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Intervenciones farmacológicas para desenlaces reproductivos, hormonales y metabólicos en el síndrome de ovario poliquístico

Pharmacological Interventions for Reproductive, Hormonal, and Metabolic Outcomes in Polycystic Ovary Syndrome

Acceso abierto

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Farfan-Cano Galo Guillermo,[a], gg.farfan@alumnos.urjc.es

a. King Juan Carlos University, Spain; Guayaquil University, Ecuador; Northern Guayaquil General Hospital Los Ceibos, Ecuador; University of Guayaquil.

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Correspondencia: Farfán Cano Galo Guillermo **Email:** gg.farfan@alumnos.urjc.es

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Resumen

Introducción: El síndrome de ovario poliquístico (SOP) se asocia a importantes problemas reproductivos y metabólicos. Métodos: Se llevó a cabo una revisión sistemática de los ensayos controlados aleatorios (ECA) publicados entre 2019 y 2024 que evaluaban nuevas intervenciones farmacológicas en el SOP. Resultados: Siete estudios cumplieron los criterios de inclusión. Las intervenciones que incluyeron letrozol, fezolinetant, hormona del crecimiento, exenatida y terapias combinadas demostraron mejoras en la ovulación, la regulación hormonal y los parámetros metabólicos, con efectos adversos mínimos. Conclusión: Estas alternativas farmacológicas se muestran prometedoras para el tratamiento personalizado del SOP y subrayan la necesidad de metodologías estandarizadas en futuras investigaciones. Se requieren más estudios para validar estos hallazgos y optimizar los protocolos de tratamiento.

Palabras Clave: Síndrome de ovario poliquístico, Ensayo clínico, Revisión sistemática, Medicina de precisión, Resistencia a la insulina, Enfermedades del sistema endocrino, Síndrome metabólico.

Conflict of Interest Statement

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Abstract:

Introduction: Polycystic ovary syndrome (PCOS) is associated with significant reproductive and metabolic challenges. Methods: A systematic review of randomized controlled trials (RCTs) published between 2019 and 2024 evaluating novel pharmacological interventions in PCOS was conducted. Results: Seven studies met inclusion criteria. Interventions including letrozole, fezolinetant, growth hormone, exenatide, and combination therapies demonstrated improvements in ovulation, hormonal regulation, and metabolic parameters, with minimal adverse effects. Conclusion: These pharmacological alternatives show promise for personalized PCOS management and underscore the need for standardized methodologies in future research. Further studies are required to validate these findings and optimize treatment protocols.

Keywords: Polycystic Ovary Syndrome, Clinical Trial, Systematic Review, Precision Medicine, Insulin Resistance, Endocrine System Diseases, Metabolic Syndrome.

Introducción

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women of reproductive age, affecting approximately 10% of the global population (1–3). PCOS is the most prevalent endocrine disorder in reproductive-aged women (11–13% prevalence) and a primary cause of anovulatory infertility. It imposes a significant U.S. economic burden, with direct medical costs for diagnosis, management, and related comorbidities (like type 2 diabetes and mental health disorders) exceeding $4–8 billion annually (4–10). PCOS is characterized by hyperandrogenism, oligoovulation or anovulation, and polycystic ovarian morphology, as defined by the Rotterdam criteria (11). These reproductive abnormalities frequently coexist with metabolic disturbances, including insulin resistance and dyslipidemia, increasing the risk of type 2 diabetes and cardiovascular disease (12–14).

Although conventional therapies, such as clomiphene citrate and metformin, remain standard, many patients do not achieve adequate symptom control, highlighting the need for innovative pharmacological strategies. Recent advancements, including letrozole, fezolinetant, growth hormone, exenatide, and combination therapies, target both reproductive and metabolic outcomes (12,15–17). This systematic review evaluates the efficacy and safety of these novel interventions in improving ovulation, hormonal balance, and metabolic health, aiming to inform personalized treatment approaches and identify gaps for future research.

Definitions and Conceptual Framework

PCOS is currently recognized as a heterogeneous endocrine–metabolic disorder characterized by reproductive dysfunction, hyperandrogenism, and metabolic abnormalities with variable phenotypic expression. The most widely accepted diagnostic framework remains the Rotterdam criteria, which require the presence of at least two of the following features: oligo-ovulation or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology, after exclusion of related endocrine disorders. However, contemporary research increasingly conceptualizes PCOS as a multisystem disorder involving neuroendocrine dysregulation, insulin resistance, adipose tissue dysfunction, and chronic low-grade inflammation, rather than solely an ovarian disease. (3,6–10,18–20)

Mechanistic reviews emphasize that PCOS should be considered a metabolic-reproductive spectrum in which endocrine abnormalities are closely linked to insulin signaling, inflammatory pathways, and ovarian folliculogenesis. These interactions explain the marked heterogeneity observed across phenotypes and the variability in treatment response. Emerging models describe PCOS as a disorder of hypothalamic-pituitary-ovarian axis dysregulation driven by hyperinsulinemia and androgen excess, resulting in impaired follicular maturation, altered gonadotropin secretion, and ovarian stromal hypertrophy. (21–30)

Advances in molecular endocrinology have demonstrated that hyperinsulinemia enhances theca-cell androgen production and reduces hepatic sex hormone-binding globulin synthesis, thereby increasing circulating free testosterone. This hormonal environment contributes to follicular arrest, anovulation, and endometrial dysfunction. Concurrently, metabolic disturbances such as dyslipidemia, visceral adiposity,

and mitochondrial dysfunction exacerbate reproductive abnormalities, reinforcing the bidirectional relationship between metabolic and reproductive components of PCOS. (31–36)

Systematic analyses further confirm that PCOS is associated with insulin resistance in both obese and lean phenotypes, although severity varies. Insulin resistance contributes to increased ovarian androgen synthesis, impaired folliculogenesis, and ovulatory dysfunction, while hyperandrogenism promotes visceral adiposity and metabolic dysregulation, establishing a self-perpetuating pathophysiologic cycle. This integrative model supports therapeutic strategies targeting both endocrine and metabolic pathways. (37–45)

Pathophysiology

The pathophysiology of PCOS is multifactorial and involves complex interactions between genetic predisposition, neuroendocrine dysregulation, metabolic abnormalities, and environmental influences. One of the central mechanisms is insulin resistance, which is present in a substantial proportion of women with PCOS independent of body mass index. Hyperinsulinemia enhances luteinizing hormone-mediated androgen production by ovarian theca cells and suppresses hepatic synthesis of sex hormone-binding globulin, increasing bioavailable testosterone and exacerbating hyperandrogenic features. (21,26,29–31,34,38,39,44–47)

Neuroendocrine abnormalities also play a key role. Women with PCOS exhibit increased gonadotropin-releasing hormone pulse frequency, resulting in preferential secretion of luteinizing hormone relative to follicle-stimulating hormone. This altered LH/FSH ratio promotes androgen synthesis and disrupts normal follicular development, contributing to chronic anovulation. Emerging studies implicate neurokinin B and kisspeptin signaling in this dysregulation. Randomized controlled trials demonstrate that neurokinin-3 receptor blockade reduces testosterone levels and decreases LH secretion, indicating restoration of hypothalamic–pituitary–ovarian axis balance. (4)

Inflammatory mechanisms further contribute to disease progression. Women with PCOS demonstrate elevated inflammatory cytokines, oxidative stress markers, and adipokines. Chronic low-grade inflammation impairs insulin signaling and alters ovarian steroidogenesis. Oxidative stress also affects granulosa cell function, leading to impaired oocyte maturation and reduced embryo quality. These findings provide a mechanistic basis for therapies targeting oxidative stress and metabolic dysfunction. Adipose tissue dysfunction is another critical component. Visceral adiposity promotes lipotoxicity, mitochondrial dysfunction, and systemic inflammation. These processes exacerbate insulin resistance and androgen excess, perpetuating reproductive dysfunction. Additionally, altered adipokine secretion, including reduced adiponectin and increased leptin, further disrupts insulin sensitivity and ovarian function. (48–52)

Etiology

The etiology of PCOS is multifactorial and involves genetic, epigenetic, metabolic, and environmental determinants. Familial clustering and twin studies suggest a strong heritable component, with susceptibility loci involving genes related to steroidogenesis, insulin signaling, and gonadotropin regulation. However, environmental influences such as diet, obesity, endocrine disruptors, and intrauterine androgen exposure also contribute to disease development. (18,20,53,54)

Hyperinsulinemia during puberty has been proposed as a triggering factor in genetically predisposed individuals. Elevated insulin levels stimulate ovarian androgen production, which disrupts folliculogenesis and leads to persistent anovulation. Prenatal androgen exposure may also predispose offspring to PCOS by altering hypothalamic regulation and ovarian development. (21,32,33,38,43,55–58)

Obesity exacerbates PCOS severity but is not required for diagnosis. Lean PCOS phenotypes exhibit similar neuroendocrine abnormalities but less pronounced metabolic dysfunction. This distinction supports phenotype-specific treatment approaches. (38,39,43,44,51,59–62)

Chronic inflammation and oxidative stress further contribute to etiologic mechanisms. Elevated cytokines impair insulin signaling and promote ovarian dysfunction. Environmental factors such as sedentary lifestyle, high-glycemic diets, and endocrine-disrupting chemicals may amplify these pathways. (49,52,63)

Clinical Syndromes and Phenotypic Variability

PCOS manifests as a spectrum of clinical phenotypes. The classical phenotype includes hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Other phenotypes include ovulatory PCOS, normoandrogenic PCOS, and metabolic-dominant PCOS. Clinical manifestations vary widely and include menstrual irregularity, infertility, hirsutism, acne, obesity, insulin resistance, and cardiometabolic risk. (64–66)

Reproductive manifestations include anovulatory infertility, impaired endometrial receptivity, and increased miscarriage risk. Metabolic manifestations include insulin resistance, dyslipidemia, impaired glucose tolerance, and type 2 diabetes. Cardiovascular risk factors include endothelial dysfunction and hypertension. Psychological manifestations such as anxiety, depression, and reduced quality of life are also common. (64,67–69)

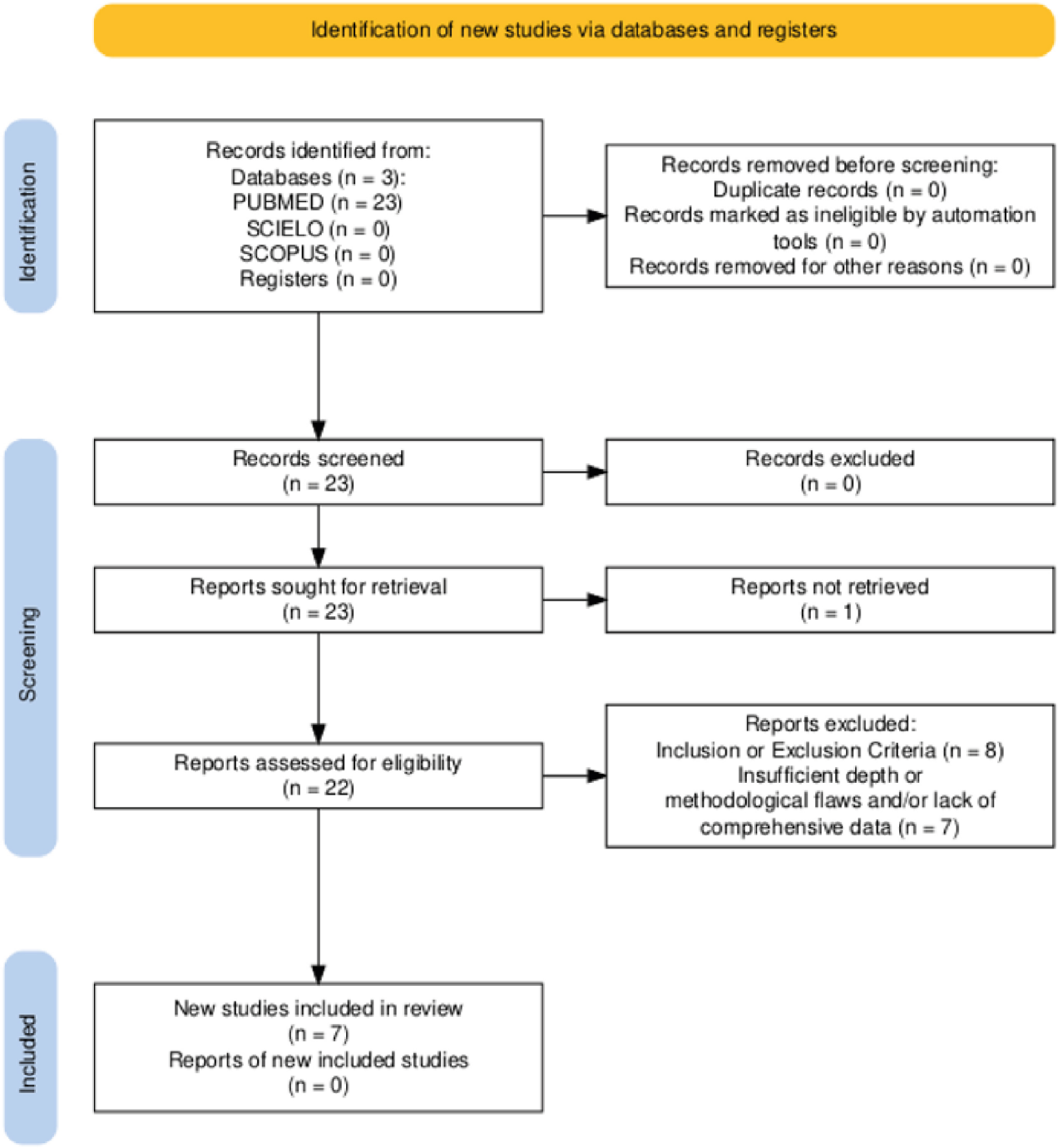
METHODS

A systematic literature search was conducted between January and March 2024 using PubMed, Scielo, and Web of Science to identify randomized controlled trials evaluating innovative pharmacological interventions for polycystic ovary syndrome (PCOS). The search strategy incorporated Medical Subject Headings and keywords including “Polycystic Ovary Syndrome,” “Treatment Outcome,” and “Drug Therapy,” combined using Boolean operators. The search was restricted to randomized controlled trials published in English between April 2019 and April 2024, and only studies available in full text were considered eligible. Reference lists of relevant publications were also screened to identify additional studies. The review was designed and reported according to PRISMA recommendations to ensure transparency and reproducibility of the search, selection, and synthesis processes. (70)

Studies were considered eligible if they were randomized controlled trials published within the previous five years, available as full-text articles, conducted in women diagnosed with PCOS, and evaluating treatment outcomes associated with novel pharmacological agents or innovative therapeutic uses of established drugs. Studies were excluded if they were observational designs, non-randomized trials, narrative reviews, conference abstracts without complete data, articles older than five years, unavailable full texts, or investigations not focused on pharmacological interventions. These criteria were defined a priori to reduce selection bias and ensure methodological consistency.

The search strategy initially identified 23 potentially relevant records, of which one article was not retrievable. Title and abstract screening excluded eight studies that did not meet eligibility criteria, leaving fourteen articles for full-text review. During full-text assessment, seven studies were excluded due to insufficient methodological rigor, incomplete outcome reporting, or lack of innovative pharmacological intervention. The remaining seven randomized controlled trials met all inclusion criteria and were included in the final analysis. The study selection process is summarized in the PRISMA flow diagram (Figure 1).

Figure 1. PRISMA flow diagram for Systematic Review



Data extraction was performed independently by two reviewers using a standardized data collection form. Extracted variables included study design, sample size, participant characteristics, intervention protocols, outcome measures, and reported adverse events. Discrepancies between reviewers were resolved through discussion and consensus. Due to heterogeneity in study populations, intervention strategies, and outcome definitions, quantitative meta-analysis was not performed. Instead, a structured qualitative synthesis was conducted to compare therapeutic effects across studies. Meta-regression and sensitivity analyses were considered but were not feasible because of the limited number of trials and variability in reported endpoints.

Methodological quality was assessed using the Jadad scale, which evaluates randomization, blinding, and withdrawal reporting. Scores range from 0 to 5, with scores of three or higher considered indicative of moderate-to-high methodological quality. All included studies achieved Jadad scores ≥3, indicating generally acceptable methodological rigor. Detailed quality assessment results are presented in Table 1.

Study	Jadad Score (0-5)	Randomization	Blinding	Withdrawal Reporting	Overall Quality
Chen et al. (15)	4	Adequate	Adequate	Reported	High
Chera-Aree et al. (11)	3	Adequate	Limited	Reported	Moderate
Fraser et al. (4)	5	Adequate	Adequate	Reported	High
Gong et al. (16)	4	Adequate	Limited	Reported	High
Steinberg Weiss et al. (17)	3	Adequate	Limited	Reported	Moderate
Tao et al. (14)	4	Adequate	Limited	Reported	High
García-Beltran et al. (13)	4	Adequate	Adequate	Reported	High

Table 1: Methodological Quality Assessment

RESULTS

Seven randomized controlled trials met the inclusion criteria and were included in the final qualitative synthesis. The main characteristics of the included studies, including design, sample size, interventions, outcomes, and adverse events, are summarized in Table 2. The trials evaluated diverse pharmacological strategies targeting reproductive, hormonal, and metabolic components of polycystic ovary syndrome, with sample sizes ranging from 100 to 300 participants.

As shown in Table 2, ovulation induction strategies demonstrated consistent reproductive benefits. Letrozole therapy achieved the highest cumulative pregnancy rate, reaching 72.7%, and significantly improved ovulation rates in infertile women with PCOS. Combination therapy with clomiphene citrate and letrozole provided modest improvements in ovulation compared with clomiphene alone, suggesting potential synergistic effects in patients with ovulatory dysfunction.

Table 2: Characteristics of the Included Studies

Study	Design	Participants	Intervention	Main Outcomes	Adverse Events
Chen et al. (15)	RCT	300	Letrozole (2.5 mg)	72.7% cumulative pregnancy rate; significant improvement in ovulation rates.	None reported.
Chera-Aree et al. (11)	RCT	150	Clomiphene + Letrozole	Combination therapy slightly outperformed clomiphene alone in ovulation rates.	None reported.
Fraser et al. (4)	RCT	200	Fezolinetant	Significant reduction in testosterone, LH, and FSH levels.	Transient headaches.
Gong et al. (16)	RCT	100	Growth Hormone	Improved oocyte and embryo quality; reduced oxidative stress.	None reported.
Steinberg Weiss et al. (17)	RCT	250	Oral contraceptives + Lifestyle	Improved metabolic health and increased sexual desire scores.	None reported.
Tao et al. (14)	RCT	300	Exenatide, Metformin	Higher remission rates of prediabetes with exenatide or combination therapy compared to metformin alone.	Mild gastrointestinal symptoms.
García-Beltran et al. (13)	RCT	200	SPIOMET	Normalized metabolic status and reduced androgen levels after one year.	None reported.

therapies also demonstrated clinically relevant effects. Lifestyle modification combined with oral contraceptives improved metabolic health and increased sexual desire scores. Similarly, exenatide, alone or in combination with metformin, achieved higher remission rates of prediabetes compared with metformin monotherapy, indicating improved insulin sensitivity. SPIOMET therapy normalized metabolic parameters and reduced androgen levels after one year of treatment, highlighting the effectiveness of multimodal pharmacological approaches targeting insulin resistance and hyperandrogenism.

The safety profile of the included interventions was favorable, as summarized in Table 2. Reported adverse events were mild and transient, including gastrointestinal symptoms with metformin-based therapy and transient headaches associated with fezolinetant. No serious adverse events were reported across studies.

Methodological quality of included trials was generally high, with Jadad scores ≥3 for all studies (Table 1). However, heterogeneity in study design, treatment protocols, and outcome measures limited direct comparisons across trials and precluded quantitative meta-analysis. Despite this variability, the findings summarized in Table 2 consistently suggest that targeted pharmacological interventions improve reproductive, hormonal, and metabolic outcomes in women with polycystic ovary syndrome.

DISCUSSION

Pathophysiological Interpretation of Therapeutic Response

PCOS is a heterogeneous endocrine-metabolic disorder characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, with substantial reproductive, metabolic, and cardiometabolic implications (20,71–74). The diagnostic framework established by the Rotterdam consensus recognizes the multifactorial nature of PCOS and highlights the variability in clinical phenotypes, which complicates therapeutic decision-making and underscores the need for individualized treatment strategies (75–80).

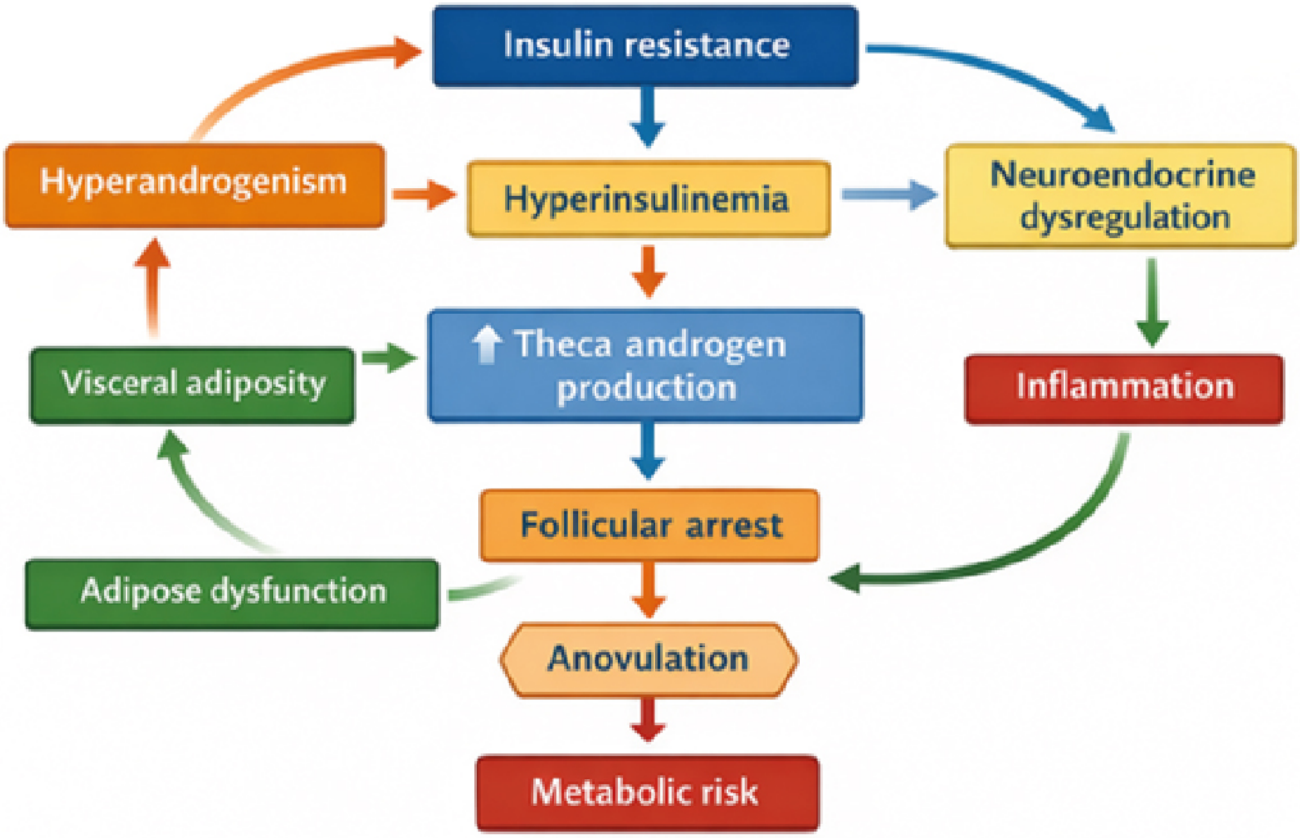


Figure 2. Integrated pathophysiological model of polycystic ovary syndrome. The schematic illustrates the central role of insulin resistance in the pathogenesis of polycystic ovary syndrome. Insulin resistance leads to compensatory hyperinsulinemia, which enhances ovarian theca cell androgen production and contributes to hyperandrogenism. Elevated androgen levels promote follicular arrest and anovulation. Neuroendocrine dysregulation, adipose tissue dysfunction, and chronic low-grade inflammation further amplify ovarian dysfunction and metabolic abnormalities. A bidirectional feedback loop between hyperandrogenism, visceral adiposity, and insulin resistance perpetuates disease progression. These interconnected mechanisms collectively contribute to reproductive dysfunction and increased metabolic risk.

More recent conceptualizations emphasize that PCOS represents a spectrum of endocrine-metabolic disturbances involving insulin resistance, neuroendocrine dysregulation, adipose tissue dysfunction, chronic low-grade inflammation, and oxidative stress, all of which contribute to reproductive impairment and long-term metabolic risk (72,73,81), Within this context, the present systematic review evaluated randomized controlled trials investigating innovative pharmacological approaches targeting both reproductive and metabolic pathways in women with PCOS (4,11,15,16,82–84).

The findings suggest that emerging therapies—including aromatase inhibitors, neurokinin-3 receptor antagonists, GLP-1 receptor agonists, combination metabolic therapies, growth hormone, and integrated multimodal regimens—offer promising improvements in ovulatory function, metabolic outcomes, and hormonal regulation (4,82,84–88).

Reproductive Outcomes and Ovulation Restoration

Letrozole emerged as the most effective agent for ovulation induction, achieving a cumulative pregnancy rate of 72.7 percent, as reported by Chen et al. (15) (see Table 2). Its combination with clomiphene citrate further improved ovulatory outcomes, reinforcing its utility in clinical practice for infertility management in PCOS. These results align with the established role of aromatase inhibition in restoring follicular development and improving endometrial receptivity. Fezolinetant, a neurokinin 3 receptor antagonist, showed substantial reductions in testosterone, luteinizing hormone, and follicle-stimulating hormone levels, indicating its potential to correct hyperandrogenism and hormonal dysregulation, a core feature of PCOS (4). These hormonal improvements may have downstream benefits on menstrual regularity and ovulatory function, suggesting that targeting central neuroendocrine pathways is a promising therapeutic approach.

The administration of growth hormone in assisted reproductive technology settings demonstrated improvements in oocyte and embryo quality, likely mediated by enhanced follicular development and reduced oxidative stress (16). Such interventions may augment the success rates of in vitro fertilization in patients with PCOS, particularly those with poor oocyte quality, highlighting the value of adjuvant therapies in reproductive outcomes. Metabolic-focused interventions also yielded clinically relevant benefits. Lifestyle modifications combined with oral contraceptives improved metabolic parameters and sexual function, emphasizing the importance of integrating non-pharmacological measures into therapeutic regimens (17). Exenatide, alone or in combination with metformin, effectively addressed insulin resistance and prediabetes, outperforming metformin monotherapy (14). SPIOMET therapy, which combines antiandrogens, antimineralocorticoids, and insulin-sensitizing agents, normalized metabolic profiles and reduced androgen levels over a one-year period (13). These findings underscore the need to address metabolic dysfunction as an integral component of comprehensive PCOS management.

The high methodological quality of the included studies, reflected in Jadad scores of three or higher (Table 1), lends credibility to the observed effects. However, heterogeneity in study design, intervention protocols, and outcome measures limits direct comparisons and generalizability. Incorporating stratification based on participant characteristics, such as body mass index, baseline hormonal profiles, and metabolic status, may reduce variability and facilitate personalized therapeutic approaches. Additionally, standardized outcome measures and consistent use of diagnostic criteria, such as the Rotterdam criteria, would improve comparability across trials and strengthen evidence synthesis (12).

Metabolic-Targeted Pharmacological Therapies

Beyond ovulation induction and short-term hormonal improvements, emerging evidence suggests that polycystic ovary syndrome should be conceptualized as a multisystem disorder involving neuroendocrine, metabolic, and inflammatory pathways (89,90). This integrative perspective supports the use of targeted pharmacological strategies that address underlying pathophysiology rather than isolated symptoms. Recent studies emphasize that insulin resistance, hyperandrogenism, and chronic low-grade inflammation interact bidirectionally, contributing to reproductive dysfunction and long-term cardiometabolic risk. Pharmacological agents targeting these mechanisms may therefore provide broader clinical benefits beyond fertility outcomes. (31,49,91)

Pharmacologic studies demonstrate that GLP-1 receptor agonists improve metabolic and endocrine

parameters through multiple mechanisms, including weight reduction, improved insulin sensitivity, and decreased androgen production (92). A 2025 meta-analysis of randomized controlled trials reported significant reductions in body mass index, fasting insulin, and HOMA-IR among women with PCOS treated with GLP-1 receptor agonists compared with metformin or placebo.

Additional systematic reviews published in 2024 confirmed improvements in anthropometric, metabolic, and hormonal parameters, supporting the role of GLP-1–based therapy as a disease-modifying strategy in PCOS management. (93)

Sodium-glucose cotransporter-2 inhibitors represent another emerging therapeutic class. These agents improve glycemic control, reduce visceral adiposity, and enhance insulin sensitivity. Recent reviews highlight that SGLT2 inhibitors may improve metabolic outcomes in PCOS by decreasing glucose toxicity, reducing inflammatory signaling, and improving adipose tissue function, although reproductive outcomes require further investigation. (94)

Glucagon-like peptide-1 receptor agonists have gained increasing attention in PCOS management due to their dual metabolic and reproductive effects. Recent randomized trials demonstrate that agents such as semaglutide and liraglutide improve weight reduction, insulin sensitivity, and menstrual regularity in women with PCOS. These effects appear to be mediated by improved adipose tissue signaling, reduction in systemic inflammation, and restoration of hypothalamic–pituitary–ovarian axis regulation. Additionally, GLP-1 receptor agonists may reduce androgen production through indirect metabolic mechanisms, further supporting their role as disease-modifying therapies. (59,82,87,88,95)

Another promising area involves sodium-glucose cotransporter-2 inhibitors, which improve glycemic control and reduce visceral adiposity. Preliminary randomized and controlled studies suggest that SGLT2 inhibitors such as empagliflozin and dapagliflozin improve insulin resistance and decrease body mass index in women with PCOS. These metabolic improvements may translate into better ovulatory function, although reproductive endpoints remain under investigation. Importantly, these agents also demonstrate cardiovascular protective effects, which may be particularly relevant in long-term PCOS management. (41,60,83,84,96,97)

Antiandrogen therapies remain a cornerstone of symptom management, particularly for hyperandrogenic manifestations. Recent investigations have explored the use of newer antiandrogens and combination regimens targeting both androgen excess and metabolic dysfunction. Combined therapy incorporating antiandrogens with insulin-sensitizing agents has demonstrated superior reductions in testosterone levels and improved metabolic markers compared with monotherapy. These findings reinforce the concept that multimodal pharmacological approaches may be more effective than single-agent strategies. (98–100)

Inflammatory pathways have also emerged as therapeutic targets. Women with PCOS exhibit elevated levels of inflammatory cytokines and oxidative stress markers. Pharmacological interventions aimed at reducing inflammation, including insulin sensitizers and metabolic modulators, have shown improvements in both endocrine and metabolic outcomes. These findings support the hypothesis that chronic inflammation contributes to ovarian dysfunction and that anti-inflammatory pharmacological strategies may represent an adjunctive therapeutic approach. (22,49,54,101)

Precision Medicine and Phenotype-Guided Treatment

Precision medicine approaches are increasingly emphasized in PCOS research. Stratification based on phenotype, including hyperandrogenic, ovulatory, and metabolic subtypes, may guide individualized pharmacological treatment. Recent studies demonstrate that treatment response varies according to baseline body mass index, insulin resistance, and androgen levels. For example, obese insulin-resistant patients may benefit more from GLP-1 receptor agonists or combination therapy, whereas lean hyperandrogenic patients may respond better to ovulation-inducing agents. This phenotype-based strategy may improve treatment outcomes and reduce unnecessary exposure to medications (81,85,90,102,103), Based on the available evidence, a phenotype-guided therapeutic approach may optimize treatment selection and clinical outcomes (Figure 3 & 4).

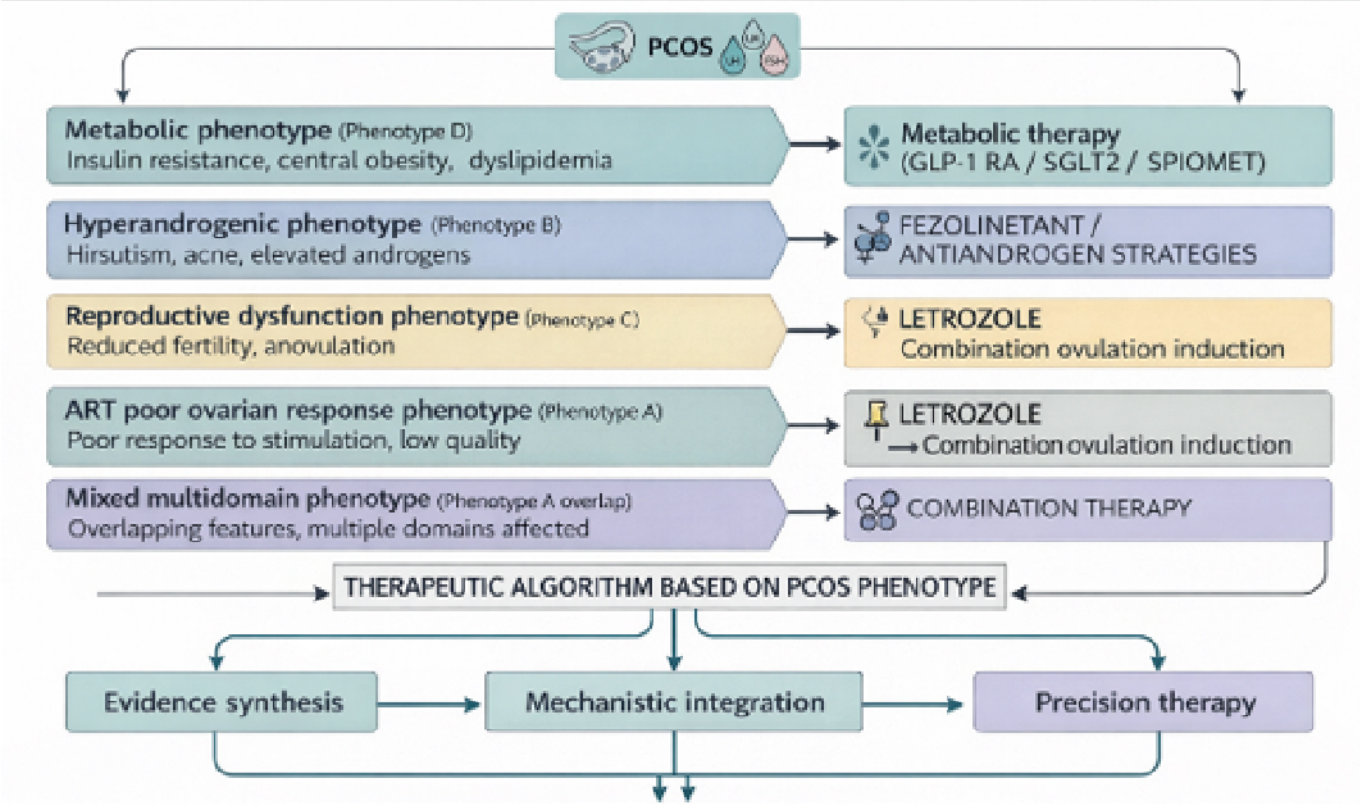


Figure 3. Phenotype-based therapeutic algorithm for polycystic ovary syndrome. The diagram illustrates a phenotype-guided treatment strategy for polycystic ovary syndrome integrating metabolic, endocrine, and reproductive domains. The metabolic insulin-resistant phenotype is characterized by insulin resistance, central obesity, and dyslipidemia, prioritizing metabolic-targeted therapies such as GLP-1 receptor agonists, SGLT2 inhibitors, or combination metabolic approaches. The hyperandrogenic phenotype includes clinical or biochemical hyperandrogenism and is directed toward neuroendocrine modulation and antiandrogen strategies. The reproductive dysfunction phenotype, defined by anovulation and reduced fertility, is primarily managed with ovulation induction using letrozole, with escalation to combination approaches when necessary. The ART poor ovarian response phenotype includes patients with suboptimal stimulation response or reduced oocyte quality, where adjunctive therapies such as growth hormone or combined ovulation strategies may be considered. The mixed multidomain phenotype represents overlapping clinical features requiring individualized combination therapy. The lower panel summarizes the integration of evidence synthesis and mechanistic interpretation leading to precision-based therapeutic selection and improved clinical outcomes.

Phenotype	Features	Metabolic Risk	Preferred Therapy
Phenotype A	Hyperandrogenism + Anovulation + PCO	High risk ↑	GLP-1 + Letrozole
Phenotype B	Hyperandrogenism + Ovulatory	Moderate ↗	Antiandrogen therapy
Phenotype C	Ovulatory + PCO	Low →	Ovulation induction
Phenotype D	Metabolic dominant	Very high ↑↑	GLP-1 / SGLT2

Reproductive outcomes in PCOS may be influenced by impaired endometrial receptivity, and emerging pharmacological approaches—such as aromatase inhibitors and metabolic agents—appear to improve implantation and pregnancy rates, potentially through normalization of estrogen signaling and enhanced uterine perfusion. While reported adverse effects are generally mild, long-term safety data remain limited, particularly regarding cardiovascular, metabolic, and reproductive risks; combination therapies may improve tolerability by allowing lower dosing without compromising efficacy. Interpretation of current evidence is constrained by heterogeneity in diagnostic criteria, treatment protocols, PCOS phenotypes, small sample sizes, and short follow-up periods, underscoring the need for standardized outcomes including ovulation, live birth, and metabolic endpoints. Future research should emphasize head-to-head comparisons, multicenter randomized trials, long-term follow-up, and phenotype-based stratification, with incorporation of biomarkers such as anti-Müllerian hormone, insulin resistance indices, and inflammatory markers to enable personalized care. Overall, the available data support individualized treatment strategies that concurrently target reproductive and metabolic dysfunction, with combination therapy and early metabolic intervention potentially improving outcomes and reducing long-term cardiometabolic risk in PCOS (Figure 4). (24,104–108)

Integration of Recent Evidence (2024–2026)

The findings of the present systematic review, completed in 2024 after a two-year evaluation period, are reinforced by emerging high-quality evidence published between 2024 and 2026. These recent studies support the clinical relevance of multimodal pharmacological strategies targeting metabolic, endocrine, and neuroendocrine pathways in polycystic ovary syndrome and validate the therapeutic trends identified in our analysis. In particular, contemporary randomized trials and meta-analyses emphasize the role of metabolic-directed therapies, neuroendocrine modulation, and phenotype-guided treatment selection as key components of modern PCOS management.

Recent meta-analyses published in 2024 demonstrated that glucagon-like peptide-1 receptor agonists significantly improve body mass index, waist circumference, insulin resistance, and androgen levels in women with PCOS, confirming their disease-modifying potential beyond weight reduction alone (93,109). These findings are consistent with the metabolic improvements observed in the trials included in our systematic review and support the incorporation of GLP-1–based therapies into integrated treatment strategies. A more recent 2025 meta-analysis further reported significant reductions in body weight, abdominal adiposity, and glucose homeostasis markers compared with metformin or placebo, reinforcing the superiority of GLP-1 receptor agonists in metabolic PCOS phenotypes. (92)

Systematic review and meta-analysis including randomized controlled trials of liraglutide demonstrated significant improvements in menstrual frequency, insulin resistance, body mass index, luteinizing hormone levels, and free androgen index, suggesting both reproductive and metabolic benefits. These findings strengthen the interpretation of our systematic review, which identified metabolic modulation as a central therapeutic target in PCOS management. (59,110,111)

Sodium–glucose cotransporter-2 inhibitors have also emerged as complementary metabolic therapies. A 2024 systematic review evaluating SGLT2 inhibitors in PCOS reported improvements in glycemic control, insulin sensitivity, and metabolic parameters, supporting their potential role in reducing cardiometabolic risk. These agents may also improve adipose tissue function and inflammatory signaling, mechanisms consistent with the pathophysiological model proposed in our review. However, reproductive endpoints remain limited, and further randomized trials are required. (112–114)

Combination metabolic therapy has also gained support in recent literature. A meta-analysis of randomized trials comparing liraglutide plus metformin versus metformin alone demonstrated superior improvements in ovulation rate, menstrual regularity, glucose metabolism, lipid profile, and spontaneous conception, supporting the multimodal therapeutic approach highlighted in the present systematic review. These findings reinforce the concept that targeting insulin resistance and hyperandrogenism simultaneously may yield superior clinical outcomes compared with monotherapy. (111,115–117)

Clinical Implications

Collectively, the evidence published between 2024 and 2026 supports a paradigm shift in PCOS management toward phenotype-guided and pathophysiology-based treatment. The consistency between the results of our systematic review and contemporary studies strengthens the clinical applicability of our findings and suggests that integrated pharmacological strategies targeting metabolic dysfunction, neuroendocrine dysregulation, and hyperandrogenism may improve both reproductive and cardiometabolic outcomes. These data also emphasize the importance of early metabolic intervention. Women with insulin-resistant phenotypes appear to benefit most from GLP-1 receptor agonists, SGLT2 inhibitors, or combination therapy, whereas ovulatory dysfunction without significant metabolic abnormalities may respond preferentially to aromatase inhibitors or neuroendocrine-targeted treatments. This phenotype-based therapeutic framework aligns with the conceptual model proposed in our systematic review and supports individualized treatment selection. (92,118–120)

Limitations of the Present Review

Despite these advances, several limitations remain. Recent studies continue to demonstrate heterogeneity in diagnostic criteria, intervention protocols, and outcome measures. Sample sizes remain modest, and long-term reproductive outcomes, including live birth rates and cardiovascular endpoints, are still limited. Furthermore, safety data beyond short-term follow-up remain insufficient, particularly for combination pharmacological strategies.

Nevertheless, the convergence between the results of the present systematic review and emerging evidence published from 2024 onward provides strong support for multimodal pharmacological management of PCOS. The integration of metabolic, endocrine, and neuroendocrine therapies may represent the most effective strategy for improving ovulatory function, metabolic health, and long-term outcomes. Future randomized multicenter trials with phenotype stratification, standardized endpoints, and long-term follow-up are required to confirm these findings and refine precision medicine approaches in PCOS.

CONCLUSIONS

This systematic review synthesizes randomized controlled trials evaluating emerging pharmacological strategies for polycystic ovary syndrome and demonstrates that targeted therapies addressing reproductive, neuroendocrine, and metabolic mechanisms provide clinically meaningful benefits. Ovulation-inducing agents, particularly letrozole, showed the strongest reproductive outcomes, while neuroendocrine modulation with fezolinetant improved hormonal profiles. Metabolic-targeted therapies, including exenatide, SPIOMET, and lifestyle-combined regimens, demonstrated improvements in insulin resistance, androgen levels, and cardiometabolic parameters. Growth hormone therapy improved oocyte and embryo quality in assisted reproductive settings. Overall, the findings summarized in Table 2 support a multidimensional therapeutic approach that simultaneously targets ovulatory dysfunction, hyperandrogenism, and metabolic impairment.

Despite these promising results, heterogeneity across studies, small sample sizes, and short follow-up periods limit direct comparisons and long-term clinical extrapolation. Emerging evidence indicates that metabolic therapies such as glucagon-like peptide-1 receptor agonists improve body weight and insulin resistance in women with PCOS, although current meta-analyses report modest short-term benefits and limited certainty regarding reproductive outcomes, highlighting the need for further high-quality trials. These limitations reinforce the need for standardized diagnostic criteria, phenotype-based stratification, and consistent reporting of reproductive endpoints such as ovulation, live birth, and metabolic risk reduction.

Pharmacological management of PCOS should be individualized according to phenotype. Ovulatory dysfunction with infertility is best addressed with aromatase inhibitors, particularly letrozole as first-line therapy. Patients with predominant hyperandrogenism may benefit from neuroendocrine modulation or antiandrogen-based combination regimens. Women with insulin resistance, obesity, or prediabetes should receive metabolic-targeted therapies, including GLP-1 receptor agonists, insulin sensitizers, or combination regimens such as SPIOMET. Assisted reproduction candidates with poor oocyte quality may benefit from adjunctive growth hormone therapy. Multimodal treatment addressing both reproductive and metabolic dysfunction appears superior to monotherapy.

Management should follow a phenotype-based strategy integrating reproductive and metabolic targets. First, ovulation induction with letrozole should be considered first-line in infertile patients. Second, metabolic evaluation including BMI, insulin resistance, and lipid profile should guide early use of insulin-sensitizing or incretin-based therapies. Third, combination pharmacological approaches should be considered in patients with mixed phenotypes. Fourth, lifestyle intervention should be integrated into all treatment pathways. Fifth, safety monitoring should include metabolic parameters, hormonal markers, and adverse effects, particularly in long-term therapy.

Future trials should prioritize head-to-head comparisons between ovulation-inducing agents, metabolic therapies, and multimodal regimens. Large multicenter randomized trials with long-term follow-up are required to evaluate live birth rates, cardiometabolic outcomes, and safety. Phenotype-based stratification using biomarkers such as anti-Müllerian hormone, insulin resistance indices, inflammatory markers, and androgen levels should be incorporated. Research should also evaluate combination therapy versus sequential treatment strategies, long-term cardiovascular outcomes, and cost-effectiveness. Additionally, studies investigating GLP-1 receptor agonists, SGLT2 inhibitors, and anti-inflammatory pharmacological strategies may clarify disease-modifying approaches in PCOS.

The available evidence supports a shift from symptom-based treatment toward mechanism-targeted, individualized pharmacological strategies in PCOS. Combining ovulation induction, hormonal regulation, and metabolic therapy may improve reproductive outcomes while reducing long-term cardiometabolic risk. Further high-quality randomized trials with standardized outcomes and phenotype-based approaches are necessary to define optimal treatment algorithms.

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