



QUALITY IN SPORT

eISSN 2450-3118 · Open Access · Peer-reviewed

apcz.umk.pl/QS Nicolaus Copernicus University in Toruń



Cite as: BISKUP, Alicja, WNEK, Agata, SMAGOWSKA, Julia, STASZKO, Natalia, KALA-KAZISZYN, Ewa, BAŁA, Kamila and STANKO, Mikołaj. Inositols in PCOS/PMOS: therapeutic role, metabolic implications, and combination with metformin. *Quality in Sport*. 2026;58:72611. <https://doi.org/10.12775/QS.2026.58.72611>

ARTICLE TIMELINE

Received: 25.05.2026. Revised: 30.05.2026. Accepted: 31.05.2026. Published: 20.06.2026.

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines: Medical Sciences; Health Sciences.

Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Nauki medyczne; Nauki o zdrowiu. © The Authors 2026.

OPEN ACCESS · CC BY-NC-SA 4.0 This article is published with open access under the License Open Journal Systems of Nicolaus Copernicus University in Toruń, Poland, and is distributed under the terms of the Creative Commons Attribution Non-commercial Share Alike License (<http://creativecommons.org/licenses/by-nc-sa/4.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the work is properly cited. The authors declare no conflict of interest regarding the publication of this paper.

Inositols in PCOS/PMOS: Therapeutic Role, Metabolic Implications, and Combination with Metformin

Authors

Alicja Biskup ORCID: 0009-0001-2228-1478 Email: alicja.b2104@gmail.com
Uniwersyteckie Centrum Stomatologii Śląskiego Uniwersytetu Medycznego w Katowicach
sp.z o.o., Bytom

Agata Wnek ORCID: 0009-0004-5384-4597 Email: agatawn.contact@gmail.com
5 Wojskowy Szpital Kliniczny z Polikliniką SP ZOZ w Krakowie

Julia Smagowska ORCID: 0009-0003-4275-0846 Email: juliasmagowska1@gmail.com
Uniwersyteckie Centrum Stomatologii Śląskiego Uniwersytetu Medycznego w Katowicach
sp.z o.o., Bytom

Ewa Kala-Kaziszyn ORCID: 0009-0006-2062-4875 Email: ewak612@gmail.com
Stomatologia Adeeb Clinic Wahab Adeeb w Dąbrowie Górniczej

Natalia Staszko ORCID: 0009-0005-8335-5257 Email: natalia.staszko@student.umw.edu.pl 4
Wojskowy Szpital Kliniczny z Polikliniką SP ZOZ we Wrocławiu

Kamila Bała ORCID: 0009-0008-2621-7677 Email: kamila.bala@wp.pl
4 Wojskowy Szpital Kliniczny z Polikliniką SP ZOZ we Wrocławiu

Mikołaj Stańko ORCID: 0009-0006-8703-4482
Email:mikolaj.stanko17501@student.akademiaslaska.pl
Academy of Silesia, Faculty of Medicine, Katowice, Poland

Corresponding Author

Alicja Biskup e-mail: alicja.b2104@gmail.com

1. Abstract

Polycystic Ovary Syndrome (PCOS) is a heterogeneous endocrine–metabolic disorder associated with reproductive dysfunction, hyperandrogenism, insulin resistance, and increased cardiometabolic risk. Following recent international consensus, the term polyendocrine metabolic ovarian syndrome (PMOS) has been proposed to better reflect the multisystem and metabolic nature of the condition. Due to the central role of insulin resistance in disease pathophysiology, insulin-sensitizing therapies, including myo-inositol (MI), D-chiro-inositol (DCI), and metformin, have gained increasing clinical interest.

This literature review aimed to evaluate current evidence regarding the efficacy of MI and DCI in women with PCOS/PMOS, with particular emphasis on metabolic, hormonal, and reproductive outcomes, as well as their role in adjunctive therapy with metformin. A literature search was conducted using PubMed, Scopus, Web of Science, and Google Scholar, including randomized controlled trials, systematic reviews, meta-analyses, and current clinical guidelines published between 2015 and 2026.

Available evidence suggests that MI and DCI may improve insulin sensitivity, reduce hyperinsulinemia, and contribute to favorable changes in selected hormonal and reproductive

parameters, including menstrual cycle regularity and ovulatory function. The 40:1 MI/DCI ratio remains the most extensively investigated formulation and appears to reflect physiological proportions between both isomers. Metformin continues to play a central therapeutic role, particularly in women with insulin resistance, overweight, or obesity, while combination therapy with inositols may offer additional benefits in selected clinical settings. However, findings remain heterogeneous and limited by methodological differences among studies.

The transition from PCOS to PMOS underscores the metabolic and multisystem complexity of the disorder and may further support individualized treatment approaches targeting insulin resistance. Nevertheless, further high-quality randomized controlled studies are required to determine the long-term efficacy and optimal clinical use of inositols in PCOS/PMOS management.

2. Introduction

2.1 Characteristics of Polycystic Ovary Syndrome

Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age. It is estimated to affect approximately 10–13% of the female population, although prevalence rates vary depending on the diagnostic criteria applied and the characteristics of the studied population. PCOS is a disorder with a heterogeneous clinical presentation, encompassing reproductive, hormonal, and metabolic disturbances, which significantly affect patients' quality of life and increase the risk of metabolic and cardiovascular diseases (1).

Currently, the most widely used diagnostic criteria are the Rotterdam criteria, according to which the diagnosis of Polycystic Ovary Syndrome requires the presence of at least two of the following three features: oligo- or anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovarian morphology identified on ultrasound examination, after excluding other causes of hyperandrogenism and menstrual irregularities. An alternative diagnostic approach has been proposed by the Androgen Excess and PCOS Society (AE-PCOS), according to which hyperandrogenism constitutes an essential criterion for diagnosis. Differences between diagnostic systems influence the identification of specific clinical phenotypes of PCOS (1,2).

Based on the Rotterdam criteria, four main phenotypes of Polycystic Ovary Syndrome are distinguished: the classic phenotype A, characterized by hyperandrogenism, ovulatory

dysfunction, and polycystic ovarian morphology; phenotype B, involving hyperandrogenism and ovulatory dysfunction; phenotype C, referred to as ovulatory PCOS, characterized by hyperandrogenism and polycystic ovarian morphology; and phenotype D, involving ovulatory dysfunction and polycystic ovarian morphology without signs of hyperandrogenism. Individual phenotypes may differ in the severity of metabolic and reproductive manifestations(3,4).

The clinical presentation of Polycystic Ovary Syndrome is heterogeneous. The most commonly observed symptoms include menstrual irregularities, such as oligomenorrhea or amenorrhea, resulting from chronic anovulation. Hyperandrogenism also remains a significant clinical feature, manifesting as hirsutism(5,6), acne (6) and androgenic alopecia. Ovulatory dysfunction is one of the leading causes of infertility in women with PCOS. Furthermore, many patients present with coexisting insulin resistance, overweight or obesity, dyslipidemia, and an increased risk of developing type 2 diabetes mellitus and metabolic syndrome(7) (8) (1).

2.2. Pathophysiology of Polycystic Ovary Syndrome

The pathophysiology of Polycystic Ovary Syndrome is multifactorial and remains the subject of extensive research. One of the most important mechanisms underlying the disorder is insulin resistance, which occurs both in women with obesity and in a proportion of patients with normal body weight. Reduced tissue sensitivity to insulin leads to compensatory hyperinsulinemia, which plays a significant role in exacerbating the hormonal disturbances observed in the course of PCOS (9) (10) (11) (12).

Hyperinsulinemia may increase androgen production by ovarian theca cells through the enhancement of luteinizing hormone (LH) activity and may also reduce the concentration of sex hormone-binding globulin (SHBG), resulting in elevated levels of circulating free androgens. Additionally, women with Polycystic Ovary Syndrome often exhibit dysfunction of the hypothalamic–pituitary–ovarian axis, leading to increased secretion of LH relative to follicle-stimulating hormone (FSH). This imbalance may impair ovarian follicle maturation and contribute to chronic anovulation(10) (13) (12).

An increasing body of evidence also suggests the involvement of chronic low-grade inflammation in the pathogenesis of Polycystic Ovary Syndrome. Patients have been shown to exhibit elevated levels of inflammatory markers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF- α), which may further exacerbate the metabolic and hormonal disturbances associated with the disorder(14) (15,16).

3. Aim

The aim of this study was to analyze current scientific evidence regarding the use of myo-inositol (MI) and D-chiro-inositol (DCI) in the treatment of Polycystic Ovary Syndrome, with particular emphasis on their effects on metabolic, hormonal, and reproductive parameters in women of reproductive age. An assessment was conducted regarding the efficacy of inositol supplementation in improving insulin sensitivity, regulating the menstrual cycle, enhancing ovulatory function, reducing hyperandrogenism, and influencing fertility outcomes in patients with PCOS. Particular attention was also devoted to analyzing the role of myo-inositol and D-chiro-inositol as adjunctive therapy to metformin, taking into account the potential benefits of combination treatment as well as the current position of inositols in therapeutic management in accordance with the latest clinical guidelines and available scientific evidence.

4. Materials and Methods

This study is a literature review based on the analysis of current scientific publications concerning the use of myo-inositol (MI) and D-chiro-inositol (DCI) in the treatment of Polycystic Ovary Syndrome/PMOS. The literature search was conducted using the PubMed, Scopus, and Web of Science databases, with supplementary searches performed through Google Scholar. The search strategy included terms such as *PCOS*, *PMOS*, *myo-inositol*, *D-chiro-inositol*, *metformin*, *insulin resistance*, *infertility*, and *hyperandrogenism*.

English-language publications from 2015–2026 were included in the analysis, including randomized controlled trials (RCTs), systematic reviews, meta-analyses, and current clinical guidelines. Case reports, studies with small sample sizes lacking control groups, and publications of limited methodological quality were excluded. The analysis focused on the effects of inositols on metabolic, hormonal, and reproductive parameters, as well as their role in combination therapy with metformin.

5. Mechanism of Action of Myo-Inositol and D-Chiro-Inositol in PCOS

5.1. Characteristics of Inositols

Inositols are cyclic sugar alcohols naturally occurring in the human body, with myo-inositol (MI) and D-chiro-inositol (DCI) being the most important isomers in the context of Polycystic Ovary Syndrome. Both compounds are involved in insulin signal transduction as components of intracellular secondary messengers, influencing glucose metabolism, the activity of insulin-

related enzymes, and the function of insulin-sensitive tissues (17,18). Disturbances in the conversion of MI to DCI, as well as abnormal ratios between these isomers, may play a role in the pathophysiology of PCOS, particularly in the context of insulin resistance, hyperinsulinemia, and impaired ovarian function (19–21).

In Polycystic Ovary Syndrome, the significance of inositols primarily stems from their potential to improve insulin sensitivity. Insulin resistance leads to compensatory hyperinsulinemia, which enhances ovarian androgen production and further exacerbates ovulatory dysfunction. For this reason, MI and DCI are being investigated as compounds that may support the metabolic treatment of PCOS, particularly in patients with impaired glucose metabolism. However, current systematic reviews indicate that despite promising findings, the effectiveness of inositols depends on dosage, duration of use, formulation type, and patient characteristics (22,23).

5.2. Myo-Inositol

Myo-inositol (MI) is considered the primary inositol isomer associated with the regulation of insulin sensitivity and ovarian function. Through its involvement in insulin signaling pathways, it may influence cellular glucose uptake and contribute to improvements in metabolic parameters, such as insulin concentration, the HOMA-IR index, and lipid profile (18,24). In the context of Polycystic Ovary Syndrome, this is of particular importance, as improved tissue responsiveness to insulin may reduce hyperinsulinemia and, consequently, decrease excessive ovarian androgen production.

MI also plays an important role in ovarian function. The literature highlights its involvement in ovarian follicle maturation, the regulation of granulosa cell responsiveness to follicle-stimulating hormone (FSH), and the support of oocyte maturation. For this reason, myo-inositol has been investigated not only in the context of improving menstrual cycle regularity and ovulation but also in assisted reproductive technologies (ART). Some studies suggest that MI may positively influence oocyte quality and ovarian response to stimulation, particularly in women with Polycystic Ovary Syndrome(17,25–28).

5.3. D-Chiro-Inositol

D-chiro-inositol (DCI) is primarily involved in mechanisms related to glucose metabolism and glycogen storage. In the human body, it is partially synthesized from myo-inositol through the

action of an insulin-dependent epimerase enzyme. In women with Polycystic Ovary Syndrome, particularly in the presence of hyperinsulinemia, disturbances in this conversion process and an abnormal MI-to-DCI ratio within ovarian tissue may occur (29,30).

DCI may influence ovarian steroidogenesis; however, its effects require particularly cautious interpretation. Some evidence suggests that excessive levels of D-chiro-inositol within the ovary may contribute to disturbances in steroid balance and negatively affect oocyte quality. For this reason, the use of high doses of DCI or formulations with an inappropriate MI:DCI ratio remains controversial, particularly in women without significant insulin resistance or in patients undergoing treatment for infertility(31–33).

It should be emphasized, however, that DCI should not be regarded solely as a potentially unfavorable compound. When administered in appropriate doses and proportions, it may complement the effects of MI, particularly with regard to improving metabolic parameters. Current literature rather highlights the importance of an appropriate ratio between the two isomers than the superiority of either one in every clinical setting(20,25).

5.4. Significance of the 40:1 Ratio

The most frequently investigated therapeutic combination is the administration of myo-inositol and D-chiro-inositol in a 40:1 ratio. The biological rationale for this proportion is based on observations indicating that it reflects the physiological MI-to-DCI ratio in plasma and may better represent the natural balance between the two isomers in the body. Experimental and clinical studies have suggested that this ratio may positively influence ovulation, ovarian steroidogenesis, and metabolic parameters in women with Polycystic Ovary Syndrome (19,31,34,35).

The 40:1 ratio is also frequently regarded as a compromise between the effects of MI, which are important for ovarian function and oocyte quality, and the actions of DCI, which are primarily associated with insulin regulation and glucose metabolism. Experimental studies suggest that the MI/DCI combination in this proportion may support the expression of genes related to aromatase and the follicle-stimulating hormone (FSH) receptor, while also reducing excessive androgen production in PCOS models(19,20).

Despite the popularity of the 40:1 ratio, its superiority over other treatment regimens has not been conclusively established. Recent systematic reviews emphasize that available studies

differ considerably in terms of sample size, treatment duration, dosage, inclusion criteria, and assessed outcomes(22,23). Therefore, inositols, including MI/DCI 40:1 formulations, should be considered a potential adjunctive therapy rather than a definitive substitute for standard treatment, particularly metformin in patients with pronounced metabolic disturbances (36,37) (1,38,39).

6. Effectiveness of Inositols in the Treatment of PCOS

6.1. Impact on Metabolic Function

Metabolic disturbances constitute one of the key components of the clinical presentation of Polycystic Ovary Syndrome. A substantial proportion of women with PCOS exhibit insulin resistance, hyperinsulinemia, impaired glucose tolerance, an increased risk of type 2 diabetes mellitus, and lipid abnormalities, regardless of the presence of obesity. Given the role of insulin resistance in the pathogenesis of the disorder, particular attention has been directed toward the use of myo-inositol (MI) and D-chiro-inositol (DCI) as compounds potentially capable of improving insulin sensitivity and exerting beneficial effects on the metabolic parameters of women with PCOS(1) (10) (9) (40).

One of the most frequently analyzed metabolic parameters is the HOMA-IR (*Homeostatic Model Assessment for Insulin Resistance*) index, which is used to assess the degree of insulin resistance(41–43). Results from numerous clinical studies suggest that inositol supplementation may lead to a reduction in HOMA-IR values in women with Polycystic Ovary Syndrome, particularly among patients with coexisting overweight, obesity, or impaired insulin metabolism. In the meta-analysis by Fitz et al. (2024), a moderate improvement in selected metabolic parameters was demonstrated; however, the authors emphasized the limited quality of some of the available evidence and the considerable heterogeneity among studies(22,41).

A positive effect of MI and DCI supplementation has also been observed with regard to fasting insulin levels and glucose metabolism. Some studies indicate a reduction in insulin concentration and improved glucose tolerance following the administration of preparations containing MI or a combination of MI/DCI, particularly in the 40:1 ratio. This mechanism is explained by the involvement of inositols in insulin signaling pathways and their ability to enhance the efficiency of glucose transport into cells. At the same time, not all studies have demonstrated statistically significant differences compared with control groups, which may

result from variations in treatment protocols, supplementation duration, and phenotypic differences among patients (44) (22,45) .

The effects of inositols on body weight and body mass index (BMI) remain less conclusive. Although some studies indicate a modest reduction in body weight and BMI, particularly among women with overweight or obesity, these effects have not been consistently confirmed across all analyses. Recent systematic reviews emphasize that inositols should not be regarded as a standalone method for weight reduction, and their metabolic efficacy appears to be greater when combined with lifestyle modifications, including dietary intervention and physical activity (22) (8,46).

An important component of the metabolic assessment in women with Polycystic Ovary Syndrome is the lipid profile. Study findings suggest that MI and DCI supplementation may exert beneficial effects on certain lipid metabolism parameters, including reductions in triglyceride levels, total cholesterol, and low-density lipoprotein (LDL) cholesterol, accompanied by an increase in high-density lipoprotein (HDL) cholesterol. However, it should be noted that data regarding lipid profile outcomes are more limited than those concerning insulin sensitivity parameters, and the observed benefits do not always reach statistical significance(18) (47) (48).

6.2. Effects of Inositols on Hormonal Function

Hormonal disturbances constitute one of the principal components of the clinical presentation of Polycystic Ovary Syndrome and primarily include hyperandrogenism and dysregulation of the hypothalamic–pituitary–ovarian axis. Given the effects of myo-inositol (MI) and D-chiro-inositol (DCI) on insulin sensitivity and ovarian steroidogenesis, their potential impact on the hormonal profile of women with PCOS has been extensively investigated (1).

Studies suggest that inositol supplementation may lead to reductions in total and free testosterone levels, primarily through improved insulin sensitivity and the reduction of hyperinsulinemia, which stimulates androgen synthesis in ovarian theca cells. Some studies have also reported increased concentrations of sex hormone-binding globulin (SHBG), which may reduce the amount of circulating free androgens and alleviate the clinical manifestations of hyperandrogenism(22) (12) (20) (45).

The effects of inositols have also been observed in relation to the LH/FSH ratio, which remains disrupted in some women with Polycystic Ovary Syndrome due to increased secretion of luteinizing hormone (LH). Normalization of the LH/FSH ratio may contribute to improved follicular maturation and ovulatory function. However, study findings remain partially inconclusive, and not all meta-analyses have demonstrated statistically significant hormonal changes following MI/DCI supplementation (44) (49).

6.3. Effects of Inositols on Menstrual Cycle Regularity and Ovulation

Menstrual irregularities and chronic anovulation are among the most common reproductive manifestations of Polycystic Ovary Syndrome. Inositols, primarily myo-inositol (MI) and D-chiro-inositol (DCI), may support ovarian function through improvements in insulin sensitivity, reduction of hyperinsulinemia, and modulation of ovarian steroidogenesis. As a result, they may indirectly contribute to the restoration of regular menstrual cycles and ovulation in a proportion of patients with PCOS (22).

Clinical studies and systematic reviews have demonstrated that inositol supplementation may positively affect menstrual cycle regularity and ovulation frequency, particularly in women with ovulatory dysfunction and insulin resistance. The recent meta-analysis by Fitz et al. (2024) suggests potential benefits of DCI with regard to ovulation; however, the authors emphasized that the quality of evidence remains limited and that not all evaluated outcomes demonstrate unequivocal improvement (22).

The effects of inositols on pregnancy rates are assessed with greater caution. Some studies have reported improvements in ovulation rates and clinical pregnancy outcomes, particularly when inositols were used as part of infertility treatment preparation or within assisted reproductive therapy. A 2025 meta-analysis concerning assisted reproductive technologies (ART) suggested an increase in clinical pregnancy rates following MI/DCI supplementation; however, these findings primarily apply to patient populations undergoing assisted reproduction procedures and therefore should not be directly generalized to all women with Polycystic Ovary Syndrome (50) (27,51).

Comparisons between inositols and metformin suggest that differences in reproductive outcomes between these therapies may be minimal or uncertain. A 2023 review comparing MI and metformin indicated comparable efficacy across certain clinical parameters, with MI demonstrating better tolerability. More recent publications, however, emphasize that despite

the widespread use of inositols in clinical practice, evidence regarding their effects on fertility remains limited and requires further randomized controlled studies (1,22,52).

6.4. The Role of Inositols in the Treatment of Infertility

Infertility in women with Polycystic Ovary Syndrome most commonly results from chronic anovulation and impaired ovarian follicle maturation. According to current clinical guidelines, letrozole remains the first-line treatment for ovulation induction in women with PCOS and anovulatory infertility, whereas IVF/ICSI is generally considered after failure of first- and second-line treatment. Inositols do not replace standard ovulation induction therapies; however, they may be considered as adjunctive treatment, particularly in patients with insulin resistance and metabolic disturbances (1,22,53).

The role of inositols has also been evaluated in patients with Polycystic Ovary Syndrome undergoing assisted reproductive procedures. In the context of IVF/ICSI, MI has been suggested to improve the follicular environment, ovarian response to stimulation, and oocyte quality. A 2025 meta-analysis involving women with PCOS undergoing assisted reproductive technologies (ART) indicated a possible improvement in ovarian function and fertility-related parameters following MI/DCI supplementation; however, the authors emphasized the need for further well-designed randomized controlled trials (41,50).

The effects of inositols on oocyte quality represent one of the most intriguing areas of research. MI participates in cellular signaling pathways that are essential for oocyte maturation and granulosa cell function. Reviews concerning assisted reproductive technologies (ART) suggest that MI supplementation may increase the proportion of mature oocytes at the metaphase II (MII) stage and improve fertilization rates; however, evidence regarding embryo quality, implantation rates, and live birth outcomes remains less conclusive (25,28,41,51).

Results regarding ART-related outcomes, such as the number of retrieved oocytes, embryo quality, implantation, clinical pregnancy, and live birth rates, remain heterogeneous. Some analyses suggest an improvement in clinical pregnancy rates following inositol supplementation, particularly among patients with Polycystic Ovary Syndrome; however, evidence concerning live birth outcomes remains limited. Therefore, inositols should be regarded primarily as a potential adjunctive support in infertility treatment rather than a standalone therapeutic approach capable of replacing ovulation induction or ART procedures (50,54) (55).

7. Metformin in the Treatment of PCOS — Current Role in Therapy

Metformin is an oral insulin-sensitizing agent whose primary mechanism of action includes reducing hepatic glucose production, improving peripheral insulin sensitivity, and decreasing hyperinsulinemia. In the context of Polycystic Ovary Syndrome, this is of particular importance, as insulin resistance and compensatory hyperinsulinemia contribute to increased ovarian androgen production and impaired ovulation. For this reason, metformin remains an important reference point for therapies aimed at improving metabolic parameters, including inositol-based interventions (36–38,56) (17,39,45).

According to the 2023 international clinical guidelines, Metformin is recommended primarily for women with Polycystic Ovary Syndrome and a body mass index (BMI) ≥ 25 kg/m² to improve anthropometric and metabolic parameters, including insulin resistance, glycemic control, and lipid profile. It may also be considered in patients with a BMI < 25 kg/m²; however, the strength of recommendation is lower in this group. In the management of hyperandrogenic symptoms and irregular menstrual cycles, combined oral contraceptives generally remain the first-line treatment, whereas metformin plays a more prominent role in the presence of coexisting metabolic disturbances (1,22).

A limitation of Metformin therapy is its variable tolerability. The most common adverse effects involve the gastrointestinal tract and include nausea, diarrhea, abdominal pain, bloating, and a metallic taste in the mouth. These symptoms may contribute to reduced adherence to therapeutic recommendations. In clinical practice, the risk of adverse effects may be minimized through gradual dose escalation, administration of the medication with meals, and the use of extended-release formulations (37,39).

8. Inositols as Adjunctive Therapy to Metformin

8.1. Combination Therapy

Combination therapy involving Metformin and myo-inositol (MI) has been investigated as a potential treatment strategy for women with Polycystic Ovary Syndrome, particularly in patients with insulin resistance, hyperinsulinemia, menstrual irregularities, or an incomplete response to metformin monotherapy. The rationale for this combination arises from the distinct yet partially complementary mechanisms of action of both substances: metformin reduces hepatic glucose production and improves peripheral insulin sensitivity, whereas MI participates in intracellular insulin signaling and may influence ovarian function (1,38).

Most available evidence concerns the combination of MI and metformin, whereas data regarding treatment regimens involving DCI and metformin remain more limited. D-chiro-inositol may support glucose metabolism and insulin activity; however, its effects on ovarian steroidogenesis likely depend on dosage and its ratio relative to MI. For this reason, both clinical practice and research more commonly focus on formulations containing MI alone or a combination of MI/DCI—most frequently in a 40:1 ratio—as an adjunct to Metformin (56) (44) (22) (1).

8.2. Effects of Combination Therapy

With regard to metabolic outcomes, combination therapy may lead to greater improvements in insulin sensitivity than metformin alone, particularly in patients with baseline insulin resistance. Studies have primarily evaluated changes in HOMA-IR, insulin concentration, glucose levels, and selected lipid profile parameters. Some analyses suggest a more favorable effect of combined therapy on insulin resistance and lipid metabolism; however, findings remain inconsistent, and studies differ in terms of dosage, treatment duration, and population characteristics (56) (45).

From a hormonal perspective, combination therapy may contribute to reduced androgen concentrations, improvement in the LH/FSH ratio, and alleviation of hyperandrogenic symptoms. A meta-analysis by Kelly et al. (2025) demonstrated that the combination of inositols and Metformin, compared with metformin alone, was associated with improved menstrual cycle regularity, reduced hirsutism, and a lower LH/FSH ratio. However, no clear superiority of combination therapy was observed with respect to BMI, fasting glycemia, or HOMA-IR (36,38,56) (41).

With regard to reproductive outcomes, combination therapy may support menstrual cycle regularity, ovulation, and preparation for ovulation induction in women with Polycystic Ovary Syndrome and insulin resistance. Studies evaluating treatment prior to ovulation induction have suggested that the addition of MI to Metformin may improve cycle regularity and selected ovulatory parameters compared with metformin alone. However, data regarding pregnancy rates and live birth outcomes remain limited and do not support considering combination therapy as a substitute for standard infertility treatment methods(22,56).

At the same time, it cannot be conclusively stated that combination therapy is more effective across all domains of Polycystic Ovary Syndrome treatment. Recent evidence indicates that the

superiority of combining Metformin with inositols has not been consistently demonstrated for BMI, body weight, fasting glycemia, or HOMA-IR. Additional limitations include the heterogeneity of available studies, differences in MI/DCI dosages, variability in treatment duration, and the relatively small sample sizes of some clinical trials (36) (22,41,45).

9. Limitations of Available Studies

Despite growing interest in the use of myo-inositol (MI) and D-chiro-inositol (DCI) in the treatment of Polycystic Ovary Syndrome, the interpretation of available studies requires caution. Although the literature indicates potential metabolic, hormonal, and reproductive benefits, the quality of some evidence remains limited. Major limitations include small study populations, heterogeneity of PCOS phenotypes, and varying supplementation durations, which complicate comparisons across studies and the assessment of long-term therapeutic efficacy. Additionally, inositol preparations differ in bioavailability, MI/DCI ratio, and composition, while the lack of full standardization limits the ability to formulate clear therapeutic recommendations.

10. PMOS — A New Perspective on Polycystic Ovary Syndrome and Potential Therapeutic Implications

In recent years, a significant development in the diagnosis and conceptualization of Polycystic Ovary Syndrome has been the proposal to rename the condition from *polycystic ovary syndrome* (PCOS) to *polyendocrine metabolic ovarian syndrome* (PMOS). This change was announced in 2026 following a long-term international consensus process involving experts, patient organizations, and scientific societies, with the aim of more accurately reflecting the multisystem nature of the disorder (57,58).

The new terminology is intended to emphasize that the disorder is not limited solely to ovarian dysfunction or the presence of polycystic ovarian morphology, which is not observed in all patients and is not a mandatory criterion for diagnosis. Experts indicate that the previous nomenclature may have contributed to an oversimplified perception of the disorder, delayed diagnosis, and insufficient recognition of the metabolic, hormonal, and psychological disturbances commonly associated with women diagnosed with Polycystic Ovary Syndrome. The term PMOS incorporates three key pathophysiological components of the condition: endocrine disturbances (*polyendocrine*), metabolic dysfunction (*metabolic*), and ovarian involvement (*ovarian*)(57).

The change in terminology may also have important practical implications in the context of treatment. A stronger emphasis on the metabolic component of the disorder may increase interest in therapies aimed at improving insulin sensitivity, including Metformin, myo-inositol (MI), and D-chiro-inositol (DCI). Current evidence indicates that metabolic disturbances, particularly insulin resistance and hyperinsulinemia, play a central role in the development of reproductive and hormonal manifestations of PCOS/PMOS, thereby providing a biological rationale for the use of metabolic therapies as part of a multidirectional treatment approach(57,58).

In the context of the present study, the PMOS concept appears particularly relevant, as it strengthens the biological rationale for the use of insulin-sensitizing therapies, such as Metformin and inositols, while also emphasizing the need for individualized treatment based on the patient's predominant metabolic and reproductive phenotype.

11. Conclusions

- Myo-inositol (MI) and D-chiro-inositol (DCI) may support the treatment of women with Polycystic Ovary Syndrome, particularly with regard to improving insulin sensitivity, menstrual cycle regularity, and selected hormonal and reproductive parameters.
- The best-documented effects of inositols concern improvements in metabolic parameters, especially the reduction of hyperinsulinemia and enhancement of insulin metabolism.
- The MI:DCI ratio of 40:1 remains the most extensively studied and biologically justified form of supplementation; however, its superiority over other regimens requires further confirmation.
- Metformin continues to play the most significant role in the treatment of PCOS/PMOS, particularly in patients with insulin resistance, overweight, or obesity, while combination therapy with inositols may provide additional clinical benefits.
- Due to the limitations of currently available evidence, further high-quality randomized controlled trials are necessary to conclusively assess the efficacy of inositols in the treatment of PCOS/PMOS.

12. Keywords

PCOS, PMOS, myo-inositol, D-chiro-inositol, metformin, insulin resistance, infertility, hyperandrogenism.

13. Disclosure

13.1 Author's Contribution

Conceptualization: Alicja Biskup, Agata Wnęk, Julia Smagowska, Ewa Kala - Kaziszyn, Natalia Staszko, Kamila Bała, Mikołaj Stańko

Formal analysis: Alicja Biskup, Agata Wnęk, Julia Smagowska, Ewa Kala - Kaziszyn, Natalia Staszko, Kamila Bała, Mikołaj Stańko

Investigation: Alicja Biskup, Agata Wnęk, Julia Smagowska, Ewa Kala - Kaziszyn, Natalia Staszko, Kamila Bała, Mikołaj Stańko

Writing rough preparation: Alicja Biskup, Agata Wnęk, Julia Smagowska, Ewa Kala - Kaziszyn, Natalia Staszko, Kamila Bała, Mikołaj Stańko

Writing review and editing: Alicja Biskup, Agata Wnęk, Julia Smagowska, Ewa Kala - Kaziszyn, Natalia Staszko, Kamila Bała, Mikołaj Stańko

Supervision: Alicja Biskup, Agata Wnęk, Julia Smagowska, Ewa Kala - Kaziszyn, Natalia Staszko, Kamila Bała, Mikołaj Stańko

All authors have read and agreed with the published version of the manuscript.

13.2 Funding Statement

The Study Did Not Receive Special Funding.

13.3 Institutional Review Board Statement

Not Applicable.

13.4 Informed Consent Statement

Not Applicable.

13.4 Data Availability Statement

Not Applicable.

13.5 Conflict Of Interest

The authors declare no conflict of interest.

Bibliography

1. Teede HJ, Tay CT, Laven JJE, Dokras A, Moran LJ, Piltonen TT, et al. Recommendations From the 2023 International Evidence-based Guideline for the

- Assessment and Management of Polycystic Ovary Syndrome. *J Clin Endocrinol Metab.* 2023 Sep 18;108(10):2447–69.
2. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. *Fertil Steril.* 2009 Feb;91(2):456–88.
 3. Baba T. Polycystic ovary syndrome: Criteria, phenotypes, race and ethnicity. *Reprod Med Biol.* 2025 Jan 22;24(1):e12630.
 4. Ma Y-C, Law K-S, Wang W-S, Chang H-M. Phenotypic variations in polycystic ovary syndrome: metabolic risks and emerging biomarkers. *J Endocrinol.* 2025 Oct 1;267(1).
 5. Spritzer PM, Marchesan LB, Santos BR, Figuera TM. Hirsutism, normal androgens and diagnosis of PCOS. *Diagnostics (Basel).* 2022 Aug 9;12(8).
 6. Joshi A. PCOS stratification for precision diagnostics and treatment. *Front Cell Dev Biol.* 2024 Feb 8;12:1358755.
 7. Lentscher JA, Decherney AH. Clinical presentation and diagnosis of polycystic ovarian syndrome. *Clin Obstet Gynecol.* 2021 Mar 1;64(1):3–11.
 8. Teede HJ, Gibson M, Laven J, Dokras A, Moran LJ, Piltonin T, et al. International PCOS guideline clinical research priorities roadmap: a co-designed approach aligned with end-user priorities in a neglected women’s health condition. *EClinicalMedicine.* 2024 Dec;78:102927.
 9. Zhao H, Zhang J, Cheng X, Nie X, He B. Insulin resistance in polycystic ovary syndrome across various tissues: an updated review of pathogenesis, evaluation, and treatment. *J Ovarian Res.* 2023 Jan 11;16(1):9.
 10. Dong J, Rees DA. Polycystic ovary syndrome: pathophysiology and therapeutic opportunities. *bmjmed.* 2023 Oct 12;2(1):e000548.
 11. Harada M. Pathophysiology of polycystic ovary syndrome revisited: Current understanding and perspectives regarding future research. *Reprod Med Biol.* 2022 Oct 8;21(1):e12487.
 12. Xu Y, Qiao J. Association of Insulin Resistance and Elevated Androgen Levels with Polycystic Ovarian Syndrome (PCOS): A Review of Literature. *J Healthc Eng.* 2022 Mar 21;2022:9240569.

13. Torchen LC, Wu M, Thompson B, Beaudouin A. POLYCYSTIC OVARY SYNDROME: ORIGINS AND IMPLICATIONS: The significance of functional adrenal hyperandrogenism in polycystic ovary syndrome across the lifespan. *Reproduction*. 2025 Jun 1;169(6).
14. Rudnicka E, Suchta K, Grymowicz M, Calik-Ksepka A, Smolarczyk K, Duszewska AM, et al. Chronic low grade inflammation in pathogenesis of PCOS. *Int J Mol Sci*. 2021 Apr 6;22(7).
15. Suthar M, Kaliberdenko V. Inflammation-Driven Pathogenesis of Polycystic Ovary Syndrome: Integrating Endocrine Imbalance, Reproductive Impairments, and Tissue-Level Change. *Recent Adv Inflamm Allergy Drug Discov*. 2026 Mar 26;
16. Aboeldalyl S, James C, Seyam E, Ibrahim EM, Shawki HE-D, Amer S. The Role of Chronic Inflammation in Polycystic Ovarian Syndrome-A Systematic Review and Meta-Analysis. *Int J Mol Sci*. 2021 Mar 8;22(5).
17. Zhao H, Xing C, Zhang J, He B. Comparative efficacy of oral insulin sensitizers metformin, thiazolidinediones, inositol, and berberine in improving endocrine and metabolic profiles in women with PCOS: a network meta-analysis. *Reprod Health*. 2021 Aug 18;18(1):171.
18. DiNicolantonio JJ, H O'Keefe J. Myo-inositol for insulin resistance, metabolic syndrome, polycystic ovary syndrome and gestational diabetes. *Open Heart*. 2022 Mar;9(1).
19. Fedeli V, Unfer V, Dinicola S, Laganà AS, Canipari R, Monti N, et al. Inositol restores appropriate steroidogenesis in PCOS ovaries both in vitro and in vivo experimental mouse models. *Cells*. 2024 Jul 9;13(14).
20. Bizzarri M, Monti N, Piombarolo A, Angeloni A, Verna R. Myo-Inositol and D-Chiro-Inositol as Modulators of Ovary Steroidogenesis: A Narrative Review. *Nutrients*. 2023 Apr 13;15(8).
21. Kalra B, Kalra S, Sharma JB. The inositols and polycystic ovary syndrome. *Indian J Endocrinol Metab*. 2016;20(5):720–4.
22. Fitz V, Graca S, Mahalingaiah S, Liu J, Lai L, Butt A, et al. Inositol for Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis to Inform the 2023 Update of the International Evidence-based PCOS Guidelines. *J Clin Endocrinol Metab*. 2024 May

- 17;109(6):1630–55.
23. Greff D, Juhász AE, Váncsa S, Váradi A, Sipos Z, Szinte J, et al. Inositol is an effective and safe treatment in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Reprod Biol Endocrinol*. 2023 Jan 26;21(1):10.
 24. Sortino MA, Salomone S, Carruba MO, Drago F. Polycystic Ovary Syndrome: Insights into the Therapeutic Approach with Inositols. *Front Pharmacol*. 2017 Jun 8;8:341.
 25. Placidi M, Casoli G, Tatone C, Di Emidio G, Bevilacqua A. Myo-Inositol and Its Derivatives: Their Roles in the Challenges of Infertility. *Biology (Basel)*. 2024 Nov 16;13(11).
 26. Gupta D, Khan S, Islam M, Malik BH, Rutkofsky IH. Myo-Inositol's Role in Assisted Reproductive Technology: Evidence for Improving the Quality of Oocytes and Embryos in Patients With Polycystic Ovary Syndrome. *Cureus*. 2020 May 12;12(5):e8079.
 27. Russo M, Forte G, Montanino Oliva M, Laganà AS, Unfer V. Melatonin and Myo-Inositol: Supporting Reproduction from the Oocyte to Birth. *Int J Mol Sci*. 2021 Aug 5;22(16).
 28. Pivazyan L, Krylova E, Obosyan L, Seregina V, Shapovalenko R, Ayryan E. Effectiveness of Myo-Inositol on Oocyte and Embryo Quality in Assisted Reproduction: Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Gynecol Obstet Invest*. 2025;90(1):78–92.
 29. Unfer V, Dinicola S, Laganà AS, Bizzarri M. Altered ovarian inositol ratios may account for pathological steroidogenesis in PCOS. *Int J Mol Sci*. 2020 Sep 28;21(19).
 30. Dinicola S, Unfer V, Soulage CO, Yap-Garcia MIM, Bevilacqua A, Benvenga S, et al. d-Chiro-Inositol in Clinical Practice: A Perspective from the Experts Group on Inositol in Basic and Clinical Research (EGOI). *Gynecol Obstet Invest*. 2024 Feb 19;89(4):284–94.
 31. Monastra G, Unfer V, Harrath AH, Bizzarri M. Combining treatment with myo-inositol and D-chiro-inositol (40:1) is effective in restoring ovary function and metabolic balance in PCOS patients. *Gynecol Endocrinol*. 2017 Jan;33(1):1–9.
 32. A double-edge sword: the role of D-chiro-inositol in oocyte and embryo quality - EGOI-PCOS [Internet]. 2019 [cited 2026 May 19]. Available from: <https://www.egoipcos.com/a-double-edge-sword-the-role-of-d-chiro-inositol-in-oocyte->

and-embryo-quality/

33. Minini M, Monastra G, Dinicola S. A double-edge sword: the role of D-chiro-inositol in oocyte and embryo quality. 2019 Dec 10;
34. Laganà AS, Myers SH, Forte G, Naem A, Krentel H, Allahqoli L, et al. Inositols in treating polycystic ovary syndrome and non-insulin dependent diabetes mellitus: now and the future. *Expert Opin Drug Metab Toxicol*. 2024 Jan 22;20(1–2):61–72.
35. Nordio M, Basciani S, Camajani E. The 40:1 myo-inositol/D-chiro-inositol plasma ratio is able to restore ovulation in PCOS patients: comparison with other ratios. *Eur Rev Med Pharmacol Sci*. 2019 Jun;23(12):5512–21.
36. Kelly FA, de Oliveira Macena Lôbo A, Cardoso JHCO, de Moraes FCA. Comparison of metformin with inositol versus metformin alone in women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Endocrine*. 2025 Feb;87(2):389–99.
37. Saadati S, Mason T, Godini R, Vanky E, Teede H, Mousa A. Metformin use in women with polycystic ovary syndrome (PCOS): Opportunities, benefits, and clinical challenges. *Diabetes Obes Metab*. 2025 Jun;27 Suppl 3(Suppl 3):31–47.
38. Russo M, Oliva MM, Nordio M, Porcaro G, Unfer V. Metformin and Myo-Inositol: A Comparative Analysis. *Gynecol Obstet Invest*. 2025 Nov 21;1–13.
39. Attia GM, Almouteri MM, Alnakhli FT. Role of Metformin in Polycystic Ovary Syndrome (PCOS)-Related Infertility. *Cureus*. 2023 Aug 31;15(8):e44493.
40. Sadeghi HM, Adeli I, Calina D, Docea AO, Mousavi T, Daniali M, et al. Polycystic ovary syndrome: A comprehensive review of pathogenesis, management, and drug repurposing. *Int J Mol Sci*. 2022 Jan 6;23(2).
41. Li Y, Wang Y, Liu H, Zhang S, Zhang C. Association between HOMA-IR and ovarian sensitivity index in women with PCOS undergoing ART: A retrospective cohort study. *Front Endocrinol (Lausanne)*. 2023 Mar 9;14:1117996.
42. González-González JG, Violante-Cumpa JR, Zambrano-Lucio M, Burciaga-Jimenez E, Castillo-Morales PL, Garcia-Campa M, et al. HOMA-IR as a predictor of Health Outcomes in Patients with Metabolic Risk Factors: A Systematic Review and Meta-analysis. *High Blood Press Cardiovasc Prev*. 2022 Nov;29(6):547–64.

43. Tahapary DL, Pratisthita LB, Fitri NA, Marcella C, Wafa S, Kurniawan F, et al. Challenges in the diagnosis of insulin resistance: Focusing on the role of HOMA-IR and Tryglyceride/glucose index. *Diabetes Metab Syndr*. 2022 Aug;16(8):102581.
44. Lete I, Martínez A, Lasaga I, Centurión E, Vesga A. Update on the combination of myo-inositol/d-chiro-inositol for the treatment of polycystic ovary syndrome. *Gynecol Endocrinol*. 2024 Dec;40(1):2301554.
45. Bodepudi R, Seher S, Khan SA, Emmanuel S, Shantha Kumar V, Nerella R, et al. Myoinositol versus metformin in the treatment of polycystic ovarian syndrome: A systematic review. *Cureus*. 2023 Jul 11;15(7):e41748.
46. Alenezi SA, Khan R, Amer S. The Impact of High BMI on Pregnancy Outcomes and Complications in Women with PCOS Undergoing IVF-A Systematic Review and Meta-Analysis. *J Clin Med*. 2024 Mar 10;13(6).
47. Guo F, Gong Z, Fernando T, Zhang L, Zhu X, Shi Y. The Lipid Profiles in Different Characteristics of Women with PCOS and the Interaction Between Dyslipidemia and Metabolic Disorder States: A Retrospective Study in Chinese Population. *Front Endocrinol (Lausanne)*. 2022 Jul 4;13:892125.
48. Li S, Chu Q, Ma J, Sun Y, Tao T, Huang R, et al. Discovery of novel lipid profiles in PCOS: do insulin and androgen oppositely regulate bioactive lipid production? *J Clin Endocrinol Metab*. 2017 Mar 1;102(3):810–21.
49. Sharon P M, P M, Manivannan A, Thangaraj P, B M L. The Effectiveness of Myo-Inositol in Women With Polycystic Ovary Syndrome: A Prospective Clinical Study. *Cureus*. 2024 Feb 10;16(2):e53951.
50. Sene AA, Saeedzarandi M, Yazdizadeh M, Ghaffari SR, Amjadi F, Zandieh Z, et al. The effect of myo-inositol on assisted reproductive technology outcomes in women with polycystic ovarian syndrome: A systematic review and meta-analysis of randomized clinical trial studies. *Int J Reprod Biomed*. 2025 May;23(5):353–76.
51. Zhang J, Zhang H, Zhou W, Jiang M, Lin X. Effect of myo-inositol supplementation in mixed ovarian response IVF cohort: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2025 Mar 21;16:1520362.
52. Palomba S, Seminara G, Aversa A. Myo-inositol in reproductive management of women with PCOS: holy grail for medical practice or demon for scientific evidence? *Reprod*

- Biomed Online. 2026 Feb;52(2):105269.
53. Rashid R, Mir SA, Kareem O, Ali T, Ara R, Malik A, et al. Polycystic ovarian syndrome-current pharmacotherapy and clinical implications. *Taiwan J Obstet Gynecol*. 2022 Jan;61(1):40–50.
 54. Wdowiak A, Bakalczuk S, Filip M, Laganà AS, Unfer V. The Clinical Use of Myo-Inositol in IVF-ET: A Position Statement from the Experts Group on Inositol in Basic and Clinical Research and on PCOS (EGOI-PCOS), the Polish Society of Andrology, and the International Scientific Association for the Support and Development of Medical Technologies. *J Clin Med*. 2025 Jan 16;14(2).
 55. Beresniak A, Russo M, Forte G, Laganà AS, Oliva MM, Aragona C, et al. A Markov-model simulation of IVF programs for PCOS patients indicates that coupling myo-Inositol with rFSH is cost-effective for the Italian Health System. *Sci Rep*. 2023 Oct 18;13(1):17789.
 56. Sharma P, Malvi A. Combination of metformin and myoinositol: a powerful weapon to combat polycystic ovary syndrome. *Int J Reprod Contracept Obstet Gynecol*. 2025 Jan 16;
 57. Teede HJ, Khomami MB, Morman R, Laven JSE, Joham AE, Costello MF, et al. Polyendocrine metabolic ovarian syndrome, the new name for polycystic ovary syndrome: a multistep global consensus process. *Lancet*. 2026 May;
 58. Rimmer A. PCOS name change to PMOS must be managed to avoid confusing patients, says expert. *BMJ*. 2026 May 15;393:s955.