Chapter

# Use of Myoinositol in PCOS

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## Abstract

Polycystic ovary syndrome (PCOS) is a prevalent and complex endocrine disorder that affects women of reproductive age. It is primarily characterized by metabolic disturbances, notably insulin resistance (IR), hyperandrogenism, and ovulatory dysfunction, often leading to menstrual irregularities and fertility challenges. Myoinositol (MI), a naturally occurring carbocyclic sugar alcohol, has gained significant attention as a promising therapeutic agent for PCOS due to its crucial role as a second messenger in insulin signal transduction. This chapter reviews the current understanding of PCOS pathophysiology and explores the multifaceted applications of myoinositol in its management. Evidence from numerous randomized controlled trials and meta-analyses suggests that MI supplementation can improve insulin sensitivity, reduce hyperinsulinemia, ameliorate hormonal imbalances by lowering androgen levels and normalizing the luteinizing hormone (LH)/follicle-stimulating hormone (FSH) ratio, restore menstrual regularity, and enhance oocyte quality and reproductive outcomes. Comparisons with metformin indicate comparable efficacy for several parameters, often with a superior tolerability profile for MI. Furthermore, combination therapies, particularly MI with D-chiro-inositol in a physiological ratio (e.g., 40:1), and MI with other agents like alpha-lactalbumin or folic acid, are discussed for their potential synergistic effects. While clinical guidelines are increasingly recognizing MI as a viable option, particularly for improving menstrual cycles and as an alternative to metformin, a clear understanding of the evidence, patient preferences, and the need for further high-quality research remains paramount for individualized patient care.

**Keywords:** polycystic ovary syndrome (PCOS), myoinositol (MI), insulin resistance, D-chiro-inositol (DCI), metformin, hormonal imbalance, ovulatory dysfunction, infertility, combination therapy

## 1. Introduction

Polycystic ovary syndrome (PCOS) is widely acknowledged as a highly prevalent and intricate endocrine condition that impacts women of reproductive age globally [1]. Due to its varied nature, PCOS presents with a wide array of clinical characteristics. Such variability can complicate diagnosis, highlighting the importance of accurately ruling out other endocrine disorders with comparable presentations [2]. Key characteristics of the syndrome usually involve a mix of hormonal disturbances,

notably hyperandrogenism (increased androgen levels), ovulatory issues leading to irregular or missed periods, and the typical polycystic ovarian morphology (PCOM) identified *via* ultrasound [3].

The health consequences associated with PCOS extend significantly beyond reproductive issues. They include substantial metabolic disturbances such as insulin resistance (IR), an increased risk of developing type 2 diabetes mellitus (T2DM), dyslipidemia, and heightened cardiovascular disease (CVD) risk [4]. Furthermore, PCOS is linked to an elevated risk for specific malignancies, most notably endometrial cancer [5], and can profoundly affect psychological health, contributing to increased rates of anxiety and depression among affected individuals [6]. The intricate nature and multi-system impact of PCOS highlight the critical need for a comprehensive understanding and effective management strategies.

Insulin resistance has emerged as a fundamental component in the pathophysiology of PCOS, affecting a significant majority of individuals with the syndrome, often independent of body weight [7, 8]. This metabolic dysfunction is intricately linked with hyperandrogenism, establishing a complex interplay that drives many of the syndrome's clinical manifestations [9]. Recognizing the central role of insulin resistance, therapeutic strategies aimed at improving insulin sensitivity have gained prominence. Within this context, myoinositol (MI), a naturally occurring isomer belonging to the vitamin B complex family, has attracted considerable research interest [10]. Myoinositol functions as an intracellular secondary messenger critical for insulin signal transduction and glucose metabolism [11]. Accumulating evidence suggests that disruptions in inositol metabolism might contribute to the insulin resistance observed in PCOS, thereby positioning MI as a potential therapeutic agent capable of addressing this core pathophysiological mechanism [12].

## 2. Definition and prevalence of PCOS

Formally, PCOS is described as an intricate endocrine condition marked by a collection of signs and symptoms mainly caused by excess androgens and impaired ovulation [13]. It stands as the predominant endocrine disorder impacting women in their reproductive years globally [14]. Diagnosis typically adheres to the Rotterdam criteria, which were internationally endorsed and established in 2003 by the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) [15]. Based on these guidelines, PCOS is diagnosed if a minimum of two of these three characteristics are observed (once other potential endocrine conditions are excluded): [1] oligo-ovulation or anovulation (evidenced by irregular or absent menstrual cycles); [2] clinical indicators (like hirsutism, acne, or alopecia) and/or biochemical proof (raised androgen levels) of hyperandrogenism; and [3] polycystic ovarian morphology identified on ultrasound, characterized by 20 or more follicles in at least one ovary, or an ovarian volume of 10 mL or more [16].

PCOS prevalence varies significantly depending on the diagnostic criteria used and the specific population studied. Worldwide, estimates generally fall between 4 and 20% for women of reproductive age [17]. Research employing the Rotterdam criteria tends to show higher prevalence numbers (often reported as 11.9 to 17.8%) than studies using the more stringent 1990 National Institutes of Health (NIH) criteria, which require both hyperandrogenism and chronic anovulation for a diagnosis [18]. Moreover, prevalence rates seem to vary among different ethnic backgrounds. Systematic analyses indicate potentially lower prevalence in Chinese women (around

5.6% with Rotterdam criteria) and Caucasian women (approximately 5.5% with NIH criteria), contrasting with potentially higher rates in Black women (about 6.1% with NIH criteria) and Middle Eastern populations (with a wide range of 6.1–16.0% based on the criteria applied) [19].

Despite its high frequency, a substantial number of women affected by PCOS, up to 70%, remain undiagnosed in the community [20]. This significant diagnostic gap highlights the inherent challenges presented by the syndrome's clinical heterogeneity and may reflect insufficient awareness or inconsistent screening practices within healthcare systems [18]. An apparent increase in PCOS prevalence, particularly noted within adolescent populations, further emphasizes its growing public health importance [21].

### 2.1 Clinical manifestation

The clinical manifestations are typically grouped into reproductive, dermatological (related to hyperandrogenism), metabolic, and psychological categories.

Reproductive manifestations: Irregular menstrual cycles are a defining feature for many women with PCOS. Oligomenorrhea (infrequent menstruation, typically cycles >35 days) or amenorrhea (absence of menstruation for ≥3 months) results from chronic oligo- or anovulation [22]. Consequently, PCOS represents a major cause of infertility due to ovulatory dysfunction [23]. Additionally, women with PCOS face increased risks of pregnancy complications, including higher rates of miscarriage (estimated at 30–50%) [24].

Dermatological Manifestations (Hyperandrogenism): Clinical evidence of excess androgen action is frequent. Common manifestations include hirsutism (excess terminal hair growth in a male-like pattern on the face, chest, abdomen, or back), persistent acne vulgaris (often resistant to standard treatments), and androgenic alopecia (thinning hair or hair loss, typically in a male pattern distribution) [25]. Another potential sign is acanthosis nigricans, characterized by dark, thickened, velvety skin, usually found in body creases like the neck or axillae, which strongly suggests underlying insulin resistance [26].

Metabolic Manifestations: Metabolic dysfunction is a prominent aspect of PCOS. IR is considered a fundamental characteristic, estimated to affect 50–70% of women with PCOS, occurring in both obese and lean [27]. This often leads to compensatory hyperinsulinemia, observed in approximately 80% of obese women with PCOS and 30–40% of their lean counterparts [28]. Obesity, especially abdominal or central adiposity, is common, affecting roughly 40–80% of women with the syndrome [29].

Psychological Manifestations: PCOS is associated with a significant psychological burden. Affected women report higher rates of anxiety and depressive symptoms compared to women without the condition [6]. Factors such as the visible symptoms of hyperandrogenism, challenges with weight management, infertility concerns, and the long-term health risks contribute to a diminished health-related quality of life [30].

### 2.2 Etiology

The etiology of PCOS is complex and remains incompletely defined. It is broadly accepted as a multifactorial disorder resulting from the intricate interplay of genetic susceptibility and various environmental factors. A single definitive cause accounting for the full spectrum of the syndrome has not been identified [31].

Genetic Factors: Evidence strongly supports a significant genetic contribution to PCOS, with heritability estimates ranging up to 79% [32]. Familial aggregation studies consistently show that first-degree female relatives of women with PCOS have a substantially higher risk (20–40%) of developing the syndrome themselves [33]. Genome-wide association studies (GWAS) have successfully identified numerous genetic loci associated with increased PCOS risk, although these known variants currently explain only a minor proportion (approximately 10%) of the overall heritability [34]. Research is increasingly focusing on the role of epigenetic modifications, such as alterations in DNA methylation patterns or microRNA expression profiles, which can be influenced by both the intrauterine environment and postnatal factors, potentially mediating gene-environment interactions in PCOS development [35].

Environmental and Lifestyle Factors: A range of environmental factors and lifestyle choices are implicated in the pathogenesis and manifestation of PCOS. The intrauterine environment is considered critical, with evidence suggesting that fetal exposure to excess androgens or elevated anti-Müllerian hormone (AMH) may program developmental pathways predisposing individuals to PCOS later in life [36, 37]. Exposure to certain environmental endocrine-disrupting chemicals (EDCs), such as bisphenol A (BPA), is another area of investigation [38]. Postnatally, lifestyle factors exert a profound influence. Unhealthy dietary patterns, sedentary behavior, and consequent weight gain or obesity are well-established contributors that can unmask or significantly worsen the clinical and metabolic features of PCOS in genetically susceptible individuals [39].

Pathophysiological Mechanisms: The pathophysiology of PCOS is characterized by several interconnected mechanisms. Hyperinsulinemia directly stimulates androgen production by ovarian theca cells and possibly the adrenal glands [40]. It may also contribute to hyperandrogenism indirectly by suppressing the liver's production of sex hormone-binding globulin (SHBG), thereby increasing the levels of biologically active free androgens [41]. Intrinsic ovarian dysfunction, including abnormal steroidogenesis and arrested follicular development, is also key [42]. Neuroendocrine disturbances play a role, often involving altered gonadotropin-releasing hormone (GnRH) pulsatility, leading to disproportionately high luteinizing hormone (LH) secretion relative to follicle-stimulating hormone (FSH) levels, which further promotes ovarian androgen synthesis and impairs follicle maturation [43].

### 2.3 Introduction to myoinositol

Myoinositol (MI) is a naturally occurring carbocyclic sugar alcohol, specifically one of the nine stereoisomers of inositol. It is ubiquitously present in the human body and obtained through dietary intake as well as endogenous synthesis, primarily in the kidneys [44]. MI serves as a fundamental structural component of cell membranes and acts as an important precursor for the synthesis of various inositol phosphates and phosphoinositides [45]. These derivatives, particularly phosphatidylinositol phosphates, function as essential second messengers in numerous intracellular signaling cascades, including those regulating cell growth, differentiation, and metabolic processes [46]. Of particular importance is the role of MI-derived inositol phosphoglycans (IPGs) in mediating the post-receptor effects of insulin, thereby influencing glucose uptake and metabolism [47].

The growing interest in myoinositol within the context of polycystic ovary syndrome arises principally from its recognized insulin-sensitizing properties [11]. Emerging research indicates that women with PCOS may exhibit alterations in

inositol metabolism, potentially leading to a relative deficiency of MI or its downstream mediators like IPGs within insulin-sensitive tissues [48].

By potentially correcting defects in insulin signal transduction, myoinositol supplementation aims to ameliorate the state of insulin resistance and reduce the compensatory hyperinsulinemia characteristic of PCOS. The following section will elaborate on the specific biochemical and physiological mechanisms by which myoinositol is thought to exert these therapeutic effects in women with PCOS.

## 3. Clinical evidence for myoinositol in PCOS management

### 3.1 Insulin sensitivity and glucose metabolism

Multiple randomized controlled trials (RCTs) have assessed MI's benefits on insulin sensitivity in PCOS patients. In a meta-analysis in 2017 by Unfer, V. et al., 490 PCOS women from 9 RCTs were evaluated. The results demonstrated that after 12–24 weeks of treatment with MI supplementation (2–4 g/day), fasting insulin levels were reduced($P = 0.009$), and a reduction in HOMA-IR ($P = 0.041$) was observed compared to placebo [49].

In another systematic review conducted by Greff et al., 26 RCTs with 1691 PCOS patients were analyzed, and the same results on reduction of fasting insulin level and HOMA-IR after treatment with MI were observed. Still, no significant difference was seen between the inositol and the metformin [50].

Furthermore, in a systematic review by Fitz et al., 30 trials with 2230 patients were included and assessed the role of myoinositol or D-chiro-inositol (DCI) for metabolic parameters. MI has fewer gastrointestinal side effects than metformin, but it may not be superior to metformin [51].

The evidence from studies indicates that MI supplementation is comparable to metformin and can enhance insulin sensitivity. MI's role in the phosphoinositide 3-kinase (PI3K) pathway can result in these effects, and by facilitating glucose transporter type 4 (GLUT4) activity, glucose uptake can be increased in peripheral tissues like skeletal muscle and adipose tissue [51].

### 3.2 Hormonal imbalance

Hormonal dysregulation is another feature of PCOS, characterized by elevated androgen levels and an imbalanced LH to FSH ratio, which may cause symptoms like hirsutism, acne, and ovulatory dysfunction.

In different RCTs and meta-analyses, MIs have been shown to reduce androgen levels and normalize gonadotropin secretion. In earlier studies and RCTs, the benefits of inositol on the hormonal profile of individuals with PCOS were established, and the administration of 2–4 mg MI for 12 weeks or 6 months, according to different RCTs, has shown improvement in hirsutism score and reduction in the androgen levels, FSH, LH, and LDL cholesterol [52–54].

These effects result from MI's insulin-sensitizing properties, which by downregulating cytochrome P450c17α enzyme activity can affect ovarian theca cell androgen production [48].

In a 2023 systematic review by Greff et al., 26 randomized controlled trials involving 1691 participants were evaluated. As shown, inositol can reduce total and free testosterone levels, as well as androstenedione levels, elevate SHBG levels, and

regularize menstrual cycles. These effects were comparable to metformin, but the side effects were fewer [50].

Unfer et al. in 2017 in a meta-analysis of 9 RCTs found that MI (2–4 g/day) may cause a reduction of testosterone concentration in comparison to control groups ($P = 0.099$), but without change in androstenedione levels. SHBG can be increased significantly after 24 weeks of treatment with MI ($P = 0.026$) [49].

Another meta-analysis of 17 RCTs, which consisted of 1083 PCOS patients, showed that MI has positive effects on androstenedione and prolactin levels. However, other endocrine parameters, including LH, FSH, estradiol, SHBG, dehydroepiandrosterone, and total testosterone levels, were not affected [55].

In a 2024 systematic review conducted for the updated international PCOS guidelines, it was emphasized that although MI appears to have effects in improving hyperandrogenism and metabolic parameters, higher-quality research and more trials are necessary to strengthen the evidence [51].

MI enhances aromatase activity, facilitating the conversion of androgens into estrogens, thereby supporting dominant follicle selection and reducing total androgen levels. Additionally, MI stimulates hepatic production of sex hormone-binding globulin (SHBG), which attaches to free androgens, effectively lowering their bioavailability [54].

### 3.3 Ovulation and menstrual regularity

In a 2003 double-blinded RCT involving 283 PCOS patients, Gerli et al. found significant improvements in the luteal phase and ovulation rate in the inositol group (100 mg, twice a day) compared to a placebo, along with significant weight loss in the inositol group [56].

A 2018 meta-analysis of 10 RCTs, evaluating 601 women with PCOS diagnosis in three groups of inositol, metformin, and placebo, found that inositol had a beneficial influence on ovulation rate and increased the frequency of menstrual cycles [57].

Another review by Tanbo et al. in 2018 emphasized that the myoinositol (2 g) and chiro-inositol (0.6 g), when taken twice per day, and for a duration of 2–6 months, according to studies, can increase the likelihood of spontaneous ovulation compared to the placebo [58].

It was shown in the studies that an excess of inositol in the ovary increases FSH sensitivity and can also improve fertilization rates and embryo quality in PCOS patients [59].

### 3.4 Reproductive outcomes

An important challenge for PCO patients is infertility due to anovulation or poor oocyte quality. MI enhances fertility outcomes—both in spontaneous conception and assisted reproductive technologies (ART)—by improving ovulation, oocyte maturation, and embryo quality. Clinical evidence from RCTs and meta-analyses demonstrates MI's efficacy as a natural adjunct.

In a meta-analysis that included 7 RCTs in 2018, 360 PCOS patients undergoing ART were observed. The results showed that MI supplementation (2–4 g/day) increased clinical pregnancy rates by 66% ($P = 0.001$) and improved oocyte quality compared to controls, and also, gonadotropin requirements were reduced by about

20% [60]. An RCT from 2015 with 60 PCOS patients candidates for *in vitro* fertilization (IVF) showed that MI (4 g/day) for 12 weeks boosted the number of mature oocytes by 30% and raised implantation rates by 18% versus placebo, and also higher fertilization rates were observed [61]. MI's enhance follicular fluid dynamics and reduce oxidative stress, which optimizes the ovarian microenvironment for oocyte development.

For spontaneous conception, a 2013 RCT with 92 PCOS women reported that a combination of MI (2 g/day) and folic acid for 6 months increased live birth rates by 22% over placebo, and 68% of treated women achieved spontaneous ovulation and subsequent pregnancies [49].

Systematic reviews emphasize MI's role in improving ovulation and oocyte quality; it is also safe and has synergy with fertility protocols [50]. MI supports mitochondrial function in oocytes and reduces follicular arrest, and so has fertility-enhancing effects both in natural conception and ART settings [62].

### 3.5 Metabolic parameters

Metabolic syndrome is a group of metabolic disturbances that can significantly elevate the risk of heart disease and type 2 diabetes. These conditions include insulin resistance, abdominal obesity, high blood pressure, and dyslipidemia [63].

These features can be consequences of metabolic dysregulation in PCOS. Studies show the efficacy of MI for addressing these metabolic abnormalities. Myoinositol supplementation can lower fasting insulin levels, facilitate glucose uptake, and reduce hyperinsulinemia through intracellular insulin signaling pathways [64].

Greff et al. in the study of 26 RCTs (2023) reported that MI can better normalize menstrual cycles and is also associated with BMI and weight reduction compared with placebo, but non-inferiority in most outcomes compared to metformin [50].

Salehpour et al. in 2016 evaluated the impact of MI on metabolic and cardiovascular health in women older than 30 years with PCOS. Over 3 months, 50 participants received MI plus folic acid, and the researchers evaluated metabolic markers before and after treatment. Results demonstrated significant improvements in insulin sensitivity, reductions in cholesterol, LDL, homocysteine, and blood pressure. The findings suggest that MI supplementation may help normalize metabolic profiles and reduce cardiovascular risks in older PCOS patients [65].

However, in the meta-analysis examined by Fitz et al. in 2024, the authors believe that the evidence supporting inositol's role in PCOS management remains limited and requires further studies [51].

MI is also important in the prevention of Gestational Diabetes by its insulin-sensitizing effects, but the effects on fetal macrosomia and neonatal hypoglycemia were not seen [66, 67].

### 3.6 Comparison with metformin

Metformin is an important and effective drug in the management of PCOS, particularly for its insulin-sensitizing potential [68]. However, as highlighted in several systematic reviews and meta-analyses, MI is a natural alternative whose efficacy is comparable to metformin and has lower side effects.

Kutenaei et al. conducted a systematic review and meta-analysis comparing myoinositol (MI) and metformin across nine studies, involving 331 patients treated

with metformin and 307 patients treated with MI. Their findings indicated that both treatments effectively improved insulin sensitivity, ovulation rates, and hormonal balance in PCOS patients. The study indicated that myoinositol (MI) may serve as a viable alternative to conventional drug therapies for PCOS patients [69].

In a meta-analysis of Greff et al. in 2023, inositol showed non-inferiority in most outcomes, such as normalizing menstrual cycles and improving metabolic parameters, compared to metformin; however, with fewer gastrointestinal adverse effects, such as bloating, nausea, and generalized weakness [50]. In another meta-analysis of 8 RCTs and 1088 PCOS patients comparing MI and metformin in assessing hormonal and metabolic parameters in women with PCOS, it was demonstrated that both drugs are equally beneficial without any significant difference [70].

A meta-analysis in 2024 on 30 RCTs and 2230 patients showed that metformin may improve waist-hip ratio and hirsutism more effectively than inositol; however, it likely has no advantage in reproductive outcomes, and the evidence remains uncertain about its impact on BMI. Myoinositol is associated with fewer gastrointestinal adverse effects [51]. In another RCT, by Ravn et al., the efficacy of MI and metformin (MI 4 g/day or MET 2 g/day.) was compared in 45 women with PCOS. The result showed that both treatments effectively reduced HOMA-IR values; however, MI had fewer gastrointestinal side effects than metformin, suggesting better tolerability [71].

Myoinositol's role in enhancing oocyte quality and embryo development in ART is assessed in different studies and discussed before; however, its effect on reducing the likelihood of OHSS has not been approved in comparison to metformin [72].

In a meta-analysis by Lijun Lin in 2024, 20 RCTs involving 1827 patients reported that both metformin and MI may reduce the risk of OHSS in PCOS patients. However, no significant improvement in pregnancy outcomes was seen. Metformin is more effective in the agonist protocol for lowering OHSS risk by reducing E2 levels on the day of trigger, and it also has a good effect on the number of mature oocytes. At the same time, myoinositol may shorten the duration of gonadotropin use. However, further RCTs are necessary to confirm the findings [73].

Both MI and metformin are effective in managing PCOS, and the choice between them often depends on individual patient preferences, tolerability, and specific clinical scenarios.

### 3.7 Mental health and mood regulation

PCOS is often accompanied by psychological challenges, like anxiety, depression, and mood swings, which are closely linked to the hormonal and metabolic disturbances [74]. Studies demonstrate that MI has benefits for both emotional and mental health.

The mechanism by which MI can affect is its role in insulin signaling, neurotransmitter activity, and cellular stability. It supports cell signaling through pathways involving phosphoinositides and inositol glycans, affecting metabolism and brain function. Inositol modulates serotonin pathways, so it can reduce symptoms of depression, panic disorder, and OCD. Its safety and effectiveness can make it an alternative to SSRIs for some patients [75].

A 2013 systematic review and meta-analysis by Mukai et al. found that inositol may provide therapeutic benefits for individuals with depression, particularly those with PMDD [76].

## 4. Dosage and administration of myoinositol in PCOS treatment

### 4.1 Standard dosage and duration of treatment

As studied in multiple articles and meta-analyses, the best dosage of myoinositol for PCOS management is '2 grams twice daily', and the total dose is '4 grams per day', which can affect insulin sensitivity and glucose metabolism, hormonal balance, and ovulatory function. According to different studies, it is recommended that a '3 to 6 months' treatment is necessary to achieve the best results [77, 78].

### 4.2 Myoinositol and D-chiro-inositol ratio in supplements

MI is converted into D-chiro-inositol (DCI) *via* the action of the epimerase enzyme, which is insulin-dependent. In healthy women, ratio of MYO/DCI in the plasma is approximately 40:1, while in ovarian follicular fluid, it reaches 100:1. However, in patients with PCOS patients, this ratio becomes inverted and can go as low as 0.2:1. So it seems the '40:1 ratio' of myoinositol to D-chiro-inositol is optimal according to its physiological concentrations and clinical evidence for best performance [79, 80].

### 4.3 General safety profile and adverse effects

According to medical research and clinical evidence, myoinositol is a safe product. MI has lower side effects in comparison to other agents like metformin. As we know, metformin is associated with gastrointestinal adverse effects such as nausea, diarrhea, and abdominal discomfort that are not tolerated by some consumers. However, more common adverse effects of MI are mild gastrointestinal discomfort, including nausea, flatulence, and diarrhea, which are rare and typically transient [81]. MI is also a safe product in patients with metabolic comorbidities since it has no impact on liver or kidney function [51]. These side effects of MI are typically dose-dependent (higher doses of myoinositol may lead to increased gastrointestinal discomfort) and occur more frequently at higher dosages exceeding 12 grams per day. For standard dosages (4 grams per day), side effects are rare and generally resolve without intervention [82].

## 5. Myoinositol in combination therapies for PCOS

Combination of MI with other supplements to synergize its effect may be a good choice due to its potential therapeutic effects. There are Many products based on inositol, and different combinations of myoinositol and other supplements have been formulated over the years [78].

### 5.1 Myoinositol and D-chiro-inositol combination

D-Chiro-Inositol is a natural isomer of inositol. Insulin stimulates the conversion of MI into DCI *via* the epimerase enzyme. MI facilitates cellular glucose uptake by inducing GLUT4 translocation to the cell membrane, inhibits adenylate cyclase activity, and reduces the release of free fatty acids from adipose tissue, so MI has a role in

glucose catabolism. DCI takes part in glycogen synthesis [44, 63]. Both MI and DCI can mimic insulin and consequently lower postprandial blood glucose [83].

MI also stimulates FSH signaling, while DCI can act as an aromatase inhibitor and is responsible for insulin-mediated androgen synthesis [84]. So, they both have benefits in terms of hormonal balance and metabolic disturbance in PCOS. According to the results of different studies, the MI and DCI combination has good benefits in all aspects of PCOS, which include improving insulin sensitivity, decreasing blood pressure, TG, TChol concentrations, and also BMI. They can also reduce serum androgen concentrations and increase SHBG. Their effectiveness in improving the menstrual cycle and ovulation rate was also studied in different studies [84–87]. Although MI alone shows positive results, the use of DCI alone is still controversial due to insufficient evidence. The best MYO/DCI ratio is when used in 40:1 [79, 84]. Studies suggest that lowering this ratio (e.g., 20:1, 10:1, or lower) is ineffective and may even diminish treatment efficacy, whereas increasing the MYO ratio appears to enhance therapeutic outcome. More studies in different ratios, such as 100:1, are required [80].

### 5.2 Myoinositol and metformin

Metformin is an antidiabetic drug that is effective in the management of PCOS, as established by multiple studies. It can lower glucose synthesis directly or indirectly by affecting the liver, and acts on the gut to enhance glucose utilization and stimulate glucagon-like peptide 1 (GLP-1) production. Metformin acts on a molecular level and can inhibit the mitochondrial respiratory chain in the liver and also reduce the expression of gluconeogenic enzymes, so it can improve insulin sensitivity and have a good effect on fat metabolism without a direct effect on pancreatic insulin production [68, 88]. The combined use of inositol and metformin has been proposed to provide therapeutic benefits for individuals with PCOS. In a double-blinded RCT in 2023, two groups of PCOS were studied in metformin (500 mg) and metformin (500 mg) plus inositol groups for 6 months. The author suggests that combining inositol and metformin significantly impacts menstrual cycle length and also improves hormonal and biochemical parameters. So they will have a synergistic effect [89]. In another systematic review and meta-analysis of 35 studies, the effectiveness of inositol, metformin, and their combination was evaluated. The results show the effectiveness of such treatments in clinical pregnancy rate, live birth rate, and the risk of OHSS in PCOS individuals candidates for ART [90].

MI and metformin in combination have a synergistic effect. While metformin is commonly associated with gastrointestinal adverse effects, the addition of myo-inositol has been shown to mitigate these adverse effects, improving overall patient compliance. This combination can also reduce HOMA-IR after 3 months of treatment [91]. Combination treatment can also improve menstrual cycles, BMI, acne score, and hormonal parameters, and is associated with better ovulatory and reproductive outcomes [84, 91].

### 5.3 Combination with folic acid

Folic acid plays a crucial role in DNA synthesis, red blood cell production, and fetal development during pregnancy. Folic acid also supports cellular health, elevates folate concentration in follicular fluid, decreases the concentration of homocysteine, and positively affects oocyte and embryo quality. So, the combination of MI and folic acid works synergistically to improve metabolic and reproductive outcomes,

especially in PCOS [92, 93]. Adding '200 micrograms of folic acid' per dose to inositol enhances its therapeutic effects according to studies [84, 93, 94]. This combination is available in different forms, like oral tablets, capsules, and powders.

### 5.4 Myoinositol and oral contraceptives combination

Oral contraceptives (OCPs) are frequently prescribed to regulate menstrual cycles and manage hyperandrogenism in women with PCOS. Although it is effective in androgen-related symptoms such as acne and hirsutism, OCPs can exacerbate insulin resistance and lipid parameters (increasing cholesterol and triglyceride levels). Simultaneously, they can lower serum levels of FSH, LH, and SHBG. The main mechanism of OCP is the suppression of FSH, which therefore reduces the endometrial cancer in the future. The combination of myoinositol with OCPs offers a promising strategy to mitigate these adverse effects while enhancing therapeutic outcomes [91, 95].

After 12 months of treatment, combination therapy with MI and OCPs has a greater impact on endocrine, metabolic, and clinical profiles in patients with PCOS compared to OCPs alone, although it does not significantly affect BMI [95, 96]. It was shown that treatment with OCP alone may increase weight, while MI + OCP together did not change patients' weight and BMI [84]. In an article published in 2021, the effect of combination therapy was evaluated in teenagers. The results showed improvements in weight and BMI parameters, and also an effective improvement in metabolic parameters. This strategy could avoid or postpone pharmacological therapy during adolescence. It also has a good effect on lifestyle [97].

### 5.5 Myoinositol and alpha-lactalbumin

Alpha-lactalbumin (α-LA) is a whey protein. It can be presented in mammalian milk (about 20–25% of whey and 22% of proteins in human milk) naturally. Because of α-LA's low immunogenicity, it is a safe alternative for individuals who have allergies. As α-LA contains essential amino acids such as tryptophan, lysine, and branched-chain amino acids and bioactive peptides, it can have antibacterial, anti-inflammatory, prebiotic, and immunomodulatory effects. α-LA significantly enhances the intestinal absorption of vital compounds like vitamins and minerals (e.g., vitamin D and iron). It is also processed by pancreatic enzymes into bioactive peptides that result in different biological activities, such as growth stimulation and immune system modulation. Additionally, α-LA has been studied for its impact on neurological functions and may have good effects on sleep, mood disorders, depression, and even cancer [98–101].

Its role in PCOS management is because α-LA promotes the secretion of glucagon-like peptide 2 (GLP-2), which upregulates the expression of SGLT-1 and GLUT-2 transporters, thereby improving the intestinal absorption of inositols. So the combination of inositol and α-LA has potentially good effects in PCOS management, even in inositol-resistant cases [102, 103].

Oliva et al. studied the effects of MI in combination with α-LA in myoinositol-resistant PCOS women were evaluated. Resistant PCOS patients who received 2gr MI without any response in 3 months were again treated with the 2gr MI in combination with 50 mg α-LA twice a day, for an additional 3 months. The results demonstrated a rise in MI plasma levels compared to baseline; also, an improvement in hormone and lipid profiles was seen [104]. In another review article by Pandya et al., emphasis

is placed on the effectiveness of α-LA on intestinal absorption of inositols, as well as improving gut dysbiosis, inflammation, and insulin resistance, and therefore improvement in metabolic and hormonal profile and ovulation rate in PCOS [105]. Kamenov et al. also showed that combination therapy with 2 g of MI and 50 mg of α-LA, compared to MI alone, has benefits on ovulation rate, menstrual cycle duration, reduction in BMI, and improvement of hyperandrogenism [106].

### 5.6 Other combination therapies and lifestyle modification

A large number of studies on the effect of alpha lipoic acid and MI or DCI in PCOS management are available. Alpha lipoic acid is an antioxidant and an enzymatic cofactor of the mitochondrial respiratory chain. Both MI and ALA activate GLUT-4, which is crucial for glucose uptake and supporting carbohydrate metabolism. So the combination of MI and ALA can potentially improve metabolic and hormonal profiles and reproductive outcomes in PCOS patients, especially in individuals with insulin resistance [84, 107].

Vitamin D deficiency is responsible for some abnormalities in PCOS, like menstrual irregularities and fertility issues. Additionally, research highlights the positive impact of vitamin D on hormonal balance in PCOS patients, influencing testosterone, LH, FSH, and AMH levels [108, 109]. Several studies demonstrated the efficacy of this supplement, especially in combination with inositol, in improving metabolic parameters and fertility outcomes [110]. In a systematic review by Katyal et al. in 2024 to assess the efficacy of inositol and vitamin D in fertility outcomes and metabolic parameters among PCOS patients, the authors showed that these supplements are a potentially beneficial option [111]. In a study evaluating the effectiveness of vitamin D plus myoinositol, folic acid, and melatonin compared to the groups that did not receive vitamin, the positive effect of combination therapy on IVF outcomes was established [112].

Other combinations of MI with different supplements like L-carnitines, L-arginine, L-cysteine, magnesium, selenium, ZINC, etc., are available, and also some of them showed improvements in metabolic and hormonal parameters, but wider studies to achieve the best combination ratio and doses are necessary [113, 114].

Lifestyle interventions, including diet and exercise in accompany with MI supplementation, can enhance metabolic and hormonal responses [115].

While combination therapies are beneficial, several factors must be considered: First is Individualization. Treatment should be based on a patient's tolerance, specific phenotype, metabolic profile, and reproductive goals to obtain the best response. Second, the safety of products. Although studies did not show any significant side effects in combination therapies, careful monitoring is often necessary. At least further studies are required for optimal dosing regimens and evaluation of the long-term efficacy of these combinations.

## 6. Current medical guidelines and recommendations for myoinositol use in PCOS

The stance of major clinical guidelines on inositol use in PCOS has evolved cautiously. The 2018 International Evidence-based Guideline initially classified inositol as an experimental therapy, advising against its routine use due to insufficient high-quality evidence for clinical efficacy, particularly for fertility outcomes [116].

However, the 2023 update of this International Guideline [117], alongside the 2025 Society of Obstetricians and Gynecologists of Canada (SOGC) Position Statement [118], reflects a nuanced shift. Informed by recent systematic reviews, these guidelines now suggest that inositol (primarily MI) could be considered for women with PCOS. This remains a conditional recommendation, based on generally low-quality evidence, emphasizing the importance of shared decision-making that incorporates individual patient preferences and values, acknowledging the limited potential for harm but also the uncertain clinical benefits for many outcomes. The SOGC statement specifically suggests MI supplementation can be used as an alternative to metformin

| Recommendation | Guideline Source | Strength of Recommendation | Quality of Evidence |
|---|---|---|---|
| For women with PCOS, any form of inositol may be an option, guided by patient preference, given its low risk of harm and potential for metabolic enhancement, though clinical benefits are currently restricted | International CPG, 2023 | Conditional | Low |
| Inositol is a possible consideration for individuals with PCOS, citing its low harm potential and some evidence suggesting benefits for metabolic function and menstrual cycle | SOGC, 2025 | Conditional | Low |
| MI supplementation may be utilized to enhance menstrual regularity and address anovulation in PCOS, serving as an alternative to metformin, contingent on patient preferences and tolerability of side effects | SOGC, 2025 | Weak | Moderate |
| Currently, inositol (any form) for treating PCOS-related infertility is classified as experimental. Emerging efficacy data underscores the necessity for additional research | International CPG, 2018 | Conditional (Against Use) | Low |
| Healthcare practitioners are advised to inquire about patients' use of supplements, including inositol, for managing their PCOS | SOGC, 2025 | Strong | High |
| Practitioners should inform patients that inositol's regulation differs from prescription medications, and robust evidence might be constrained by study limitations (e.g., sample size, design, and dosage variations) | SOGC, 2025 | Strong | High |
| Ensuring women can access impartial, evidence-based information, while acknowledging and respecting individual patient choices, is a duty of policy makers and healthcare | International CPG, 2023 | Practice Point | N/A |
| Patients utilizing inositol or other complementary treatments should be prompted to discuss this use with their healthcare professional | International CPG, 2023 | Practice Point | N/A |
| Due to a lack of high-quality evidence, specific formulations, dosages, or combinations of inositol cannot be definitively endorsed at this time | International CPG, 2023 | Practice Point | N/A |

**Table 1.**
*Summary of clinical practice guidelines recommendations for MI use.*

for improving menstrual cycle regularity and anovulation, citing moderate-certainty evidence for comparable efficacy but better tolerability [118].

These updated recommendations are grounded in systematic reviews synthesizing data from numerous, often small and methodologically limited, randomized controlled trials (RCTs). Evidence regarding metabolic benefits is mixed; some analyses show potential improvements in certain markers (like triglycerides or SHBG) with MI or DCI compared to placebo or metformin, while others find metformin superior for parameters like fasting insulin or waist-hip ratio. Robust evidence supporting significant improvements in live birth rates or overall clinical pregnancy rates with inositol remains lacking. Hormonal effects are similarly inconsistent across studies. A key finding, however, is the consistent observation that MI is generally well-tolerated and correlates with significantly lower gastrointestinal side effects than metformin. The overall quality of evidence across most outcomes is frequently downgraded due to risk of bias, small sample sizes, heterogeneity, and imprecision, underpinning the cautious and conditional nature of current recommendations.

In practice, current guidelines advise that healthcare providers should proactively inquire about supplement use, including inositol, and counsel patients appropriately. This counseling should include information about the regulatory status of inositols (often classified as natural health products or supplements, not drugs), the limitations of the existing scientific evidence regarding efficacy for many clinical outcomes, the lack of robust long-term safety data, and the potential variability in product quality and dosage. While research often investigates 4 grams of MI daily, sometimes in combination with DCI (often in a 40:1 ratio), guidelines emphasize that there is currently insufficient evidence to strongly recommend any specific type, dose, or combination of inositols. The decision to use MI should therefore be individualized, focusing on patient priorities (e.g., preference for avoiding metformin side effects when addressing cycle irregularity) and a clear understanding of the evidence gaps. The summary of clinical practice guideline (CPG) recommendations is provided in **Table 1**.

## 7. Conclusion

Myoinositol has emerged as a significant and promising therapeutic agent in the multifaceted management of PCOS. Its primary mechanism of action, centered on enhancing insulin sensitivity *via* its role as a precursor to inositol phosphoglycans, directly addresses a core pathophysiological defect in a majority of women with PCOS. The extensive body of clinical evidence, including numerous RCTs and systematic reviews, supports the efficacy of MI (typically at doses of 2–4 grams per day) in improving key metabolic parameters such as fasting insulin and HOMA-IR, correcting hormonal dysregulations including hyperandrogenism and elevated LH/FSH ratios, and promoting reproductive health by restoring ovulation, improving oocyte quality, and increasing pregnancy rates.

A notable advantage of myoinositol is its excellent safety profile and tolerability, particularly when compared to metformin, with which it demonstrates comparable benefits for several outcomes, such as menstrual cycle regulation, but often with fewer gastrointestinal side effects. The combination of MI with D-chiro-inositol, especially in the physiological 40:1 ratio, has shown particular promise in leveraging the distinct roles of these isomers in glucose metabolism and steroidogenesis. Other combination therapies, such as with folic acid or alpha-lactalbumin, may further

enhance therapeutic efficacy or improve MI bioavailability, especially in individuals who may exhibit inositol resistance.

Current international clinical guidelines have evolved to conditionally recommend inositol for women with PCOS, particularly for improving menstrual regularity and as an alternative to metformin, emphasizing the importance of shared decision-making based on individual patient needs and preferences. However, it is acknowledged that the quality of evidence for some outcomes varies, and further high-quality, large-scale, long-term studies are still warranted to definitively establish optimal dosing regimens, long-term benefits and safety, and its role across the diverse spectrum of PCOS phenotypes.

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## Conflict of interest

The authors declare no conflict of interest.

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