonists	Appetite, body weight, glucose regulation	Weight reduction and metabolic improvement	Reproductive benefit not yet established	Pregnancy safety limitations; contraception required
Letrozole	Aromatase inhibition / follicular recruitment	Ovulation induction	Preferred first-line therapy for anovulatory infertility	Off-label in some countries
Clomiphene citrate	Estrogen receptor modulation	Ovulation induction	Alternative oral fertility therapy	Multiple pregnancy risk; anti-estrogenic effects
Metformin +	Metabolic +	Combined	Useful in	Increased

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clomiphene	ovulatory pathways	metabolic and ovulation support	selected patients	treatment complexity
Gonadotropins	Direct ovarian stimulation	Follicular growth and ovulation	Second-line fertility therapy	OHSS and multiple follicular development
Inositol	Insulin signaling pathways	Possible modest metabolic benefit	Experimental for infertility	Low-certainty evidence and variable product quality

DISCUSSION

The pharmacological management of PCOS has evolved from a relatively uniform approach toward a phenotype-oriented model in which treatment is selected according to the dominant metabolic, endocrine, and reproductive abnormalities. This development is clinically important because PCOS is not a single pathological state but a syndrome encompassing multiple combinations of insulin resistance, obesity, androgen excess, altered follicular dynamics, and infertility.

The original metabolic-reproductive model of PCOS provides an important framework for drug selection. Hyperinsulinemia can potentiate ovarian androgen production, while androgen excess and disrupted granulosa-cell function may contribute to arrested follicular development. AMH concentrations and antral follicle number reflect aspects of follicular excess but do not independently determine which pharmacological therapy should be used. The distinction between biomarkers and therapeutic targets is particularly important. HOMA-IR may identify an insulin-resistant phenotype in research, yet it is not a universal clinical diagnostic threshold. Likewise, elevated AMH can support characterization of ovarian morphology but does not establish the need for insulin-sensitizing treatment. Pharmacotherapy should be driven by clinically relevant metabolic risk and reproductive goals rather than by an isolated laboratory value. Metformin provides the clearest example. Evidence consistently supports modest beneficial effects on glucose-insulin metabolism, adiposity-related parameters, and selected endocrine features. The 2023 meta-analysis demonstrated reductions in BMI, HOMA-IR, and fasting glucose compared with placebo, confirming a genuine but moderate metabolic effect [8]. Metformin is therefore most appropriately positioned as a metabolic modifier rather than as an obligatory treatment for every woman with PCOS.

In contrast, letrozole directly addresses anovulatory infertility. Its position as first-line pharmacological ovulation induction illustrates that correction of insulin resistance is not a prerequisite for successful fertility treatment in all women. Nevertheless, metabolic optimization before conception remains important because obesity and insulin resistance may influence fertility-treatment success and pregnancy risk.

The emerging 2026 evidence regarding preconception insulin resistance strengthens this connection. In a secondary analysis of 746 women with PCOS undergoing ovulation induction, progressively higher HOMA-IR was associated with lower ovulation, clinical

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pregnancy, and live-birth rates and a greater risk of gestational diabetes [7]. Although observational associations cannot prove that pharmacologically lowering HOMA-IR will necessarily improve live birth, these data suggest that metabolic phenotype is clinically relevant to fertility prognosis. The therapeutic role of GLP-1 receptor agonists represents one of the most important evolving areas. Their ability to reduce body weight makes them attractive in PCOS with overweight or obesity, especially where lifestyle intervention alone has been insufficient. However, enthusiasm should be tempered by the current evidence base. The 2026 systematic review found short-term weight benefit but insufficient evidence for robust reproductive conclusions [10]. At present, using GLP-1 receptor agonists specifically to improve fertility would therefore exceed the strength of available evidence. This distinction is especially important because weight reduction may indirectly restore more regular cycles in some women, potentially increasing the possibility of spontaneous conception during a period when pregnancy exposure to GLP-1 receptor agonists is undesirable. Effective contraception and explicit pregnancy planning are therefore integral to safe prescribing. The role of inositol also demonstrates the need to distinguish widespread use from evidence-based pharmacology. Inositol preparations are extensively marketed to women with PCOS, often with claims concerning insulin sensitivity, ovulation, and fertility. Yet contemporary systematic evidence remains uncertain, and product standardization is limited. In a drug-research context, future trials require standardized formulations, clearly defined doses, validated metabolic endpoints, and clinically meaningful reproductive outcomes.

Another important issue is pregnancy itself. Women with PCOS have increased risks of miscarriage, gestational diabetes, hypertensive pregnancy disorders, and several adverse birth outcomes [13,14]. Preconception pharmacological strategies therefore need to be evaluated not only according to ovulation and conception but also according to maternal and neonatal outcomes. Metformin treatment during pregnancy illustrates this uncertainty. Although metformin is extensively used before conception, current international recommendations do not support routine continuation in all pregnant women with PCOS solely to prevent gestational diabetes or other complications. Emerging studies examining preconception and first-trimester use may modify future recommendations, but evidence remains insufficient to justify indiscriminate continuation. Future drug research should therefore move beyond the simplistic question of whether a medication “works in PCOS.” Trials should stratify participants according to insulin resistance, BMI, waist circumference, androgen phenotype, ovulatory status, AMH or follicle number where relevant, and current reproductive intention. The same drug may produce different clinically meaningful benefits in different phenotypes.

An insulin-resistant woman with central obesity and no immediate pregnancy goal may appropriately receive metabolic pharmacotherapy. A woman with anovulatory infertility and a relatively favorable metabolic profile may primarily require letrozole. A woman with both significant obesity and infertility may benefit from staged treatment in which metabolic risk is addressed before fertility induction. This sequencing should be evaluated prospectively rather than assumed. The concept of pharmacological sequencing may become particularly important with increasing availability of potent anti-obesity agents. Research is needed to define whether preconception weight reduction with GLP-1

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receptor agonists produces durable improvements in ovulatory function after treatment discontinuation and whether these improvements translate into higher live-birth rates without unacceptable delay in fertility treatment, particularly in older reproductive-age women.

The central limitation of current PCOS pharmacotherapy evidence is heterogeneity. Diagnostic criteria, obesity prevalence, insulin-resistance definitions, ethnicity, baseline fertility status, drug doses, duration of therapy, and outcome selection vary considerably across trials. Metabolic surrogate markers such as HOMA-IR cannot substitute for patient-important outcomes such as ovulation, clinical pregnancy, live birth, gestational diabetes, and long-term metabolic health. A future precision-pharmacology framework for PCOS should integrate metabolic phenotype, reproductive objective, age, adiposity, androgen status, glucose tolerance, previous response to therapy, and safety considerations. Such an approach is more consistent with the biological complexity of PCOS than treatment algorithms based on ovarian morphology alone.

CONCLUSION

PCOS requires a multidimensional pharmacological strategy because metabolic dysfunction and reproductive impairment arise from interacting but not identical pathways. Insulin resistance, central adiposity, dyslipidemia, hyperandrogenism, altered folliculogenesis, and anovulation should be evaluated as interconnected components of the syndrome rather than as isolated abnormalities.

Metformin remains the principal established insulin-sensitizing pharmacological therapy and is most strongly supported for metabolic indications. Its reproductive benefits are clinically relevant in selected women but do not replace dedicated ovulation-induction therapy. Letrozole should be regarded as the preferred first-line pharmacological approach for anovulatory infertility in women with PCOS without other infertility factors. Clomiphene citrate and metformin–clomiphene combinations remain important alternatives, while gonadotropins provide effective second-line therapy under appropriate monitoring. GLP-1 receptor agonists represent a promising development for women with PCOS and excess weight, with increasingly consistent evidence for weight reduction. Their direct effects on ovulation, pregnancy, and live birth, however, require further high-quality investigation, and pregnancy planning is essential because reproductive safety data remain limited.

Inositol should be considered an adjunctive or experimental option rather than an evidence-equivalent alternative to established pharmacological therapies. The most promising future direction is phenotype-oriented pharmacotherapy in which metabolic characteristics and reproductive goals jointly determine drug selection and treatment sequence. Prospective randomized studies should determine whether targeted preconception correction of insulin resistance and obesity improves not only surrogate metabolic markers but also ovulation, clinical pregnancy, live birth, pregnancy safety, and long-term maternal health.

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