2026 Volume: 02 Issue: 05 www.ijrpa.com ISSN 2456-9995 Review Article

International Journal Research Publication Analysis

Page: 01-13

CURRENT AND EMERGING TREATMENT STRATEGIES FOR POLYCYSTIC OVARY SYNDROME: AN INTEGRATIVE REVIEW

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Article Received: 22 March 2026
Article Revised: 12 April 2026
Published on: 02 May 2026

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DOI: https://doi-doi.org/101555/ijrpa.8289

ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a common endocrine and metabolic disorder affecting women of reproductive age, characterized by hyperandrogenism, menstrual irregularities, ovulatory dysfunction, and polycystic ovarian morphology, and is associated with significant reproductive and metabolic complications. Women with PCOS have a higher risk of insulin resistance, impaired glucose tolerance, type 2 diabetes mellitus, cardiovascular disease, infertility, and endometrial abnormalities, making timely diagnosis and effective management essential. Current treatment strategies are mainly symptom-oriented, with lifestyle modification considered the first-line approach, as weight loss through dietary changes and regular physical activity improves hormonal balance, insulin sensitivity, menstrual regularity, ovulation, and pregnancy outcomes, even with modest weight reduction of around 5% of initial body weight. Pharmacological treatment plays an important role, particularly insulin-sensitizing agents such as metformin, which has been extensively studied and shown to improve metabolic parameters, reduce androgen levels, and enhance ovulatory function in selected PCOS populations. For the management of infertility, ovulation induction agents including clomiphene citrate, aromatase inhibitors, and gonadotropins are commonly used, while surgical options and assisted reproductive techniques are reserved for cases unresponsive to medical therapy. In recent years, emerging and adjunctive therapies such as statins, inositols, melatonin, and resveratrol have gained attention due to their potential benefits in improving insulin resistance, lipid profile, androgen excess, and inflammatory

markers; however, current evidence remains limited and further clinical studies are required to confirm their safety and effectiveness. Overall, the complex and multifactorial nature of PCOS highlights the need for an integrated, individualized, and evidence-based treatment approach to optimize both short- and long-term health outcomes.

KEYWORDS: Polycystic ovary syndrome (PCOS); hyperandrogenism; insulin resistance; cardiovascular risk; pharmacotherapy; microRNA (miRNA); inflammasome; stem cell-based therapy.

1. INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is one of the most prevalent endocrine disorders affecting women of reproductive age, with a global prevalence ranging from 6% to 20%, depending on the diagnostic criteria applied (Teede et al., 2018). Among the criteria, the Rotterdam 2003 guidelines are the most widely used, requiring the presence of at least two of the following:

oligo- or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004). PCOS is a heterogeneous, multifactorial condition that encompasses reproductive, metabolic, dermatologic, and psychological disturbances. Clinically, it often presents with menstrual irregularities, hirsutism, acne, alopecia, and subfertility. Biochemically, affected women frequently exhibit elevated androgen levels and insulin resistance, the latter affecting up to 70% of cases and contributing to an increased risk of type 2 diabetes, dyslipidemia, nonalcoholic fatty liver disease, and cardiovascular disease (Moran et al., 2010; Dunaif, 2012). Moreover, PCOS imposes a significant psychosocial burden, with higher rates of anxiety, depression, body image dissatisfaction, and reduced quality of life reported among affected individuals (Cooney et al., 2017). The etiology of PCOS remains incompletely understood, with evidence pointing to complex interactions between genetic, environmental, and intrauterine factors that disrupt the hypothalamic-pituitary-ovarian axis, insulin signaling, and androgen biosynthesis (Goodarzi et al., 2011). These diverse pathophysiological mechanisms, along with variations across racial, ethnic, and geographic populations, highlight the need for personalized, multifactorial management strategies. This article aims to provide a comprehensive review of current treatment modalities for PCOS, including lifestyle interventions, pharmacologic therapies, surgical options, and emerging approaches. By synthesizing recent clinical evidence, it seeks to guide healthcare providers in optimizing care for the heterogeneous phenotypes of PCOS and to

identify areas requiring further research.

2. LITERATURE REVIEW

2.1. Individualized Treatment Approaches Based on PCOS Phenotypes

Recent studies highlight the critical importance of personalized treatment strategies for women with PCOS due to the syndrome's heterogeneous nature. Distinct PCOS phenotypes—ranging from hyperandrogenic to reproductive and metabolic variants—exhibit unique clinical and biochemical profiles, which significantly influence therapeutic response (Teede et al., 2018). For women presenting with anovulatory infertility, ovulation induction remains a cornerstone of management, with letrozole and clomiphene citrate frequently used as first-line agents. Conversely, for patients with predominant metabolic disturbances, insulin sensitizers such as metformin are preferred, given their ability to improve insulin resistance, regulate menstrual cycles, and enhance fertility outcomes (Legro et al., 2014; Palomba et al., [year]).

2.2. Lifestyle Modifications as First-Line Therapy

Lifestyle modification, encompassing dietary adjustments, regular physical activity, and behavioral interventions, is universally recommended as first-line therapy for women with PCOS, particularly those who are overweight or obese. A meta-analysis by Moran et al. (2011) demonstrated that lifestyle interventions significantly improve reproductive outcomes, insulin sensitivity, and lipid profiles. Similarly, a recent systematic review by BehboudiGandevani et al. (2023) confirmed that lifestyle-based strategies are more effective than placebo in restoring menstrual cyclicity and reducing androgen levels. Moreover, emerging non-pharmacological approaches, such as electroacupuncture combined with structured physical activity and caloric management, have shown promising results in lowering serum testosterone and enhancing insulin resistance (Ma et al., 2024).

2.3. Pharmacological Advances: Insulin Sensitizers and Ovulation Induction

Pharmacological management of PCOS has advanced considerably over the past decade. Metformin, a well-established insulin sensitizer, has been shown to improve menstrual regularity, reduce androgen levels, and enhance the efficacy of ovulation induction agents (Lord et al., 2003; Tso et al., 2021). Letrozole has now surpassed clomiphene citrate as the first-line ovulation induction agent due to its higher ovulation and live birth rates, as demonstrated in a pivotal multicenter trial (Legro et al., 2014). Recent evidence also highlights the potential of glucagon-like peptide-1 (GLP-1) receptor agonists, such as liraglutide, in

promoting significant weight loss and improving insulin sensitivity among obese women with PCOS (Elkind-Hirsch et al., 2022). These agents further reduce serum androgen levels, offering a dual therapeutic benefit in the management of PCOS.

2.4. Novel and Complementary Therapies: Inositols, Anti-Androgens, and GLP-1 Agonists

The use of inositol isomers—particularly myo-inositol and D-chiro-inositol—has gained considerable attention as a safe and effective approach for improving ovulatory function and metabolic outcomes in women with PCOS. A meta-analysis by Unfer et al. (2021) reported that inositols significantly enhance ovulation, reduce serum insulin levels, and help restore regular menstrual cycles. Anti-androgens, including spironolactone and finasteride, are commonly prescribed for the management of hirsutism and acne. These agents are typically combined with oral contraceptives to minimize teratogenic risk (Futterweit & Shapiro, 2023). Emerging therapies such as GLP-1 receptor agonists, previously discussed in the context of insulin sensitization and weight management, further exemplify the expanding pharmacological and complementary strategies available for comprehensive PCOS management.

2.5. Persistent Gaps in PCOS Treatment Research

Despite significant advancements, notable gaps remain in the understanding and management of PCOS, particularly in lean women, adolescents, and regarding long-term cardiovascular risk. Lean women with PCOS are often underdiagnosed, despite exhibiting risks of insulin resistance and cardiovascular complications comparable to those in overweight or obese patients (Diamanti-Kandarakis et al., 2007; Lim et al., 2019). Adolescents with PCOS frequently face delays in diagnosis, and there is limited consensus on optimal long-term treatment strategies for this population (Ibáñez et al., 2020). Additionally, robust long-term safety and comparative efficacy data for various pharmacologic treatments remain scarce, particularly concerning cardiovascular outcomes, cancer risk, and quality-of-life measures. Addressing these gaps is essential for the development of individualized and evidence-based management strategies for all women with PCOS.

2.6. Integrative and Complementary Medicine

Integrative medicine approaches—including acupuncture, herbal remedies, and mind-body interventions (MBIs) such as yoga and meditation—are increasingly explored for symptom management in PCOS. A recent meta-analysis reported that acupuncture may enhance

ovulation and reduce hyperandrogenism (Lim et al., 2021). Mind-body practices have also been associated with improvements in anxiety, depression, and self-esteem among women with PCOS (Zheng et al., 2024). Despite these promising findings, the overall quality of evidence remains variable. High-quality, large-scale randomized controlled trials are needed to clarify the efficacy and safety of integrative interventions and to define their role alongside conventional therapies.

3. Treatment Options for PCOS

3.1. Lifestyle Interventions

DietaryManagement

Lifestyle modification remains the first-line treatment for women with PCOS, particularly those who are overweight or obese (Teede et al., 2018). Dietary strategies, including low glycaemic index (GI) diets, calorie-restricted plans, and Mediterranean dietary patterns, have been shown to improve insulin sensitivity and reduce serum androgen levels. The Mediterranean diet, characterized by high intake of monounsaturated fats, fibre, and antioxidants, is also associated with reduced inflammation and improved endocrine and metabolic profiles in women with PCOS (Barrea et al., 2020).

Exercise

Regular aerobic and resistance exercise, typically totaling at least 150 minutes per week, enhances insulin sensitivity and supports weight management in women with PCOS. Exercise, whether performed alone or in combination with dietary modifications, has been shown to improve ovulatory function, reduce hyperandrogenism, and enhance psychological well-being (Harrison et al., 2012; Patel et al., 2021).

Behavioural Therapy

Cognitive-behavioural therapy (CBT) has demonstrated effectiveness in addressing psychological comorbidities commonly associated with polycystic ovary syndrome (PCOS), including depression, anxiety, and body image concerns. Given the significant emotional burden linked to symptoms such as weight gain, hirsutism, infertility, and menstrual irregularities, CBT provides structured strategies to help individuals identify and modify maladaptive thoughts and behaviours. Interventions that integrate CBT with lifestyle counselling—such as dietary guidance, physical activity support, and behavioural goal-setting—have been associated with improved treatment adherence and enhanced quality of life outcomes (Dokras et al., 2018; Bazarganipour et al., 2020). This combined approach

addresses both the psychological and physical dimensions of PCOS, promoting more comprehensive and sustainable management.

3.2 Pharmacological Treatments

Hormonal Therapies

Hormonal therapy remains a cornerstone in the pharmacological management of conditions characterized by menstrual irregularities and hyperandrogenism, particularly in anovulatory women. Combined oral contraceptives (COCs), typically composed of ethinyl estradiol and a progestin such as drospirenone, are widely recommended as first-line therapy. These agents effectively regulate menstrual cycles and improve clinical manifestations including acne and hirsutism. The therapeutic efficacy of COCs is primarily mediated through suppression of luteinizing hormone (LH) secretion, which consequently reduces ovarian androgen production. By decreasing circulating androgen levels, COCs contribute to the improvement of hyperandrogenic symptoms (Azziz et al., 2016). In addition to COCs, progestins administered either cyclically or continuously play a crucial role in endometrial protection. In anovulatory women who are not actively seeking pregnancy, prolonged unopposed estrogen exposure increases the risk of endometrial hyperplasia. Progestin therapy counteracts this effect by inducing regular endometrial shedding and maintaining endometrial integrity (ACOG, 2018). Overall, hormonal therapies not only address symptomatic concerns but also reduce long-term complications associated with chronic anovulation.

Insulin Sensitisers

Insulin sensitising agents play a central role in the management of polycystic ovary syndrome (PCOS), particularly in women exhibiting insulin resistance and metabolic dysfunction. Among these agents, metformin is the most widely used pharmacological option. Metformin improves peripheral insulin sensitivity, reduces hepatic glucose production, and lowers circulating insulin levels. Through the reduction of hyperinsulinemia, it indirectly decreases ovarian androgen synthesis, thereby contributing to improved menstrual regularity and ovulatory function. It is especially beneficial in women with impaired glucose tolerance or those at increased risk of type 2 diabetes mellitus (Morley et al., 2017). In addition to metformin, inositols have gained increasing attention as emerging therapeutic agents. Myo-inositol and D-chiro-inositol function as insulin sensitizers by acting as secondary messengers in insulin signalling pathways. Their use has been associated with improved insulin sensitivity, restoration of ovulation, and enhanced menstrual cyclicity. Furthermore, inositols

demonstrate a favourable safety and tolerability profile, making them an attractive option for long-term management in women with PCOS (Unfer et al., 2021). Overall, insulin sensitising therapies address both the metabolic and reproductive abnormalities characteristic of PCOS, thereby contributing to comprehensive disease management.

Ovulation Induction

Ovulation induction represents a key therapeutic strategy in women with polycystic ovary syndrome (PCOS) who desire pregnancy. Currently, letrozole, an aromatase inhibitor, is recommended as the first-line pharmacological agent for ovulation induction. Letrozole exerts its effect by inhibiting aromatase activity, thereby reducing estrogen synthesis and increasing follicle-stimulating hormone (FSH) secretion through negative feedback mechanisms. Clinical evidence demonstrates that letrozole is associated with higher live birth rates and improved endometrial receptivity compared to clomiphene citrate, making it the preferred initial treatment option (Legro et al., 2014). Clomiphene citrate**,** a selective estrogen receptor modulator, has historically been the standard first-line therapy and remains effective in approximately 75–80% of women. It induces ovulation by blocking estrogen receptors at the hypothalamus, thereby enhancing gonadotropin release. However, a subset of women exhibit resistance to clomiphene, limiting its efficacy in certain cases. For patients who do not respond to oral ovulation induction agents, gonadotropins are considered second-line therapy. These agents directly stimulate ovarian follicular development but require careful monitoring due to the increased risk of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS) (Brown et al., 2016). In summary, ovulation induction therapies are selected based on individual patient response, safety considerations, and reproductive goals, with letrozole currently regarded as the most effective first-line pharmacological option in women with PCOS.

Anti-Androgens

Anti-androgen therapy is primarily indicated for the management of clinical hyperandrogenism in women with polycystic ovary syndrome (PCOS), particularly in cases presenting with hirsutism, acne, and androgenic alopecia. Agents such as spironolactone, flutamide, and finasteride act through different mechanisms to reduce the effects of excess androgens at the target tissue level. Spironolactone functions as an androgen receptor antagonist and also inhibits androgen synthesis, thereby reducing hair growth and improving dermatological manifestations. Flutamide, a non-steroidal anti-androgen, competitively

blocks androgen receptors, while finasteride inhibits 5-alpha reductase, preventing the conversion of testosterone to its more potent form, dihydrotestosterone (DHT). Although these agents are effective in reducing hyperandrogenic symptoms, they do not address underlying ovulatory dysfunction. Importantly, anti-androgens carry a risk of teratogenicity, particularly affecting male fetal development. Therefore, their use must be combined with reliable contraception to prevent pregnancy during treatment (Carmina et al., 2020). Overall, anti-androgens serve as adjunctive therapy for symptomatic control of hyperandrogenism in women with PCOS.

3.3 Surgical Options

Laparoscopic ovarian drilling (LOD) is a minimally invasive surgical intervention indicated in women with polycystic ovary syndrome (PCOS) who are resistant to clomiphene citrate therapy. The procedure involves the use of electrocautery or laser energy to create multiple punctures in the ovarian cortex, thereby reducing androgen-producing stromal tissue. This reduction in intra-ovarian androgen levels helps restore normal hypothalamic–pituitary–ovarian axis function and may lead to spontaneous ovulation (Amer et al., 2017). LOD offers the advantage of potentially inducing ovulation without the need for prolonged pharmacological stimulation and may reduce the risk of multiple pregnancies compared to gonadotropin therapy. However, the procedure is not without risks. Potential complications include pelvic adhesions, perioperative morbidity, and a possible reduction in ovarian reserve due to excessive thermal damage. Therefore, careful patient selection and surgical expertise are essential when considering LOD as a second-line treatment option in women with clomiphene-resistant PCOS.

3.4 Emerging Therapies

GLP-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as promising therapeutic agents in the management of polycystic ovary syndrome (PCOS), particularly among women with obesity and metabolic dysfunction. Agents such as liraglutide and semaglutide were initially developed for the treatment of type 2 diabetes mellitus and obesity but have demonstrated potential benefits beyond glycaemic control. GLP-1 receptor agonists promote weight loss through appetite suppression, delayed gastric emptying, and enhanced satiety. In women with PCOS, weight reduction is strongly associated with improved insulin sensitivity, decreased hyperinsulinemia, and reduced ovarian androgen production. Emerging evidence

suggests that these agents may also contribute to the restoration of ovulatory function and improvement in menstrual regularity (Elkind-Hirsch et al., 2022). Given their dual metabolic and potential reproductive benefits, GLP-1 receptor agonists are increasingly being investigated as adjunctive therapy in PCOS management. However, further large-scale, long-term studies are required to establish their definitive role, optimal dosing strategies, and safety profile in reproductive-aged women.

Herbal Medicine and Supplements

Complementary and alternative therapies have gained increasing attention in the management of polycystic ovary syndrome (PCOS), particularly for women seeking adjunctive or non-pharmacological approaches. Several herbal supplements, including cinnamon**,** berberine, and N-acetylcysteine (NAC), have demonstrated potential benefits in improving metabolic and reproductive parameters. Cinnamon has been associated with enhanced insulin sensitivity and improved menstrual cyclicity in some clinical studies. Berberine, a bioactive compound extracted from various medicinal plants, has shown promising effects on glucose metabolism, lipid profiles, and androgen levels. Notably, some studies suggest that berberine may produce improvements in insulin resistance and hyperandrogenism comparable to those observed with metformin therapy (Wei et al., 2012; Oulad Saheb Madarek et al., 2020). N-acetylcysteine (NAC), an antioxidant and precursor of glutathione, has also been reported to enhance insulin sensitivity, promote ovulation, and improve menstrual regularity. Despite these encouraging findings, the current body of evidence is limited by small sample sizes and variability in study design. Therefore, large-scale, high-quality randomized controlled trials are necessary to confirm the efficacy, safety, and optimal dosing of these herbal and supplemental therapies in women with PCOS.

Bariatric Surgery

Bariatric surgery is considered a therapeutic option for women with polycystic ovary syndrome (PCOS) who are morbidly obese and have not achieved adequate clinical improvement with lifestyle modification and conventional medical therapies. Given the strong association between obesity, insulin resistance, and reproductive dysfunction in PCOS, substantial weight reduction can lead to meaningful metabolic and hormonal improvements. Surgical weight-loss procedures have been shown to produce significant and sustained reductions in body weight, which are accompanied by improvements in insulin sensitivity, decreased hyperandrogenism, and restoration of ovulatory function. Furthermore, evidence

suggests that bariatric surgery may enhance fertility outcomes and increase pregnancy rates in appropriately selected patients (Skubleny et al., 2016). Despite these benefits, bariatric surgery carries potential perioperative and long-term risks, including nutritional deficiencies and surgical complications. Therefore, careful patient selection, multidisciplinary evaluation, and long-term follow-up are essential to optimize outcomes in women with PCOS undergoing bariatric procedures.

CONCLUSION

Polycystic Ovary Syndrome (PCOS) represents a significant clinical and public health challenge owing to its complex pathophysiology, heterogeneous presentation, and long-term health consequences. As a multifactorial disorder affecting reproductive, metabolic, dermatological, and psychological domains, PCOS requires a comprehensive and patient-centered management strategy. Given its phenotypic variability, no single therapeutic approach is universally effective. Clinical decision-making should therefore be individualized, taking into account symptom severity, reproductive goals, metabolic risk profile, and patient preferences. Lifestyle modification remains the cornerstone of PCOS management, particularly in overweight and obese women. Dietary optimization, structured physical activity, and behavioral interventions have consistently demonstrated improvements in insulin sensitivity, ovulatory function, and hyperandrogenism. Even modest weight reduction can yield significant metabolic and reproductive benefits. Importantly, lifestyle interventions may also positively influence psychological well-being, addressing anxiety, depression, and body image concerns that are frequently under-recognized components of PCOS care. Pharmacological therapies serve as essential adjuncts for symptom control and fertility management. Combined oral contraceptives remain first-line therapy for menstrual irregularities and hyperandrogenic manifestations. Insulin sensitizers, including metformin and inositols, target underlying metabolic dysfunction and contribute to improved endocrine balance. For women desiring pregnancy, letrozole has emerged as the preferred first-line ovulation induction agent due to superior live birth outcomes compared with clomiphene citrate. In cases of treatment resistance, second-line interventions such as gonadotropins or laparoscopic ovarian drilling may be considered under careful monitoring. Emerging therapies, including GLP-1 receptor agonists and selected nutraceuticals such as berberine and N-acetylcysteine, demonstrate promising dual metabolic and reproductive effects. Nevertheless, robust randomized controlled trials are necessary to establish their long-term safety, optimal dosing strategies, and comparative effectiveness. Despite advances in

therapeutic options, important knowledge gaps persist. Long-term data regarding cardiovascular outcomes, malignancy risk, and quality of life remain limited. Additionally, lean women with PCOS and adolescent populations are underrepresented in clinical research, despite facing distinct diagnostic and therapeutic complexities. The integration of precision medicine approaches—incorporating biomarkers, genomics, and phenotype-specific strategies—may represent a future direction for individualized PCOS management. In conclusion, optimal management of PCOS must be holistic, evidence-based, and tailored to individual patient needs. An interdisciplinary approach integrating lifestyle modification, pharmacological therapy, surgical options, and emerging interventions is essential to address the multidimensional nature of the disorder. Future research should prioritize long-term outcomes, adolescent-specific care, and personalized treatment frameworks to enhance both clinical effectiveness and patient-centered outcomes.

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