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Review Article

Role of Metformin and Myo- inositol in Management of Insulin Resistance in PCOS

Mali Vedika*, Kelgonkar Prajakta, Khandagale Ashwini, Jadhav Pratiksha, Shaikh Agaz

Channabasweshwar Pharmacy College, Latur, Maharashtra, India - 413512

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting women of reproductive age and is frequently associated with insulin resistance, hyperinsulinemia, hyperandrogenism, menstrual irregularities, infertility, and long-term metabolic complications. Insulin resistance plays a central role in the pathogenesis of PCOS and contributes to both reproductive and metabolic abnormalities. Among the available insulin-sensitizing agents, metformin has long been considered the standard pharmacological therapy, while myo-inositol has emerged as a promising nutraceutical with favorable efficacy and tolerability. Objective: This review aims to evaluate the current evidence regarding the role of metformin and myo-inositol in the management of insulin resistance in women with PCOS, with particular emphasis on their mechanisms of action, clinical efficacy, safety profile, and the potential benefits of combination therapy. Methods: A comprehensive narrative review was conducted using published randomized controlled trials, systematic reviews, meta-analyses, clinical practice guidelines, and review articles available through PubMed, PubMed Central (PMC), Wiley Online Library, and other peer-reviewed databases. Approximately 30 relevant research and review articles published between 2002 and 2025 were analyzed to summarize current evidence regarding metformin, myo-inositol, and their combined use in women with PCOS. Results: The available evidence demonstrates that metformin improves insulin sensitivity primarily by reducing hepatic glucose production, enhancing peripheral glucose uptake, and decreasing circulating insulin levels. Myo-inositol acts as an intracellular insulin-signaling mediator, restoring insulin sensitivity, improving ovarian function, promoting ovulation, and reducing androgen excess. Clinical studies and recent meta-analyses indicate that both agents significantly improve metabolic and reproductive outcomes in women with PCOS. Furthermore, combination therapy with metformin and myo-inositol appears to provide greater improvements in insulin resistance, menstrual regularity, ovulation, hormonal balance, and metabolic parameters than either treatment alone, while also improving gastrointestinal tolerability and patient adherence. Conclusion: Current evidence supports both metformin and myo-inositol as effective insulin-sensitizing therapies for women with PCOS. Although metformin remains the standard pharmacological treatment, myo-inositol represents a safe and effective alternative or adjunct therapy. Combination therapy may offer superior clinical benefits by simultaneously targeting multiple mechanisms involved in insulin resistance and ovarian dysfunction. Further large-scale, multicenter randomized controlled trials with long-term follow-up are warranted to establish optimal dosing strategies and define the role of combination therapy in routine clinical practice.

Keywords: Polycystic ovary syndrome, PCOS, insulin resistance, metformin, myo-inositol, combination therapy, hyperinsulinemia, ovulation, insulin sensitizers, reproductive health.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine and metabolic disorders affecting women of reproductive age, with an estimated global prevalence ranging from 8% to 13%, depending on the diagnostic criteria used. The syndrome is characterized by a combination of hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, along with various metabolic

abnormalities. Beyond reproductive complications such as menstrual irregularities, anovulation, infertility, and pregnancy-related complications, PCOS is also associated with obesity, insulin resistance, dyslipidemia, type 2 diabetes mellitus, metabolic syndrome, and an increased risk of cardiovascular disease. Consequently, PCOS is recognized as a lifelong multisystem disorder that significantly affects the physical, reproductive, metabolic, and psychological health of affected women. Insulin resistance (IR) is considered a central pathophysiological feature of PCOS and is present in approximately 50–70% of affected women, irrespective of body mass index. In women with PCOS, insulin resistance results in compensatory hyperinsulinemia, which enhances ovarian androgen production by stimulating theca cells and suppressing hepatic synthesis of sex hormone-binding globulin (SHBG). Elevated androgen levels contribute to follicular arrest, chronic anovulation, menstrual dysfunction, hirsutism, acne, and infertility. Furthermore, prolonged insulin resistance increases the risk of impaired glucose tolerance, type 2 diabetes mellitus, non-alcoholic fatty liver disease, hypertension, and cardiovascular disorders. Therefore, improving insulin sensitivity has become one of the principal therapeutic strategies in the management of PCOS. Metformin, a biguanide insulin-sensitizing agent, has been widely used for several decades in women with PCOS because of its ability to reduce hepatic glucose production, improve peripheral glucose uptake, decrease circulating insulin concentrations, and indirectly reduce ovarian androgen production. Numerous randomized controlled trials, systematic reviews, and international clinical guidelines have demonstrated that metformin improves menstrual cyclicity, ovulation, metabolic parameters, and insulin sensitivity, particularly in overweight or obese women and those with impaired glucose tolerance. However, gastrointestinal adverse effects and variable patient tolerance may limit long-term adherence in some individuals. Myo-inositol, a naturally occurring carbocyclic polyol belonging to the vitamin B-complex family, has recently gained considerable attention as an effective insulin-sensitizing agent in PCOS. It functions as a precursor of inositol phosphoglycans, which serve as intracellular second messengers in insulin signaling pathways. Restoration of intracellular myo-inositol levels enhances insulin sensitivity, improves glucose metabolism, reduces hyperinsulinemia, restores normal ovarian function, promotes follicular maturation and ovulation, and lowers circulating androgen concentrations. Unlike metformin, myo-inositol is generally well tolerated and is associated with a favorable safety profile, making it an attractive therapeutic option, particularly for women who are intolerant to metformin. Recent clinical trials and meta-analyses suggest that combining metformin with myo-inositol may produce additive or synergistic therapeutic effects. Because the two agents improve insulin sensitivity through different but complementary mechanisms, combination therapy has been reported to produce greater improvements in insulin resistance, hormonal balance, menstrual regularity, ovulation rates, and metabolic outcomes than either agent alone while potentially reducing treatment-related adverse effects. Nevertheless, differences in study design, treatment duration, dosage regimens, and patient characteristics have resulted in some variability among published findings, highlighting the need for continued research. Given the growing burden of PCOS worldwide and the increasing availability of evidence regarding insulin-sensitizing therapies, a comprehensive evaluation of metformin and myo-inositol is warranted. This review critically summarizes the current literature on the role of metformin and myo-inositol in the management of insulin resistance in women with PCOS. It discusses the Pathophysiology of insulin resistance, mechanisms of action of both agents, clinical evidence, comparative studies, combination therapy, safety profile, current international recommendations, and future research directions to provide an evidence-based overview of their role in improving both metabolic and reproductive outcomes in women with PCOS

Mechanism of action: Metformin in PCOS

Metformin is a first-line insulin-sensitizing agent widely used in the management of type 2 diabetes mellitus and polycystic ovary syndrome (PCOS). Its therapeutic effects in PCOS extend beyond glucose control and include improvements in insulin sensitivity, hyperandrogenism, ovulation, menstrual regularity, and long-term metabolic health. The primary mechanism of metformin involves

suppression of hepatic gluconeogenesis and activation of the adenosine monophosphate-activated protein kinase (AMPK) pathway, although several AMPK-independent mechanisms have also been identified.

1. Reduction of Hepatic Glucose Production

The principal glucose-lowering effect of metformin is the inhibition of hepatic gluconeogenesis. Metformin accumulates within hepatocytes through organic cation transporters (OCTs), where it partially inhibits mitochondrial respiratory chain complex I. This reduces intracellular ATP production while increasing AMP concentrations, leading to decreased hepatic glucose synthesis. As a result, fasting blood glucose and circulating insulin levels decline, reducing compensatory hyperinsulinemia—a key contributor to insulin resistance in PCOS.

2. Activation of AMP-Activated Protein Kinase (AMPK)

Metformin activates AMPK, an intracellular energy-sensing enzyme that regulates glucose and lipid metabolism. Activation of AMPK produces several beneficial metabolic effects, including:

- Increased glucose uptake by skeletal muscle.
- Enhanced translocation of GLUT-4 transporters to the cell membrane.
- Inhibition of hepatic gluconeogenesis.
- Suppression of fatty acid and cholesterol synthesis.
- Promotion of fatty acid oxidation.
- Improvement in overall insulin sensitivity.

Through AMPK activation, metformin restores metabolic homeostasis and reduces the insulin resistance commonly observed in women with PCOS.

3. Improvement of Peripheral Insulin Sensitivity

Metformin enhances insulin-mediated glucose utilization in skeletal muscle and adipose tissue by improving insulin receptor signaling and increasing GLUT-4-mediated glucose transport. Consequently, peripheral tissues require less circulating insulin to maintain normal glucose levels, thereby reducing chronic hyperinsulinemia and improving whole-body insulin sensitivity.

4. Reduction of Hyperinsulinemia

Hyperinsulinemia plays a central role in the pathogenesis of PCOS by stimulating ovarian androgen production. By improving insulin sensitivity and reducing hepatic glucose output, metformin lowers circulating insulin concentrations. Reduced insulin levels decrease ovarian stimulation, helping to correct endocrine abnormalities associated with PCOS.

5. Reduction of Ovarian Androgen Production

Insulin directly stimulates ovarian theca cells to increase androgen synthesis through activation of steroidogenic enzymes such as CYP17A1. Metformin indirectly suppresses androgen production by lowering circulating insulin concentrations. In addition, experimental evidence suggests that metformin may directly inhibit steroidogenesis within ovarian theca and granulosa cells through AMPK-mediated mechanisms, leading to reduced testosterone concentrations and improvement of clinical hyperandrogenism.

6. Increase in Sex Hormone-Binding Globulin (SHBG)

Hyperinsulinemia suppresses hepatic synthesis of sex hormone-binding globulin (SHBG), resulting in increased free testosterone levels. Metformin reduces insulin concentrations, allowing hepatic SHBG production to increase. Higher SHBG levels reduce biologically active free testosterone, contributing to improvements in acne, hirsutism, and menstrual abnormalities.

7. Restoration of Ovulation and Menstrual Regularity

By lowering insulin resistance and androgen excess, metformin promotes normal follicular development and ovulation. Many clinical trials have demonstrated improved menstrual cyclicity, increased ovulation rates, and enhanced fertility, particularly in overweight or insulin-resistant women with PCOS. These reproductive benefits result primarily from correction of the underlying metabolic disturbance rather than direct stimulation of ovulation.

8. Effects on Lipid Metabolism and Body Weight

Metformin favorably influences lipid metabolism by reducing triglyceride synthesis, decreasing hepatic lipogenesis, increasing fatty acid oxidation, and modestly reducing body weight. It also improves serum lipid profiles by lowering total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides while improving overall metabolic health. These effects reduce cardiovascular risk in women with PCOS.

9. Anti-inflammatory and Antioxidant Effects

Chronic low-grade inflammation contributes significantly to insulin resistance in PCOS. Metformin suppresses inflammatory signaling pathways, including nuclear factor-kappa B (NF-κB), decreases pro-inflammatory cytokines such as TNF-α and IL-6, reduces oxidative stress, and improves endothelial function. These actions further enhance insulin sensitivity and may reduce long-term cardiovascular complications.

10. Overall Clinical Benefits in PCOS

Through its multiple metabolic and endocrine actions, metformin:

1. Improves insulin sensitivity.

2. Reduces hepatic glucose production.

3. Lowers fasting insulin concentrations.

4. Decreases ovarian androgen production.

5. Increases SHBG levels.

6. Restores ovulation and menstrual regularity.

7.Improves fertility outcomes.

8. Reduces body weight and improves lipid profile.

9. Lowers the risk of type 2 diabetes mellitus and metabolic syndrome.

These mechanisms make metformin one of the most effective pharmacological therapies for women with insulin-resistant PCOS and provide the scientific rationale for its widespread recommendation in international clinical guidelines.

Mechanism of action: Myo inositol in PCOS

Myo-inositol (MI) is a naturally occurring six-carbon cyclic polyol that belongs to the inositol family and is widely distributed in human tissues. It serves as a structural component of cell membranes and acts as a precursor for phosphatidylinositol phosphates and inositol phosphoglycans, which function as essential second messengers in insulin signal transduction. Increasing evidence from randomized controlled trials, systematic reviews, and international guidelines supports the role of myo-inositol as an effective insulin-sensitizing agent for women with polycystic ovary syndrome (PCOS). Unlike metformin, which primarily reduces hepatic glucose production, myo-inositol restores intracellular insulin signaling and improves both metabolic and reproductive functions with excellent tolerability.

1. Restoration of Insulin Signal Transduction

The principal mechanism of myo-inositol is the restoration of normal insulin signaling. Following insulin binding to its receptor, intracellular inositol phosphoglycans derived from myo-inositol act as second messengers that transmit the insulin signal to target tissues. In women with PCOS, impairment of this signaling pathway contributes to insulin resistance. Supplementation with myo-inositol replenishes intracellular inositol stores, improves insulin receptor signaling, and restores cellular responsiveness to insulin.

2. Enhancement of GLUT-4 Translocation and Glucose Uptake

Myo-inositol promotes translocation of glucose transporter type-4 (GLUT-4) from intracellular vesicles to the plasma membrane of skeletal muscle and adipose cells. Increased GLUT-4 expression enhances glucose uptake into peripheral tissues, lowers circulating blood glucose concentrations, and decreases compensatory hyperinsulinemia. Improved glucose utilization is one of the major mechanisms by which myo-inositol reduces insulin resistance in PCOS.

3. Improvement of Insulin Sensitivity

By restoring intracellular insulin signaling, myo-inositol increases tissue responsiveness to insulin without increasing insulin secretion. Improved insulin sensitivity reduces circulating insulin concentrations, thereby interrupting the vicious cycle of insulin resistance and hyperinsulinemia characteristic of PCOS. Clinical trials consistently demonstrate reductions in fasting insulin levels and HOMA-IR following myo-inositol therapy.

4. Regulation of Ovarian Function

Myo-inositol plays an essential role in ovarian physiology and is highly concentrated within ovarian follicles. It functions as an intracellular second messenger for follicle-stimulating hormone (FSH), promoting granulosa cell proliferation, follicular maturation, and oocyte development. Restoration of normal ovarian myo-inositol concentrations improves follicular growth, enhances oocyte quality, and increases spontaneous ovulation rates in women with PCOS.

5. Reduction of Hyperandrogenism

Hyperinsulinemia stimulates ovarian theca cells to produce excessive androgens while simultaneously suppressing hepatic synthesis of sex hormone-binding globulin (SHBG). By improving insulin sensitivity and lowering circulating insulin concentrations, myo-inositol indirectly reduces ovarian androgen synthesis. Experimental evidence also suggests that myo-inositol enhances aromatase activity within granulosa cells, facilitating the conversion of androgens into estrogens and thereby reducing hyperandrogenism. These endocrine effects contribute to improvements in acne, hirsutism, and menstrual dysfunction.

6. Correction of the Ovarian Myo-Inositol/D-Chiro-Inositol Imbalance

Under physiological conditions, the ovary maintains a high myo-inositol to D-chiro-inositol ratio. In PCOS, excessive insulin promotes conversion of myo-inositol to D-chiro-inositol, resulting in depletion of ovarian myo-inositol and impaired follicular development (the “ovarian paradox”). Supplementation with myo-inositol restores this balance, improves follicular function, and supports normal ovarian steroidogenesis. Evidence suggests that a physiological 40:1 ratio of myo-inositol to D-chiro-inositol provides optimal metabolic and reproductive benefits.

7. Improvement of Ovulation and Menstrual Regularity

Restoration of insulin sensitivity and normalization of ovarian hormone production promote resumption of regular ovulation. Numerous randomized controlled trials have shown that myo-inositol therapy improves menstrual cyclicity, ovulation rates, and fertility outcomes in women with PCOS. Improved oocyte quality further enhances reproductive success, particularly in women undergoing assisted reproductive techniques.

8. Anti-inflammatory and Antioxidant Effects

Myo-inositol also exerts indirect anti-inflammatory and antioxidant effects by reducing hyperinsulinemia and improving cellular metabolism. Reduced oxidative stress and inflammatory cytokine production contribute to improved endothelial function, enhanced insulin sensitivity, and lower long-term cardiometabolic risk in women with PCOS.

9. Clinical Significance in PCOS

Through its multiple molecular and endocrine actions, myo-inositol:

1. Restores intracellular insulin signaling.
2. Enhances GLUT-4-mediated glucose uptake.
3. Improves insulin sensitivity.
4. Lowers fasting insulin and HOMA-IR.
5. Reduces ovarian androgen production.
6. Improves follicular maturation and oocyte quality.
7. Restores ovulation and menstrual regularity.
8. Improves fertility outcomes.

9. Has a favorable safety profile with minimal adverse effects.

Because of these properties, myo-inositol is now considered an effective insulin-sensitizing therapy and an important alternative or adjunct to metformin in the management of insulin-resistant PCOS.

Clinical Evidences and Comparative Studies:

Insulin resistance is a major therapeutic target in women with polycystic ovary syndrome (PCOS). Over the past two decades, numerous randomized controlled trials (RCTs), systematic reviews, and meta-analyses have evaluated the effectiveness of metformin and myo-inositol, either as monotherapy or in combination. Overall, current evidence indicates that both agents improve insulin sensitivity and reproductive outcomes, although they differ in their mechanisms of action, tolerability, and clinical applications.

1. Clinical Evidence for Metformin

Metformin has been extensively investigated as the first pharmacological insulin-sensitizing agent for PCOS. Clinical studies consistently demonstrate that metformin reduces hepatic glucose production, improves peripheral insulin sensitivity, lowers fasting insulin concentrations, and decreases the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). These metabolic improvements are accompanied by reductions in serum testosterone levels, increases in sex hormone-binding globulin (SHBG), restoration of menstrual cyclicity, and improved ovulation rates. Women with obesity, impaired glucose tolerance, or type 2 diabetes appear to derive the greatest metabolic benefit from metformin therapy. Long-term treatment also reduces the risk of progression to type 2 diabetes mellitus and improves lipid metabolism.

2. Clinical Evidence for Myo-Inositol

Myo-inositol has emerged as an effective insulin-sensitizing therapy because it restores intracellular insulin signaling. Randomized clinical trials have demonstrated significant improvements in fasting insulin, HOMA-IR, menstrual regularity, ovulation frequency, ovarian function, and oocyte quality following myo-inositol supplementation. Several studies have also reported reductions in serum androgen concentrations, improvement in acne and hirsutism, and better fertility outcomes. Importantly, myo-inositol is associated with very few adverse effects, making it well tolerated even during prolonged treatment. However, the 2023 international evidence-based guideline concluded that although some metabolic and reproductive benefits are supported, the certainty of the available evidence remains low because of heterogeneity among studies.

3. Comparative Studies: Metformin versus Myo-Inositol

Several randomized controlled trials have directly compared metformin with myo-inositol. A 2019 systematic review and meta-analysis including six randomized clinical trials involving 355 women reported no statistically significant differences between metformin and myo-inositol regarding fasting insulin, HOMA-IR, serum testosterone, SHBG concentrations, or body mass index (BMI). Both therapies demonstrated comparable efficacy in improving metabolic and hormonal parameters. However, women receiving metformin experienced significantly more gastrointestinal adverse effects than those treated with myo-inositol, resulting in lower treatment tolerability. Similarly, the 2023 systematic review by Bodepudi et al., which evaluated randomized trials and previous meta-analyses, concluded that metformin and myo-inositol provide comparable improvements in insulin resistance, endocrine profile, menstrual function, and ovulation. The review emphasized that myo-inositol has a superior safety profile and may serve as an effective alternative in women who cannot tolerate metformin because of gastrointestinal side effects.

4. Evidence for Combination Therapy

Recent clinical investigations have focused on combination therapy using metformin together with myo-inositol, based on their complementary mechanisms of action. Metformin primarily suppresses hepatic gluconeogenesis and activates AMP-activated protein kinase (AMPK), whereas myo-inositol restores intracellular insulin signaling through inositol phosphoglycan second messenger pathways. A recent systematic review and meta-analysis of randomized controlled trials comparing

metformin alone with metformin plus myo-inositol found that combination therapy significantly improved hirsutism scores and reduced the luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio compared with metformin alone. Improvements in BMI and HOMA-IR favored combination therapy but did not reach statistical significance, possibly because of the limited number of participants and relatively short treatment duration. Several individual clinical trials have also reported better menstrual regularity, improved ovulation rates, enhanced hormonal balance, and higher patient satisfaction with combination therapy than with either agent alone. These findings suggest additive therapeutic effects when both drugs are administered together.

5. Safety and Tolerability

Safety remains an important consideration during long-term management of PCOS. Gastrointestinal adverse effects, including nausea, abdominal discomfort, diarrhea, and bloating, are the most frequently reported side effects of metformin and may reduce treatment adherence. In contrast, myo-inositol has demonstrated excellent tolerability with minimal adverse events across clinical studies. Meta-analyses consistently report significantly fewer gastrointestinal adverse effects among women treated with myo-inositol than among those receiving metformin. Consequently, myo-inositol is increasingly considered an attractive option for women who are unable to tolerate metformin or who prefer a nutraceutical approach.

6. Current Evidence-Based Perspective

Current evidence indicates that both metformin and myo-inositol are effective insulin-sensitizing therapies for women with PCOS. Metformin remains the preferred pharmacological therapy for women with obesity, impaired glucose tolerance, or significant metabolic abnormalities because of its robust evidence base and long-term clinical experience. Myo-inositol represents a safe and effective alternative, particularly for women seeking improved tolerability or fertility support. Combination therapy appears promising because it targets insulin resistance through complementary molecular pathways and may provide additional reproductive and endocrine benefits. Nevertheless, further large multicenter randomized controlled trials with standardized treatment protocols and longer follow-up are required to determine the optimal dosing strategy, duration of therapy, and patient populations most likely to benefit from combination treatment. Several susceptibility genes involved in insulin signaling, glucose metabolism, steroidogenesis, and inflammation have been implicated in the development of PCOS. Environmental factors such as sedentary lifestyle, high-calorie diet, obesity, sleep disturbances, and psychological stress further increase insulin resistance and accelerate disease progression. Although genetic predisposition cannot be modified, lifestyle interventions remain essential for improving insulin sensitivity and reducing long-term metabolic complications.

7. Clinical Consequences of Insulin Resistance

Insulin resistance has significant reproductive and metabolic consequences in women with PCOS. Persistent hyperinsulinemia contributes to chronic anovulation, menstrual irregularities, infertility, recurrent pregnancy loss, gestational diabetes, and poor reproductive outcomes. Metabolically, insulin resistance increases the risk of impaired glucose tolerance, type 2 diabetes mellitus, metabolic syndrome, dyslipidemia, hypertension, non-alcoholic fatty liver disease (NAFLD), endothelial dysfunction, and cardiovascular disease. Because insulin resistance represents the central pathological mechanism linking metabolic abnormalities with ovarian dysfunction, improving insulin sensitivity has become a primary therapeutic goal in PCOS management. Pharmacological agents such as metformin and myo-inositol improve insulin signaling through complementary mechanisms. Metformin primarily decreases hepatic glucose production and enhances peripheral glucose uptake via activation of AMP-activated protein kinase (AMPK), whereas myo-inositol functions as a second messenger in insulin signaling pathways, restoring insulin sensitivity and improving ovarian function. Recent evidence suggests that combination therapy with metformin and myo-inositol provides greater improvements in insulin resistance, endocrine abnormalities, and reproductive outcomes than either therapy alone.

CONCLUSION

Polycystic ovary syndrome (PCOS) is a complex endocrine and metabolic disorder in which insulin resistance plays a central role in the development of hyperinsulinemia, hyperandrogenism, ovulatory dysfunction, infertility, and long-term metabolic complications. Therefore, improving insulin sensitivity remains one of the primary therapeutic goals in the management of PCOS. The evidence reviewed in this paper indicates that both metformin and myo-inositol are effective insulin-sensitizing agents that improve metabolic and reproductive outcomes through different but complementary mechanisms. Metformin primarily acts by suppressing hepatic gluconeogenesis, activating AMP-activated protein kinase (AMPK), enhancing peripheral glucose uptake, and reducing circulating insulin concentrations. These effects improve insulin resistance, reduce androgen production, restore menstrual cyclicity, promote ovulation, and decrease the risk of type 2 diabetes mellitus and metabolic syndrome. Consequently, metformin remains the most established pharmacological therapy for women with PCOS, particularly those with obesity, impaired glucose tolerance, or significant metabolic abnormalities. Myo-inositol, in contrast, restores intracellular insulin signaling by acting as a precursor of inositol phosphoglycan second messengers. Clinical studies have demonstrated that myo-inositol improves insulin sensitivity, lowers fasting insulin and HOMA-IR, enhances ovarian function, promotes follicular maturation, improves oocyte quality, restores ovulation, and regulates menstrual cycles. In addition, myo-inositol is associated with an excellent safety profile and significantly fewer gastrointestinal adverse effects than metformin, making it an attractive option for women who are unable to tolerate metformin or who prefer a well-tolerated insulin-sensitizing therapy. Comparative clinical studies and recent meta-analyses suggest that metformin and myo-inositol produce broadly similar improvements in many hormonal and metabolic parameters, although metformin may provide greater benefits for central adiposity and hirsutism in some patient groups. Emerging evidence also indicates that combination therapy with metformin and myo-inositol may provide additive or synergistic benefits by targeting insulin resistance through complementary molecular pathways, resulting in greater improvements in insulin sensitivity, endocrine abnormalities, menstrual regularity, ovulation, and overall reproductive outcomes than either therapy alone. Nevertheless, the magnitude of these additional benefits varies among studies because of differences in patient populations, treatment duration, and study design. Overall, current evidence supports the use of metformin as the first-line pharmacological insulin-sensitizing therapy in appropriately selected women with PCOS, while myo-inositol represents a safe and effective alternative or adjunctive treatment. Individualized therapy based on patient characteristics, metabolic profile, reproductive goals, treatment tolerance, and shared decision-making is likely to provide the greatest clinical benefit. Future large-scale, multicenter randomized controlled trials with standardized treatment protocols and longer follow-up are required to determine the optimal dosage, duration, and patient selection for combination therapy and to strengthen the evidence base for integrating myo-inositol into routine clinical practice.

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REFERENCES

1. Bodepudi R, et al. Myoinositol versus Metformin in the Treatment of Polycystic Ovarian Syndrome: A Systematic Review. Cureus. 2023;15(7):e41748. Doi:10.7759/cureus.41748.
2. Kelly FA, Lôbo AD, Andrade IB, et al. Comparison of Metformin with Inositol versus Metformin Alone in Women with Polycystic Ovarian Syndrome (PCOS): A Systematic Review and Meta-analysis of Randomized Controlled Trials. 2024.
3. Youssef MA, et al. Effects of Myo-Inositol vs. Metformin on Hormonal and Metabolic Parameters in Women with PCOS: A Meta-analysis. Irish Journal of Medical Science. 2023. Doi:10.1007/s11845-023-03388-5.
4. Facchinetti F, Bizzarri M, Benvenga S, et al. Inositol for Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis to Inform the 2023 International Evidence-Based PCOS

Guideline. Journal of Clinical Endocrinology & Metabolism. 2024.
5. Bizzarri M, Carlomagno G. Metformin and Myo-Inositol: A Comparative Analysis. Gynecologic and Obstetric Investigation. 2025.
6. Genazzani AD, Lanzoni C, Ricchieri F, Jasonni VM. Myo-Inositol Administration Positively Affects Hyperinsulinemia and Hormonal Parameters in Women with PCOS.
7. Gerli S, Mignosa M, Di Renzo GC. Effects of Myo-Inositol on Ovarian Function and Metabolic Factors in Women with PCOS.
8. Costantino D, Minozzi G, Minozzi E, Guaraldi C. Metabolic and Hormonal Effects of Myo-Inositol in Women with PCOS.
9. Unfer V, Carlomagno G, Dante G, Facchinetti F. Effects of Myo-Inositol in Women with PCOS: A Systematic Review.
10. Nordio M, Proietti E. The Combined Therapy with Myo-Inositol and D-Chiro-Inositol Reduces Insulin Resistance in PCOS.
11. Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and Metabolic Effects of D-Chiro-Inositol in Women with Polycystic Ovary Syndrome.
12. Palomba S, Falbo A, Zullo F, Orio F Jr. Evidence-Based and Potential Benefits of Metformin in the Polycystic Ovary Syndrome.
13. Lord JM, Flight IHK, Norman RJ. Metformin in Polycystic Ovary Syndrome: Systematic Review and Meta-analysis.
14. Morley LC, Tang T, Yasmin E, Norman RJ, Balen AH. Metformin for Women with Polycystic Ovary Syndrome.
15. Teede HJ, Misso ML, Costello MF, et al. International Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. 2023.
16. Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline.
17. Diamanti-Kandarakis E, Dunaif A. Insulin Resistance and the Polycystic Ovary Syndrome Revisited.
18. Dunaif A. Insulin Resistance in Women with Polycystic Ovary Syndrome.
19. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-Sensitizing Drugs (Metformin) for Women with PCOS.
20. Baillargeon JP, Iuorno MJ, Nestler JE. Insulin Sensitizers for the Treatment of PCOS.
21. Carlomagno G, Unfer V. Inositol Safety and Clinical Applications in PCOS.
22. Facchinetti F, Orrù B, Grandi G, Unfer V. Myo-Inositol in Reproductive Medicine.
23. Unfer V, Carlomagno G. Myo-Inositol: Basic and Clinical Aspects in PCOS.
24. Bevilacqua A, Bizzarri M. Physiological Role of Inositols in Insulin Signaling.
25. Croze ML, Soulage CO. Potential Role and Therapeutic Interests of Myo-Inositol in Metabolic Diseases.
26. Genazzani AD, Santagni S, Rattighieri E. Myo-Inositol in the Treatment of Insulin Resistance Associated with PCOS.
27. Orio F Jr, Muscogiuri G, Palomba S. Metabolic Features of Polycystic Ovary Syndrome and Current Pharmacological Management.
28. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R. Polycystic Ovary Syndrome: Etiology, Pathogenesis, and Diagnosis.
29. Escobar-Morreale HF. Polycystic Ovary Syndrome: Definition, Aetiology, Diagnosis, and Treatment.
30. Azziz R, Carmina E, Chen Z, et al. Polycystic Ovary Syndrome. Nature Reviews Disease Primers. 2016; 2:16057.

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