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Review Article

Inositols in Polycystic Ovary Syndrome: A Comprehensive Review

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Abstract

Keyword:

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ABSTRACT

Polycystic ovary syndrome (PCOS) affects up to 13 % of women of reproductive age, yet no single therapy corrects its metabolic, reproductive, and psychological burden. This narrative review synthesizes studies on the two predominant inositol stereoisomers—myo-inositol (MI) and d-chiro-inositol (DCI). We outline inositol chemistry, endogenous distribution, and insulin-sensitizing mechanisms, then critically appraise evidence by preparation: MI 2–4 g/day, DCI 300–1,200 mg/day, and physiological 40:1 MI: DCI combinations. MI consistently lowers fasting insulin, HOMA-IR, and free testosterone, while restoring ovulation in up to two-thirds of participants; DCI shows similar metabolic gains but less robust reproductive data. Combined formulations accelerate improvements and may enhance in vitro fertilization outcomes. Across trials, adverse events are mild and gastrointestinal, with no serious safety signals. Ongoing multicenter randomized controlled trials (RCTs) targeting live-birth rate, long-term metabolic health, and pharmacogenomic predictors will clarify clinical positioning. Currently, inositols represent a safe, patient-preferred adjunct that can complement lifestyle change and first-line pharmacotherapy in selected PCOS phenotypes. Findings support personalized inositol use in routine practice.

1. INTRODUCTION

1.1. Epidemiology and clinical impact of PCOS

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age. It affects an estimated 6–13% of women worldwide, although many cases go undiagnosed. PCOS is a leading cause of anovulation and infertility (1). The syndrome is characterized by irregular or absent menstrual periods, hyperandrogenism (hirsutism, acne), and polycystic ovaries, often in the context of obesity. Women with PCOS have markedly higher long-term health risks: on average, 2–5 times higher rates of developing type 2 diabetes, as well as increased incidence of metabolic syndrome and cardiovascular risk factors (2). Obesity (seen in ~70–80% of PCOS patients) and chronic insulin resistance amplify these risks (3). Additionally, PCOS patients exhibit elevated prevalence of mental health disorders, including depression, anxiety, and eating disorders, which amplify disease impact and compromise quality of life (4).

1.2. Current therapeutic landscape and unmet needs

Current management of PCOS requires a multi-pronged approach tailored to patient goals. Lifestyle modification (diet and exercise) is universally recommended as first-line therapy, since even modest weight loss improves insulin sensitivity and ovulatory function (5). Pharmacological treatments are then chosen based on the individual patient's needs: combined hormonal contraceptives (estrogen/progestin pills or progestins) are the mainstay for regulating menstrual cycles and reducing androgenic symptoms (hirsutism, acne) (6). For ovulation induction in women desiring fertility, letrozole (an aromatase inhibitor) has become first-line over clomiphene citrate in many guidelines (7). Metformin, an insulin-sensitizer, is frequently used to address insulin resistance and metabolic abnormalities (glucose intolerance, obesity). Spironolactone or other anti-androgens may be added for hirsutism if needed (8).

Despite this range of options, many women with PCOS have unmet needs. No single therapy effectively addresses all features of the syndrome. For example, metformin improves insulin and menstrual regularity, but in practice it is **not** a potent agent for weight loss or for treating severe hirsutism (9, 10). Oral contraceptives regulate

menstruation and hirsutism, but do nothing to improve insulin resistance, and can cause weight gain or mood changes in some (11). Many women experience side effects: gastrointestinal intolerance is common with metformin, often limiting its use. As one recent meta-analysis noted, even though metformin can modestly reduce weight or improve waist–hip ratio, it is associated with frequent (albeit mild) GI side effects (12). These limitations mean that patients and clinicians often seek additional or alternative therapies – especially supplements with insulin-sensitizing action – to fill the gaps in care.

1.3. Why revisit inositol? Clinical and patient-driven motivations

Inositols (especially myo-inositol and d-chiro-inositol) have a strong theoretical rationale as insulin sensitizers and ovarian modulators, but until recently evidence has been mixed. Nevertheless, there is intense clinical and patient interest in inositol supplements for PCOS. Surveys and guideline panels have ranked inositol research as a high priority for PCOS patients worldwide (13, 14). Many women with PCOS, attracted by the idea of a "natural" therapy, already self-administer inositol hoping to improve fertility or metabolic health (15). This demand has pushed clinicians to re-examine the topic scientifically. Importantly, international evidence-based guidelines have begun to address inositol: the 2023 PCOS guidelines recognize that inositol is widely used but caution that current evidence is limited and inconclusive (13). Thus, inositol stands at the intersection of clinical curiosity and patient-driven demand, motivating a fresh, rigorous review of its role in PCOS.

2. BIOCHEMISTRY OF INOSITOLS

2.1. Structure and stereoisomers (MI, DCI, others)

Inositols are six-carbon cyclohexane polyols, stereoisomers of hexahydroxycyclohexane. There are natural stereoisomers, of which myo-inositol (MI) and D-chiro-inositol (DCI) are most abundant and physiologically important (16). Each inositol isomer has the same molecular formula as glucose, but differs in the arrangement of its six hydroxyl groups. MI predominates in human tissues, whereas DCI (and to a lesser extent scyllo-inositol) are present in lower amounts. Both MI and DCI serve as components of inositolphosphoglycans and secondary messenger molecules involved in insulin signaling and other hormone pathways. Chemically, MI

is often referred to as cis-inositol or cis-1,2,3,5/4,6-cyclohexanehexol, and DCI as cis-1,2,4/trans-3,5,6-cyclohexanehexol (17).

2.2. Tissue distribution and endogenous synthesis

Tissue levels of MI and DCI differ markedly. Systemically, about 99% of the inositol pool is MI, reflecting high intracellular stores. However, target organs vary in their MI/DCI ratio (17). For example, liver, muscle and adipose tissue express a high insulin-dependent epimerase that converts MI into DCI, resulting in relatively more DCI in these tissues (18). In contrast, the ovary and brain largely retain MI. Under normal conditions, this epimerase maintains roughly a **40:1 MI:DCI ratio** in plasma and tissues (19, 20). Notably, insulin itself stimulates this conversion process (17). Endogenously, MI can also be synthesized from glucose: glucose-6-phosphate is converted to inositol-3-phosphate by the enzyme ISYNA1, which is then dephosphorylated to yield MI. Thus inositol in the body comes both from diet (common in fruits, beans, nuts) and from this de novo pathway (21, 22).

2.3. Pharmacokinetics and metabolic conversion (MI → DCI)

When taken orally, inositols are absorbed by sodium-dependent transporters (SMIT1/2) in the intestine (21). GI absorption is generally good, but can be competitively inhibited by high glucose levels – glucose and inositol share transporter pathways in gut and kidney, so hyperglycemia can hamper inositol uptake. Once absorbed, inositol circulates in plasma and is taken up into tissues by the same type of sodium-coupled symporters. The kidneys filter and reabsorb inositol (via SMIT transporters) to maintain balance, so excretion in urine is normally low unless transport is saturated (23). Within cells, MI is partly converted to DCI by the NAD-dependent epimerase mentioned above. This conversion is one-way and tissue-specific: for example, muscle and liver generate more DCI to aid glycogen synthesis, while the ovary mostly uses MI. In insulin-resistant states, the activity of this enzyme and the resulting MI→DCI conversion may be impaired, leading to tissue-specific inositol imbalances (24).

3. MECHANISTIC RATIONALE IN PCOS

3.1. Insulin-signalling pathways and inositol phosphoglycans

A key rationale for inositol therapy is its role in insulin signaling (25). Insulin exerts some of its effects via glycosylphosphatidylinositol-linked secondary messengers called inositol phosphoglycans (IPGs). There is evidence that a DCI-containing IPG mediator (sometimes called IPG-P) is released in response to insulin and activates glycogen synthesis and other insulin actions. In PCOS and type 2 diabetes, impaired release of DCI-IPG has been reported. For example, insulin-resistant PCOS patients show blunted changes in blood DCI-IPG after a glucose load, correlating with their insulin resistance (26). Importantly, interventions that improve insulin sensitivity also boost DCI-IPG release. In one study, metformin therapy in PCOS increased the DCI-IPG response to glucose, accompanied by better insulin sensitivity (27). Likewise, weight loss or thiazolidinediones have been shown to raise IPG levels in PCOS (28). These findings suggest that relative deficiency of DCI-IPG contributes to PCOS insulin resistance, and that supplementing its precursors might restore proper signaling. Thus MI and DCI are thought to augment the endogenous insulin signaling pathway, helping to correct the hyperinsulinemia of PCOS (29).

3.2. Effects on ovarian steroidogenesis and oocyte quality

Inositols also have ovarian effects. Within the ovary, MI and DCI appear to play distinct roles. MI promotes follicle-stimulating hormone (FSH) signaling and helps granulosa cells mature oocytes, while DCI mediates insulin-driven androgen synthesis in theca cells (30). In normal physiology, this balance supports healthy folliculogenesis. In PCOS, chronic hyperinsulinemia may drive excess conversion of MI to DCI within the ovary, skewing this balance towards androgen production. The result is relative MI depletion in the follicular environment, which can impair FSH signaling and oocyte development (17, 31). Clinically, supplementing MI (often 2 g twice daily) has been observed to improve ovarian outcomes. For example, in one controlled trial, 2 g/day MI (plus folic acid) restored ovulation in 88% of anovulatory PCOS women, reduced serum testosterone, and induced regular cycles within 6 months (32). In vitro fertilization (IVF) studies also suggest that MI improves oocyte competence: women treated with MI had more mature (metaphase II) eggs and higher fertilization rates than controls (33). Overall, by enhancing insulin sensitivity in ovarian tissue and restoring a more normal MI/DCI balance, inositols appear to favorably influence androgen levels, follicular milieu and oocyte quality in PCOS (34).

3.3. Anti-inflammatory and antioxidant actions

PCOS is associated with a low-grade inflammatory and oxidative stress state, which can damage tissues and impair fertility (35). Some preclinical and small clinical studies suggest that inositols may have antioxidant or anti-inflammatory effects in PCOS, although data are limited. For instance, PCOS patients often show oxidative modifications in erythrocyte membranes (e.g. protein and lipid oxidation) consistent with systemic stress. In one trial of 1200 mg/day MI for 12 weeks, markers of oxidative stress in PCOS were significantly reduced alongside improvements in insulin resistance (36). Similarly, DCI has been found to lower intracellular oxidative stress markers in treated PCOS blood cells (37). These effects are generally thought to be indirect – i.e. by improving glycemic control and reducing androgen excess, inositols may secondarily decrease reactive oxygen species (25). Direct antioxidant mechanisms have been proposed in some animal studies, but human evidence is scarce (38).

4. CLINICAL EVIDENCE BY PREPARATION

4.1. MI monotherapy (2–4 g/day)

MI alone has been widely studied in PCOS. Typical regimens use 2–4 g of MI per day (often given as 1–2 g twice daily) for several months. Many randomized trials (mostly versus placebo) have examined metabolic and reproductive outcomes. Meta-analyses show that MI monotherapy produces statistically significant but modest benefits over placebo. For example, one meta-analysis found that MI significantly lowers fasting insulin and HOMA-IR, raises SHBG, and modestly reduces total and free testosterone in PCOS women. MI also improves menstrual cyclicity: pooled data indicate higher rates of cycle regularization and ovulation on MI versus placebo (e.g., pooled risk ratio ~1.8 for normalized cycles). On average, MI-treated women experienced small but significant decreases in BMI and waist circumference compared to placebo (39). In clinical trials, MI monotherapy has often restored ovulation in about half to two-thirds of patients and led to pregnancy in many women over 3–6 months of use (32, 40). In one trial of 61 adolescents with PCOS, a cohort of 20 patients given 4 g/day MI plus 400 mg folic acid, treatment produced statistically significant reductions in body weight, body-mass index (BMI), fasting glucose, C-peptide, insulin, the homeostasis model assessment of insulin resistance (HOMA-IR), free testosterone (FT) and luteinizing hormone (LH). By contrast, sex-hormone-binding globulin (SHBG), total testosterone (TT), the free-androgen index (FAI), dehydroepiandrosterone-sulfate (DHEA-S) and anti-Müllerian hormone (AMH) remained unchanged (41). Overall, MI

monotherapy appears safe and can improve insulin resistance, androgen excess and ovulatory function, but its effects are generally moderate. Benefits on fertility endpoints (pregnancy/live birth) have been reported anecdotally but are not yet confirmed in large trials (32, 39, 40).

4.2. DCI monotherapy (300–1,200 mg/day)

DCI has also been studied as a single agent, though fewer trials exist. The landmark study in 1999 compared 1200 mg/day DCI to placebo in 44 women with PCOS. After 6–8 weeks, 19 of 22 women in the treatment arm ovulated, compared with only 6 of 22 on placebo. Mean testosterone levels also dropped sharply (from ~1.1 to 0.5 ng/dL) in the DCI-treated group. Blood pressure and triglycerides improved as well. These findings demonstrated that DCI alone can markedly enhance insulin action and ovulatory rates in PCOS (42). In a small trial of lean PCOS women, 600 mg/day DCI for 6–8 weeks significantly decreased free testosterone and insulin levels, with 60% ovulating on treatment (43).

4.3. Combined MI : DCI therapy

- **Physiological 40:1 ratio – key trials and outcomes:** Because MI and DCI play complementary roles, many studies have used a combination at the "physiological" plasma ratio (~40:1). For example, one RCT treated PCOS women with a soft-gel formulation containing 550 mg MI and 13.8 mg DCI per capsule plus folic acid twice daily (total 1100 mg MI + 27.6 mg DCI per day) for 6 months. This group was compared to placebo. The combined 40:1 therapy led to significant reductions in LH, free testosterone, fasting insulin and HOMA-IR, as well as an increase in 17-beta-estradiol levels. Clinically, menstrual regularity and ovulation rates improved in the MI+DCI group (44). Similarly, another trial in overweight PCOS women found that adding DCI to MI (550 mg + 13.6 mg twice daily) produced earlier improvements in metabolic markers compared to MI alone, suggesting a synergistic benefit (45). Based on such data, many experts now advocate a 40:1 MI:DCI combination (usually with added folic acid) as the first-line inositol regimen, especially for infertile or metabolically at-risk women. Formulations at this ratio have become widely available as nutritional supplements or medical foods (46, 47).
- **Alternative ratios:** In a double-blind RCT of 60 PCOS patients undergoing Intracytoplasmic Sperm Injection (ICSI), the high-DCI combination—MI 550

mg + DCI 150 mg twice daily (≈ 3.7 : 1 MI : DCI)—achieved markedly better outcomes than the low-DCI, near-physiologic formulation of 550 mg MI + 13.8 mg DCI (≈ **40 : 1**) given for the same 12 weeks. Pregnancy and live-birth rates were 65.5 % and 55.2 % with the 3.7 : 1 ratio versus 25.9 % and 14.8 % with the 40 : 1 ratio (RR = 0.40, $p = 0.003$; RR = 0.27, $p = 0.002$, respectively), while the risk of ovarian hyperstimulation syndrome trended lower (3.4 % vs 18.5 %, $p = 0.07$). Thus, raising the DCI fraction from 40 : 1 to about 4 : 1 substantially improves ICSI success and may reduce ovarian hyperstimulation syndrome (OHSS) risk in women with PCOS (48).

4.4. Novel formulations (inositol + α-lactalbumin; sustained-release capsules)

One approach is combining MI with α-lactalbumin (a whey protein) to enhance absorption. In a pharmacokinetic study, adding α-lactalbumin to 2 g oral MI significantly increased the plasma concentration of MI within 180 minutes. The authors concluded that "better myo-inositol absorption when administered with α-lactalbumin can be beneficial in non-responder patients" (49).

5. PREGNANCY AND GESTATIONAL DIABETES RISK

There is growing interest in using inositols to reduce gestational diabetes (GDM) risk in pregnant women with PCOS or impaired glucose tolerance, since insulin resistance often worsens in pregnancy. A meta-analysis of 7 RCTs involving 1,319 high-risk pregnant women found that inositol supplementation significantly reduced the risk of GDM (OR 0.40), along with improvements in fasting and post-load glucose levels. It also lowered the incidence of pregnancy-induced hypertension and preterm birth. In a subset of 4 trials including women with established GDM, inositol further improved insulin resistance (50). Moreover, a 2022 systematic review and meta-analysis of four RCTs evaluated the impact of MI supplementation on overweight and obese pregnant women. The findings showed that MI significantly reduced the incidence of GDM, lowered fasting glucose, 1-hour OGTT, and 2-hour OGTT levels . Additionally, it reduced the risk of gestational hypertension and preterm delivery, with no significant differences observed in other pregnancy outcomes. These results support MI as a safe and effective strategy for GDM prevention in overweight and obese women (51).

However, major guidelines have not yet endorsed this use and more evidence is needed. Importantly, inositols appear safe in pregnancy: they are natural dietary components and have been used in studies of GDM without adverse outcomes (52, 53).

6. SAFETY PROFILE

Inositols are exceptionally safe. Systematic reviews and clinical trials report only mild and infrequent adverse events. The most commonly noted side effects (at very high doses) are gastrointestinal: nausea, bloating, flatulence or diarrhea. For instance, one safety review found that only very high doses of MI (≥12 g/day) produced mild GI symptoms (54). In typical PCOS doses (2–4 g/day), side effects are rare. By comparison to metformin, inositol causes far fewer GI complaints. No serious or long-term adverse effects have been documented in PCOS trials. There are no absolute contraindications; inositol is even safe in pregnancy. Patients with severe malabsorption or taking interfering diuretics (which may affect renal reabsorption) might require monitoring, but no formal contraindications exist. Overall, inositol's safety profile makes it an attractive option for patients who cannot tolerate first-line drugs (55).

7. CURRENT GUIDELINES AND RECOMMENDATIONS

Major PCOS guidelines have only recently addressed inositol. The 2023 international evidence-based guideline on PCOS explicitly reviewed inositol therapies and found the evidence to be "limited and inconclusive". It did not make a strong recommendation for routine use of inositol; instead it advised clinicians to recognize the uncertainty of benefit. No major society (ACOG, ESHRE, Endocrine Society) currently endorses inositol as a standard treatment for PCOS. Some smaller associations or expert panels may list inositol as an "emerging option" but with caution. In contrast, patient-driven organizations (e.g., SOGC in Canada) have noted the popularity of inositol but also urge practitioners to rely on evidence. In short, guidelines treat inositol as optional and emphasize shared decision-making due to the low quality of data (14).

8. LIMITATIONS OF CURRENT EVIDENCE

The current evidence base has several important limitations. Most published RCTs are small (often <100 women) and short-term (months). Studies vary widely in patient characteristics (age, BMI, PCOS phenotype) and in inositol formulations and doses, making comparisons difficult (high heterogeneity). Many trials lack placebo control or blinding, and outcome measures differ. Follow-up durations have been too short to assess long-term impacts (e.g. on diabetes or cardiovascular events). In addition, there is potential publication bias, as many studies are industry-sponsored (for example by supplement manufacturers) and negative trials may go unreported. The 2023 guideline review explicitly notes that the body of evidence is low quality and inconclusive (14). In practice, this means that while meta-analyses often show statistically significant effects, the clinical significance is uncertain. Clinicians should be mindful of these limitations and interpret positive findings with caution.

9. FUTURE DIRECTIONS

Future research is addressing these gaps. Several ongoing clinical trials aim to provide longer-term data. For example, prospective RCTs are underway to compare letrozole with and without inositol for infertility, or to test MI plus α-lactalbumin in "inositol-resistant" PCOS cases. Studies are also examining combinations of inositol with other nutraceuticals (e.g., alpha-lipoic acid) or with anti-obesity medications. Beyond trials, research into personalized medicine may clarify who benefits most: for instance, genetic markers of inositol metabolism (epimerase polymorphisms) or gut microbiome profiles could predict response. Long-term endpoints like incident type 2 diabetes, cardiovascular outcomes, or pregnancy/live-birth rates need assessment. Given the popularity of inositol, there will likely be more high-quality multicenter RCTs with ≥12-month follow-up in the next years. Ultimately, these studies will determine whether inositol can be refined into a targeted therapy for specific PCOS subgroups.

10. CONCLUSION

Inositols (myo-inositol and D-chiro-inositol) are biochemically plausible, well-tolerated supplements that target key pathophysiologic features of PCOS. Clinical trials in women with PCOS show that inositol therapy can improve insulin resistance, lower androgens, and restore ovulation in a sizable proportion of patients. Meta-analyses support statistically significant benefits over placebo, and inositol performs similarly to metformin on many endpoints but with fewer side effects. However, current studies

are small and heterogeneous, so the overall efficacy remains uncertain. For the clinical audience, the practical takeaway is that inositol may be considered as an adjunct therapy in selected PCOS patients (especially those with metabolic concerns or ovulatory infertility who prefer a supplement). It should not replace established treatments but can complement them under close monitoring.

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