

Metformin, myo-inositol and D-chiro-inositol use and ART outcomes in women with PCOS: current results and future perspectives

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ABSTRACT

Polycystic ovary syndrome (PCOS) remains the most common endocrine disorder in women worldwide. PCOS affects 5-18% of women, and is a reproductive, metabolic, and psychological condition. Oligomenorrhea, obesity, infertility, hyperandrogenemia and insulin resistance (IR) constitute the common features of PCOS. IR has a critical role in the pathogenesis of PCOS. Metabolic abnormalities in PCOS patients are manifested by IR, dysregulation of glucose metabolism, lipid metabolism disorders. The primary defect in IR in PCOS is the postreceptor defect. The association between hyperinsulinemia, hyperandrogenism, and ovulatory dysfunction in PCOS formed a basis for treatment with insulin-sensitizing agents such as inositol derivatives and metformin. Reducing IR in these patients has a positive effect on both metabolic and reproductive outcomes. Current data support the notion that inositol isoforms myo-inositol (MYO), D-chiro inositol (DCI) and metformin may be effective in the treatment of patients with PCOS. In combination with MYO and DCI, it has metabolic and hormonal effects similar to those of merformin in PCOS. In terms of in vitro fertilization/Intractoplasmic sperm injection (IVF/ICSI) IVF results, both MYO and MYO plus DCI use have positive effects on ovarian response. However, the effects on clinical pregnancy rate (CPR) and live birth rates (LBR) appear to be limited. As a supplement, preventive strategies and IVF results of these treatments are presented and discussed in detail. The controversial aspect of the issue begins at this point and future perspective approaches are presented along with current results. In this review, metabolic, hormonal and reproductive results are collected holistically.

Keywords: PCOS, inositol, metformin, insülin resistance, IVF, pregnancy

INTRODUCTION

PCOS is a condition that affects 5-13% of women of reproductive age and is characterised by anovulation and metabolic complications. The current diagnostic criteria for PCOS are the Rotterdam (2003) criteria: (i) oligo-amenorrhea, (ii) Hyperandrogenism (clinical or biochemical), and (iii) polycystic ovarian morphology on ultrasonography. The presence of two of these criteria was found to be sufficient for diagnosis. Type A (HA+OA+PCOM), type B (HA+O-AN)), type C (HA+PCOM), and type D (O-AN+PCOM).² IR, glucose metabolism disorders and lipid and low-grade inflammation play a key role in PCOS. The primary defect in IR in PCOS is the postreceptor defect. IR is manifests with a decreased utilization of glucose due to a defective glucose transport across the plasma membrane by glucose transporter type 4 (GLUT4). (Figure 1). The prevalence of IR in the PCOS population is as high as 75. Approximately 50% of IR patients progress to metabolic syndrome. Metabolic syndrome (MS) is defined as a group of conditions including, central adiposity, hypertension, dyslipidemia and glucose intolerance. PCOS encompasses all known risk factors for the development of MS. The use of inositol and metformin plays an important role

in the correction of IR in PCOS. Reducing IR in these patients has a positive effect on both metabolic and reproductive outcomes. The most promising results in PCOS supplement applications have been obtained with inositol derivatives. Inositol plays important functional roles in cell membrane integrity and intracellular signaling.² Two of these are myo-inositol (MYO) and D-chiro-inositol (DCI), which play different relevant biological functions as insulin-sensitizing agents. Current data support the notion that inositol isoforms may be effective in the treatment of patients with PCOS like metformin. In this narrative review, the results of studies using only MYO, MYO plus DCI, MYO and metformin are discussed ovulation induction, IVF/ICSI and metabolic aspects patients with PCOS.

SEARCH STRATEGY

A literature search was performed using PubMed and Google Scholar in the English language until July 2025. The following combinations of search terms were used: "PCOS", "myo-inositol", DCI, metformin, "anovulation",

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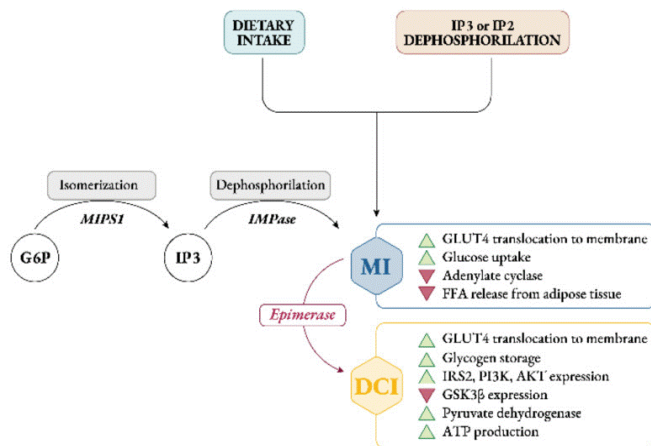


Figure 1. Synthesis, sources and role of MYO and DCI in insulin signaling pathway.²

MYO: Myo-inositol, DCI: D-chiro-inositol

“hyperandrogenism”, “insulin resistance”, “ovulation induction”, “in vitro fertilization”, “IVF”, “assisted reproductive technology (ART)” and “treatment outcome.” A narrative review was done. The eligibility criteria were: human randomized controlled study (RCT), review and meta-analysis patients with PCOS and non-PCOS ovulation induction and IVF/ICSI, the administration of MYO, DCI and metformin supplements. Studies conducted in animal models, in vitro models, only as abstracts or repeated publications were excluded. Eligible studies that were compared six treatment combinations were compared in this study. Titles and abstracts of included studies were scanned and verified, and additional references from included studies were used when necessary. The full text of these potentially eligible articles was retrieved and assessed for eligibility. The results were collated the evidence and summarize anovulation, ovarian stimulation and IVF outcomes (stimulation duration, ovulation rate, oocyte quality, fertilization, CPR and ovarian hyperstimulation syndrome (OHSS). Results from the studies with LBR were also reviewed. Positive and negative IVF outcome results were collected and the study results were reviewed.

METFORMIN ON PCOS

The use of metformin is associated with increased menstrual cyclicity, reduction in circulating androgen levels and improved ovulation in PCOS. Metformin (a biguanide) acts by inhibiting hepatic glucose production, decreasing intestinal glucose uptake and increasing insulin sensitivity in peripheral tissues. Metformin, as long-used sensitizer, increases CPR, especially combined with other drugs, but does not clearly improve LBR alone in PCOS women undergoing IVF. If lifestyle changes are not sufficient, metformin may be recommended. In women PCOS who are not pregnant, metformin (1000-2000 mg/day, 3-6 month) can help improve IR, hormone levels, and menstrual regularity, among those who are overweight or have signs of IR. Higher metformin doses have been beneficial in reducing weight and improving lipid profiles, particularly in obese PCOS population. Metformin alone is not a first choice treatment for ovulation because ovulation induction is more effective than metformin. When combined with ovulation

induction (mainly gonadotrophins) or IVF/ICSI, it may offer additional benefits. Metformin in pregnant women with PCOS has not been shown to prevent poor obstetrics outcomes. Tso et al.³ conducted a systematic review and meta-analysis on the effect of metformin before or during IVF/ICSI cycles and found no difference LBR (RR: 1.30, 95% confidence interval (CI) 0.94 to 1.79; 6 RCTs; 651 women; $I^2=47\%$; low-quality evidence), but ovarian hyperstimulation risk (OHSS) risk was observed to be lower (RR:0.46, 95% CI 0.29 to 0.72; 11; $I^2=38\%$).

INOSITOL ISOFORM ON PCOS

MYO and DCO are two isomers of inositol that are effective in the intracellular signalling pathway throughout the body. MYO and DCI produce synergistic effects on glucose metabolism. MYO can improve IR and plays a pivotal role in both signaling pathways in women with PCOS^{3,4} MYO plays an important role in the follicular microenvironment and affects oocyte maturation and embryo development. The expression of three genes associated with oocyte quality (RGS2, PGK1, and CDC42) was higher in the MYO group. Elevated concentration of MYO in the follicular fluid appears to exert a positive effect on follicular maturity and is a marker of good quality oocytes in women with or without PCOS.⁴

MYO improves insulin metabolism, lowers androgen levels, supports follicle maturation, and enhances oocyte quality. In PCOS, while IR is present in other organs and tissues, increased insulin sensitivity occurs in the ovary, and insulin, together with LH, produces a co-gonadotropin effect through IGF-1. Three-fold higher epimerase activity has been detected in theca cells in PCOS. Although muscle and liver are insulin resistant in women with PCOS, the ovaries retain normal insulin sensitivity. This is the so-called “DCI paradox” in the ovary. A decrease in MYO concentration may lead to excessive DCI due to epimerase overactivation, resulting in depleted MYO levels and subsequent decline in embryo quality in PCOS women.⁵ The deficiency of MYO could be responsible for the poor oocyte quality and the impairment of the FSH signaling in ovary. Follicular fluid MYO levels are associated with blastocyst development. DCI supplementation would be ineffective in such women as they already have high levels of this molecule in the ovary in PCOS women. (Figure 2).⁶

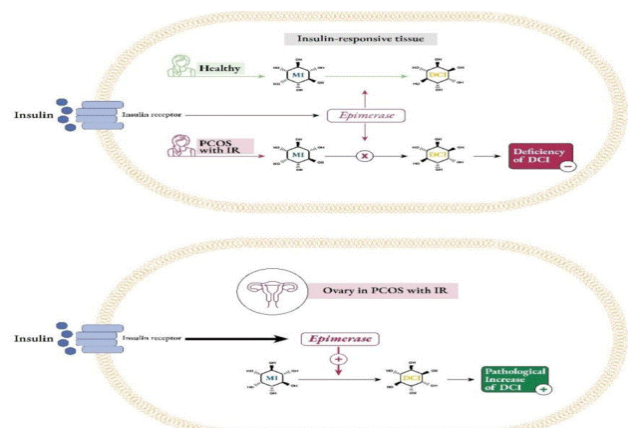


Figure 2. Insulin stimulates epimerase enzyme to convert MYO to DCI. The classic insulin target tissues of PCOS women with IR show less epimerase activity and consequently result in a systemic deficiency of DCI. Ovaries of PCOS women with IR maintain the normal insulin sensitivity (“ovarian paradox”); the hyperinsulinemia overstimulates epimerase to convert MI to DCI, resulting in a pathological increase in DCI.²

INOSITOL IN PCOS PATIENTS OVULATION INDUCTION

MYO vs Placebo

In a study by Kamenov et al.⁷ 50 anovulatory PCOS patients with IR were given MYO for three spontaneous cycles. In this study, ovulation and pregnancy were achieved in 61.7% and 37.9% of women. Unfer et al.⁸ a review in which six RCT were analyzed. Authors described a marked reduction of LH levels and LH/FSH ratio after MYO supplementation. Similar findings were demonstrated by Artini et al.⁹ who showed 50 overweight PCOS patients which were divided into two groups; group A was given MYO 2g plus folic acid 200mg daily for 12 weeks and group B was given folic acid 200mg daily. They found significant restoration of anovulation in group A. In the MYO group the duration of stimulation was shorter, the dose of r-FSH were lower and estradiol levels evaluated at the day of hCG administration were lower than in control group. In MYO group there was a significant reduction in plasma LH, prolactin, insulin levels, and LH/FSH. IR measured as glucose-to-insulin ratio were significantly reduced. Another, RCT was carried out with MYO in 30 PCOS women undergoing ovulation induction; patients were administered 4g MYO daily. Treated patients, compared with controls, increased frequency of spontaneous menstrual cycles, and this finding suggested that MYO may be useful in the treatment of infertility in PCOS.¹⁰ Pundir et al.¹¹ meta-analysis ten RCT, a total of 362 women revealed that CPR with MYO compared with placebo (RR: 3.3; 95% CI 0.4-27.1, I²: 24.4, p<0.05) in PCOS women with undergoing ovulation induction. Administration of MYO combined with folic acid 2 g twice a day showed maintenance of normal ovulatory activity in 72%, with singleton pregnancy rate of 40% during the 6-month observation period in PCOS patients. Based on these results, MYO appears to improve ovulation in PCOS (Table 1).

DCI vs Placebo

Nestler et al.¹² study found that the frequency of ovulation was greater in the DCI group (1200 mg/daily) compared to placebo (86% vs. 27%). Iurno et al.,¹³ In 20 lean in women PCOS with infertility, treatment was initiated with either 600 mg of DCI or placebo orally once daily for 6 to 8 weeks. In lean women with the PCOS, DCI reduces circulating insulin, decreases serum androgens, and ameliorates the metabolic abnormalities. Gerli et al.¹⁴ used a lower dose of DCI 100 mg twice daily and achieved successful results in ovulation

in women PCOS with ovulation induction (in the DCI vs. placebo group; 8/136 vs. 17/147). Based on this results, DCI improves ovulatory function. However, the three studies had a small sample size and utilised different doses of DCI (Table 1).

DCI, unlike MYO, produces dose-dependent aromatase inhibition in the ovary. The increased DCI concentration in ovarian cells could amplify insulin action in PCOS theca cells, leading to increased intra-cellular synthesis of testosterone. Healthy volunteers were treated with 1200 mg of DCI (high dose) for a short period of time will paradoxically enhance androgen synthesis and impair ovulation by decreasing aromatase activity. These observations support the notion that any further increase in DCI is detrimental to ovarian function. From these results, the use of high doses of DCI in infertile women with PCOS has been avoided. However, this effect of DCI has opened up a new area of use in patient groups with non-PCOS and non-IR. In these patients, the use of 600-1200mg of DCI per day increased intrafollicular androgen by aromatase inhibition, thus providing a folliculogenesis-inducing effect. In such specific cases DCI probably acted mainly on aromatase expression, impairing estrogen biosynthesis and contributing to FSH release.^{15,16}

MYO plus DCI vs DCI

Colazingari et al.¹⁷ investigated the role of MYO plus DCI (1.1 g MYO plus 27.6 mg of DCI) in comparison to DCI alone in PCOS patients undergoing IVF. In this study showed that reduced number of degenerated oocytes, increased fertilization rate and number of transferred embryos, and improved embryo quality in the MYO plus DCI group. Administration of both MYO plus DCI has been shown to be effective in achieving better clinical results in PCOS patients in a combination the plasma physiological ratio (40:1 ratio).¹⁸ A results, the combination of MYO plus DCI has proven to improve the oocyte quality and the pregnancy outcomes in women with PCOS undergoing IVF.

MYO vs Metformin

Rajasekaran et al.¹⁹ revealed RCT hat MYO is equally beneficial as metformin in reducing the risk of OHSS. In this study, fertilization, number of top good grade embryos and CPR were significantly higher in MYO group. According the results, MYO has better than metformin IVF outcome in PCOS women undergoing IVF cycles. Pundir et al.¹¹ meta-analysis ten randomised trials, revealed that CPR were significantly higher in the MYO group compared with metformin (RR 1.5; 95% CI 0.7-3.1) in PCOS women undergoing ovulation

Table 1. The results of ovulation induciton MYO vs placebo and DCI vs placebo

References	Study type	Intervention	LH/FSH ratio	Ovulation rate	Pregnancy rate
Kamenov (2015) ⁷	Randomized controlled	MYO (2 gr daily) vs placebo	Reduced	61.7%	31.9%
Unfer (2016) ⁸	Randomized controlled	MYO (2 gr daily) vs placebo	Reduced	NA	NA
Artini PG (2013) ⁹	Randomized controlled	MYO (2 gr daily) plus folic acide vs placebo	NA	72%	40%
Nestler (1999) ¹²	Randomized controlled	1200 mg/daily DCI vs placebo	NA	86%	27%
Iurno (2002) ¹³	Randomized controlled	600 mg/daily DCI vs placebo	Reduced	NA	NA
Gerli (2003) ¹⁴	Randomized controlled	100 mg/daily DCI vs placebo	NA	8/136 vs 17/147	NA

MYO: Myoiositol, DCI :D-chiro inositol, LH: Luteinising hormone FSH: Follicle stimulating hormone

induction. A meta analyses by Unanyan et al.²⁰ 35 RCTs were included for qualitative analysis reporting on 4668 participants. In group of metformin treatment were included 1891 patients, in MYO group 281, in MYO+metformin group were included 110 participants and in control group (placebo or absence of treatment) 1865 women with PCOS. In this meta-analysis, CPR were higher in the MYO group than in the metformin group (RR=1.52, 95% CI: 1.05 to 2.18, p=0.03).

MYO vs MYO plus Metformin

Prabhakar et al.²¹ RCT to evaluate the benefits of MYO plus metformin versus MYO alone PCOS women undergoing ovulation induction cycles. Group I (n=57): metformin (1500 mg) plus MYO (4g) per day; Group II (n=59): MYO 4g per day. Subjects were advised to try for spontaneous conception. MYO (4g) might be used alone as sensitizer to improve metabolic, hormonal and reproductive outcome in infertile PCOS women. According to the results of this study, 4g MYO alone gave more effective results than the combination of 4g inositol and metformin.

MYO plus DCI vs MYO

Nordio M and Proietti E compared MYO plus DCI (40:1 ratio) to MYO. Fifty overweight women with PCOS were enrolled and divided in two groups to receive MYO and MYO plus DCI or MYO alone.¹⁸ The combined supplementation with MYO plus DCI resulted to be more effective, compared to the MYO group (550 mg/day), after three months of treatment. The MYO plus DCI group (40:1) was administered as 550 mg MYO plus 13.8 mg DCI in a softgel capsule twice daily. In this study, hormonal, metabolic and reproductive outcomes were better in the MYO plus DCI. The combined supplementation with MI and DCI resulted to be more effective, compared to the MI group, after three months of treatment. According to this results, the combined administration of MYO/DCI in physiological plasma ratio (40:1) should be considered as the first line approach in PCOS overweight patients. The search for the optimal rate for combined use of MYO and DCI continues.

Inositol in PCOS Patients Intrauterin Insemination

In a study by Özyay et al.²³ in which they administered 4 g/day MYO and 400 mcg/day folic acid to 98 infertile patients undergoing controlled ovarian hyperstimulation with rFSH and intrauterin insemination (IUI) PCOS IUI cycles. They found an increase in CPR and a decrease in total FSH dose and induction time in the MYO group. In another study, in IUI cycles, the combination of metformin and MYO provided higher success in terms of both CPR and LBR in women with PCOS. In this study found combined MYO and metformin therapy increased LBR (55% vs. 26.7%) and CPR (63.3% vs. 33.3%) after IUI.²⁰

INOSITOL IN PCOS PATIENTS POSITIVE IVF OUTCOMES

Only MYO

Lagana et al.²⁴ meta-analysis of eight studies incorporating 912 women investigated the amount of gonadotropin units required

in combination with MYO versus a control treatment. This analysis observed a significant reduction in the required units of gonadotropins required for stimulation protocols in women with PCOS undergoing IVF. These evidences demonstrate that MYO improves FSH sensitivity and beneficially affects ovarian function and oocyte development. The randomized study conducted by et Druckman et al.²⁵ that revealed a MYO therapy in women with PCOS results in better fertilization rates and improved embryo quality. In another a randomized trial conducted by Sene et al.²⁶ demonstrated the benefits of MYO supplementation in patients PCOS undergoing IVF cycles. In this metaanalysis, MYO increased metaphase II oocytes, improved fertility rates and resulted in a greater number of high-quality embryos. Another trial showed MYO use before IVF doubled cumulative pregnancy rates compared to metformin (43.2% vs. 22.7%) with comparable reduction in OHSS risk.²⁰

A review by Merviel et al.²⁷ investigated the impact of MYO on IVF outcome in women PCOS with undergoing IVF. They showed that MYO is effective improving oocyte and embryo quality. Pacchiarotti et al.²⁸ randomized 526 PCOS patients into three groups: control (folic acid: 400 mcg), group A (MYO:4000 mg, folic acid: 400 mcg, and melatonin: 3 mg daily), and group B (MYO:4000 mg and folic acid: 400 mcg daily). All patients received their treatment from first day of the menstrual cycle until 14 days. Patients in group A required decreased dose of gonadotropins (p<0.001) and had improved quality of oocytes and embryos, suggesting the synergistic effect of MYO and melatonin on improving oocyte and embryo quality. Similarly, Gateva et al.⁷ reported that in IVF, MYO and the combined treatment are able to improve clinical outcomes. Artini et al.²⁹ reported that MYO can positively affect in PCOS women undergoing IVF, in terms of oocyte quality and CPR. In a meta-analysis of six trials and 913 women, Zheng et al.³⁰ investigated the efficacy of MYO in studies including in women PCOS with undergoing IVF. In this analysis, MYO supplementation led to significant improvements in CPR (OR, 1.45; 95% CI, 1.08–1.95; p=.003) and the required units of gonadotrophin (MD, -229.42; 95% CI, -387.65 to -71.18; p=.004). This author reports a 27% decrease in miscarriages (95% CI 0.08–0.50, p: 0.0006). In addition, the proportion of grade 1 embryos is significantly increased. More recently, a meta analysis by Zhang et al.³¹ in which eleven eligible studies only with MYO supplementation were included with 981 participants, reported the IVF outcomes of the MYO group versus the control group. In this metaanalysis, MYO supplementation improves the MII oocyte rate (OR 1.55, 95% CI 1.04–2.31, p=0.03) and the fertilization rate (OR 1.62, 95% CI 1.21–2.16, p<0.01) in PCOS women undergoing IVF.

MYO plus DCI

Sene et al.³² a systematic review and meta-analysis. MYO/DCI supplementation significantly increased the CPR (RR: 1.20, 95% CI: 1.03; 1.41, I2: 18.44%, p=0.27) and top-grade embryos (RR: 1.17, 95% CI: 1.08; 1.28, I2: 83.36%, p=0.00). This meta-analysis provides reliable evidence on the effects of MYO/DCI on fertility and ovarian function in women PCOS undergoing ART. Sene et al.²⁶ the results of the present meta-analysis showed that in women PCOS consuming MYO/DCI

had a 17% higher likelihood of increasing the number of top-grade embryos compared to those in the placebo group. In this results showed that in the MYO plus DCI user group, the probability of OHSS was 16% lower than that of the placebo group (RR: 0.79, 95% CI: 0.46; 1.37, I²: 0.00%, *p*=0.78).

INOSITOL IN PCOS PATIENTS NEGATIVE IVF OUTCOMES

MYO plus DCI

A meta-analyses by Bhide et al.³³ in which included 18 trials, revealed that the combination of MYO and/or DCI did not show positive results on CPR in PCOS women undergoing IVF. In this meta-analysis, there was no difference between the MYO and/or DCI groups and the control groups in terms of number of totally oocytes (mean difference -0.39, 95% confidence interval [CI]-1.11 to 0.33), number of metaphase II oocytes (mean difference 0.29, 95% CI-0.83 to 1.40), number of top grade embryos (RR 1.02, 95% CI 0.93-1.12), CPR (RR 1.16, 95% CI 0.87-1.53), and risk of OHSS (RR 0.73, 95% CI 0.39-1.37). Included studies used MYO doses ranging from 1 to 4 g/day for 12 weeks of treatment. Two studies used DCI at 300-1200 mg/day for 8-12 weeks.

Only MYO

A metanalysis by Mendoza et al.³⁴ it has been demonstrated that MYO was insufficient to improve the oocyte quality, embryo quality or pregnancy rate in PCOS women undergoing IVF. Similar findings were reported by Aragona et al.³⁵ who showed retrospective IVF study MYO supplementation in the treatment group significantly reduced the number of units of rFSH used in COH, however, no changes were seen in other measured IVF outcomes.

LBR

The current literature reveals that there are very few studies evaluating LBR in IVF inositol studies. Vartanyan et al.³⁶ comparison of in women PCOS undergoing IVF (received inositol 1000 mg+folic acid 0.1 mg) with normal reserve in IVF cycles, take baby home rates were similar to the non-PCOS group. Artini et al.³⁷ reported a significant improvement in LBR following treatment with MYO compared with placebo. Cochrane Review, by Showell et al.³⁸ in which included 13 trials involving 1472 subfertile women with PCOS. This Cochrane Review found no increase in LBR. In contrast to the results of Cochrane Review, Seyedoshohadaei et al.³⁹ showed that LBR in the MYO group were significantly higher than in the controls (*p*=0.04). A meta-analysis by Sene.³² that showed, in the group consuming MYO/DCI, LBR was 1.24 times higher than in the placebo group (RR: 1.24, 95% CI: 0.78; 1.98, I²: 34.17%, *p*=0.19) (Table 2).

Inositol in Non-PCOS Patients IVF Outcomes

A systematic review confirmed the efficacy of MYO supplementation in improving CPR and reducing the units of rFSH in infertile non-PCOS patients undergoing ICSI or IVF.²³ A meta-analysis, by Zhang et al.³⁰ revealed that eleven eligible studies with 981 participants reported the IVF outcomes of the MYO group poor responders IVF. MYO

supplementation improves the MII oocyte rate (OR 1.59, 95% CI 1.16-2.18, *p*<0.01) and the fertilization rate (OR 1.87, 95% CI 1.52-2.31, *p*<0.01). With respect to women with an expected poor response to ovarian stimulation, preliminary work has suggested that 4 g of myo-inositol may have a favourable benefit on ovarian stimulation. A randomized controlled study by Mohammadi et al.⁴⁰ provided evidence of MYO efficacy in poor ovarian responders. The study observed that MYO supplementation in these patients significantly improved fertilization rate and ovarian sensitivity index (Table 1). As a result, MYO supplementation gives favourable results in non-PCOS groups undergoing IVF/ICSI.

Metformin vs Inositol on Metabolic Outcomes in Women With PCOS

As an insulin sensitizing agent, many studies have shown that MYO and/or DCI have positive effects on the metabolic, endocrine and hormonal systems in PCOS. Based on these observations, MYO and DCI may be an alternative or complement to metformin therapy in PCOS patients. In women PCOS who overweight or IR, metformin (1000-2000 mg/day, 3-6 month) can help improve IR, hormone levels, and menstrual regularity. MYO and DCI are relevant biological functions as insulin-sensitizing agents. MYO and DCI have enhance insulin sensitivity, lower androgen levels, reduce LH/FSH ratio, and improve oocyte quality. Azizi et al.⁴¹ could not establish any differences between metformin and MYO concerning the hormonal profile and the ovarian function. Similarly, Greff et al.⁴² meta-analyses (26 RCT) that MYO showed non-inferiority compared to metformin regarding its effect on free and total testosterone, androstenedione, and SHBG. Zheng et al.⁴³ also reported similar results in the meta-analysis in terms of metabolic effects in the MYO and metformin groups. Overall, clinical trials and meta-analysis comparing MYO to metformin in PCOS women indicate comparable effects on key hormonal and metabolic parameters after 3-6 months of treatment. MYO has a significantly better safety profile with an absence of adverse effects compared to in the metformin group (RR=5.17, 95% CI: 1.1-7.2 I²: 21.44%, *p*=0.22)^{41,42} In contrast to Greff and Zheng et al.,⁴³ the results of a recent meta-analysis based on high-quality randomized trials by Fitz et al.⁴⁴ metformin is superior to MYO in improving clinical outcomes such as waist-hip ratio and Feriman Gallwey score.

DISCUSSION

PCOS is the cause of 80% of anovulatory infertility. In terms of ovulation induction, MYO and/or DCI improve ovulation in women PCOS with ovulation induction. MYO combined with folic acid 2 g twice a day for 6 months in PCOS patients showed maintenance of normal ovulatory activity in 72%. Supplementation with MYO and/or DCI leads to an improvement of ovulation frequency in women PCOS with anovulation.¹¹ Based on current studies, the gonadotrophin dose was low, the cycle duration was short and the OHSS rates were significantly lower in cycles using MYO and/or DCI in women with PCOS anovulation. This is attributed to MYO increasing FSH activity and shortening the duration of gonadotropin use. In addition, this results support the

Table 2. The characteristics of selected studies related to effect of MYO vs placebo,, MYO/DCI vs placebo on IVF outcomes with PCOS and non-PCOS undergoing IVF/ICSI

References	Study type	Intervention	Positive IVF outcomes	Negative IVF outcomes	Live birth rate	Conclusion
Lagana (2018) ²⁴	Meta-analysis (eight studies)	Mix studies; MYO (1, 1.1, 2 g)+folic acid (200 µg) sachet twice daily. Control group: folic acid (200 µg) for 3 months.	-Decreased amount of gonadotrophins -Decreased the length of ovarian stimulation (P<0.01) -Decreased OHSS		NA	Beneficial effect of amount of gonadotrophins and stimulation day
Akbari (2019) ²⁵	Double-blind randomized placebo-controlled study	MYO (4 g) + folic acid (200 µg) sachet one daily. Control group: folic acid (200 µg) for 1 months.	-Increased the number of metaphase II oocyte -Increased fertilization (p: 0.002)		NA	Increase in oocyte quality and fertilization rate
Unfer V (2017) ¹⁵	Meta-analysis (six studies)	Mix studies; MYO (2 g-4 g) + folic acid (200 µg) sachet twice daily	-Decreased amount of gonadotrophins -Decreased the length of ovarian stimulation -Increased the number of Metaphase II oocyte (p<0.05)		NA	Beneficial effect of amount of gonadotrophins and stimulation day. MYO increases oocyte quality
Artini PG (2013) ²⁸	Randomized placebo-controlled study	Patients are divided into two groups: one treated with MYO 2 g and folic acid 200 µg daily (Group A) and the other one receiving only folic acid 400 mg (Group B-controls)	-The duration of stimulation is lower than in control group -rFSH units used are fewer -Higher pregnancy rate(P<0.01)		+	Increase in the pregnancy rate Beneficial effect of amount of gonadotrophins and stimulation day.
Pacchiarotti (2016) ²⁸	Randomized, controlled, double-blind trial	Five hundred twenty-six PCOS women into three groups: controls (only folic acid: 400 mcg), Group A (a daily dose of MYO: 4000 mg, folic acid: 400 mcg, and melatonin: 3 mg), and Group B (a daily dose of myoinositol: 4000 mg and folic acid: 400 mcg)	Increased oocyte and embryo quality (p<0.05)		NA	Beneficial effects on embryo and oocyte quality
Ozay (2017) ²³	Randomized controlled study	196 women: 98 receiving MYO 4 g/day and FA 400 µg/day vs 98 receiving FA 400 µg/day-3 months before FSH and during FSH stimulation and IUI	Decrease in total FSH dose and duration of stimulation (p<0.05); increase in pregnancy rate (18.6 with MYO and FA vs 12.2% with FA alone) in IUI		NA	MYO-inositol increases pregnancy rate, and decreases total FSH dose and duration of stimulation
Colazingari (2013) ⁵	Randomized controlled study	100 women without hyperinsulinism: 47 undergoing MYO 1.1 g/day and DCI 27.6 mg/day vs 53 undergoing DCI 1 g/day-3 months prior to FSH treatment	Decrease in total FSH dose (1569 vs 1899 IU; p<0.05) and increase in good quality embryos (0.96 vs 0.73; p < 0.001)		NA	MYO+DCI increases oocyte and embryo quality
Mendoza (2017) ³⁴	Meta-analysis (eight studies, involving 1019 PCOS women)	Mix studies; MYO (1, 1.1, 2 g) + folic acid (200 µg) sachet twice daily. Control group: folic acid (200 µg) for 1-3 months.		A not significant trend towards improvement in oocyte quality (OR: 2.2; 95% CI 0.8–5.8), embryo quality (OR 1.6; 95% CI 0.3–6.7) and pregnancy rate (OR: 1.2; 95% CI 0.8-1.8) with MYO administration.	NA	No beneficial effects on embryo, oocyte quality and pregnancy rate
Bhide P (2019) ³³	Meta-analysis(18 trials)	Mix studies; MYO/DCI (40:1 ratio)+folic acid (200 µg) sachet twice daily. Control group: folic acid (200 µg) for 1-3 months.		No significant differences between MYO/DCI and control group were reported on number of oocytes, metaphase II oocytes, top grade embryos, clinical pregnancy rate and OHSS	-	No beneficial effects IVF outcomes in PCOS IVF

Showell (2018) ³⁸	Cochrane database analysis	11 trials involving 1472 women with PCOS and IVF	No pooled evidence is available for use of MYO women with PCOS undergoing pre-treatment to IVF	-	No beneficial effects IVF outcomes in PCOS IVF
Zheng (2017) ³⁰	Meta-analysis (six studies, 913 PCOS women)	Mix studies; MYO (1, 1.1, 2 g) + folic acid (200 µg) sachet twice daily. Control group: folic acid (200 µg) for 3 months.	Increase in clinical pregnancy rates after pre-treatment with MI: 33.3 vs 27.6%, i.e. OR: 1.45 (95% CI 1.04-1.96, p: 0.03).	NA	Beneficial effects IVF outcomes in PCOS IVF
Seydoshohadaei (2022) ³⁹	Randomized controlled study	2000 mg of MYO-inositol and 200 mcg folic acid twice a day for 2 months and the control group received 200 mcg of folic acid twice a day for 2 months in the IVF/ICSI cycles (from the third day of cycle until the end of the second month).	The clinical pregnancy and live birth rates in the intervention group were significantly higher than in the controls (p=0.04).	+	Significant increase in mean numbers of oocytes, oocyte quality, clinical pregnancy, and live birth rates in the treatment group versus controls.
Mohammadi (2021) ⁴⁰	Double-blind randomized control trial	MYO (4 g)+folic acid (400 µg) daily. Control group: folic acid (400 µg) daily for 3 months prior to COH.	Significantly higher fertilization rate and significantly reduced total gonadotropin units required for COH in the study group versus the control.	NA	Beneficial effect of amount of gonadotrophins and stimulation day and fertilization rate
Rajasekaran (2022) ¹⁹	Double-blind randomized controlled trial	MYO (2 g) twice daily for 3 months. Metformin group: metformin (850 mg) twice daily for 3 months. Following therapy, both groups began COH	A significantly higher clinical pregnancy rate, fertilization rate, and number of good-quality embryos were observed in the MYO group	NA	Beneficial effects IVF outcomes in PCOS IVF
Sene (2025) ³²	Meta-analysis (17 intervention studies)	MYO/DCI-inositol supplementation	Increased the clinical pregnancy rate (RR: 1.64, 95% CI: 1.25-2.15; I ² =13.5%; p=0.32) and top-grade embryos (RR: 1.12, 95% CI: 1.02-1.23; I ² =85.43%; p=0.0001)	NA	Beneficial the effects of MYO/DCI on fertility and ovarian function in women with PCOS undergoing IVF.

MYO: Myo-inositol, DCI: D-chiro inositol, NA: Not assessed, CI: Confidence interval, RR: Relative risk, OHSS: Ovarian hyperstimulation syndrome, PCOS: Polycystic ovary syndrome, IVF: In vitro fertilization, FSH: Follicle-stimulating hormone

relevant role of MYO as second messenger of FSH signal and stimulation on the granulosa cells.^{12,23,24}

Recent studies have evaluated the role of inositol in IVF outcome in women with PCOS. Inositol plays an important role in the follicular microenvironment and affects oocyte maturation and embryo development. In the ovary, MYO mediates glucose uptake and FSH signaling, whereas DCI ameliorates insulin-induced androgen synthesis. MYO induces nuclear and cytoplasmic oocyte maturation and promotes embryo development. In contrast, high dose DCI appears to exert opposite and detrimental effects on the ovary. To date, the role of MYO and/or DCI supplementation in PCOS women undergoing IVF/ICSI to improve oocyte quality, embryo quality and chances to achieve pregnancy has been investigated. There are conflicting reports in the literature with respect to the potential benefit of MYO and/or DCI in women with undergoing IVF. According to the results of randomized trials and meta-analysis that gave positive IVF outcomes, MYO and/or DCI can significantly improve CPR compared to placebo in women with PCOS undergoing IVF.^{5,19,25,26,27,36} However, a meta-analysis that gave negative IVF outcomes,

does not provide adequate high-quality evidence to support the use of MYO and/or DCI in PCOS women undergoing IVF/ICSI.^{34,38} Some meta-analyses showed no evidence of a significant difference between MYO and control groups for any IVF outcome. The quality of evidence was assessed as very low. Overall, current meta-analysis in the literature results are contradictory. CPR and LBR have been investigated in IVF outcomes of MYO and/or DCI in non-PCOS patient groups. Limited studies have only found improvements in fertilization rates in non PCOS IVF. Finally, based on comprehensive meta-analysis and existing study results no good quality evidence to support the use of MYO and/or DCI to improve CPR and LBR in women with PCOS undergoing IVF.³⁴⁻³⁶ A review by Gupta et al.⁴⁵ in which included nine articles were finalized, there is a lack of evidence to support the use of MYO and/or DCI in increasing the quality of oocyte and/or embryo. The results of recent meta-analysis based on randomized and comparative studies, the results regarding CPR and LBR following IVF in these women appear to be very mixed. A meta-analysis by Sene et al.,³² in which included 17 studies, the supplementation of MYO and/or DCI has a notable impact on the CPR, increasing the number of high-quality embryos in PCOS patients undergoing

IVF. Sene et al.³² suggested that these results provide reliable and sufficient evidence for the outcomes of MYO and/or DCI combined supplement therapy in PCOS women undergoing IVF. The effect of inositols on LBR outcomes appears controversial in women with PCOS undergoing IVF. On the other hand, a meta analysis by Bhide et al.³³ in which included 18 studies, reported that the combination of MYO and/or DCI did not show positive results on CPR in PCOS women undergoing IVF. According to the results of the Cochrane Review in which 13 studies were included, no positive effect of MYO use on LBR was found.³⁸ On the other hand, in a very recent study, LBR was reported to be 1.2 times higher in the MYO group.³² In this respect, the results are contradictory and no definitive conclusion can be drawn. Therefore, current evidence suggests that MYO effects on CPR and LBR in these women is much more limited.^{19,26,32} MYO and/or DCI is cost effective in PCOS, and side effects are low. Overall, MYO and/or DCI administered 3 months prior to the start of ovarian stimulation, reduces the doses of FSH required for the follicular response, stimulation duration and the number of cancelled cycles.²⁴ However, the effects of MYO and/or DCI on oocyte and embryo quality and pregnancy outcomes still appear to be limited. In current studies, MYO doses varied between 1 and 4g/day, some studies included additional combined agents to MYO. Some studies have evaluated IR before treatment, while others have not. In addition, heterogeneity is high in many published studies to date. Comprehensive randomized prospective studies are needed to assess the effects on CPR and LBR.

The ratio 40:1 was based on physiological plasma ratio of the two molecules. The usual ratio of MYO/DCI in the follicular fluid is 100:1 but is altered to 0.2:1 in PCOS patients. At present, a ratio of 40:1 is considered the best ratio. In current studies, ovulation induction and IVF PCOS and non-PCOS patients, MYO doses 4g per day (2g twice per day), three months prior to ovarian stimulation, is effective in normalizing ovarian function, improving oocyte and embryo quality in PCOS. The authors investigated supplementation with different MYO to DCI ratios (namely 3.6:1; 5:1; 20:1; 40:1 and 80:1) for PCOS patients. Some researchers have suggested that the amount of DCI (13.8-27.6 mg/day) used at a 40:1 ratio is too low.¹⁷⁻¹⁹ In a RCT, Mendoza et al.²² compared the use of 3.6:1 MYO/DCI with 40:1. The daily conversion of MYO to DCI by epimerase is estimated to be 300 mg in a healthy person. In this study, the amount of DCI was set at 300 mg per day and the 3.6:1 ratio was tested with a 40:1 ratio. MYO/DCI and achieved a higher pregnancy rate in the 3.6:1 group. In this study, CPR were significantly higher in the group receiving the 3.6:1 ratio than in the group receiving the 40:1 ratio. The results of the 3.6:1 ratio also seem promising in terms of IVF results. Nordio et al.¹⁸ defined the high dose for ovarian-harming DCI as 1200 mg/day for more than 3 months or 2400 mg/day. Mendoza et al.²² tested 300 mg/day DCI at as 3.6:1 ratio. This ratio is 10 times higher than the 40:1 DCI ratio, but well below the DCI doses considered harmful.¹⁸ The 300 mg/day dose used in this study was well below these rates and had a positive effect on pregnancy rates when compared with the 40:1 ratio (DCI; 13.8-27.6 mg/day). Thus, increase in concentration of DCI causes the beneficial effects at the reproductive level.²² However, this

study had a small number of patients, and randomized studies with larger patient numbers are needed to confirm these rates. Meta-analyses and randomized controlled trials indicate that MYO combined with DCI (40:1 MYO/DCI ratio), improves IVF and ovulation induction outcomes by enhancing oocyte quality, increasing CPR and LBR.⁷ However, the debate on the appropriate MI/DCI ratio remains unresolved. On the other hand, the outcomes of MYO:DCI combination therapy combined with folic acid, alpha-lipoic acid, and metformin. Further research is needed to determine whether inositol supplementation, possibly in combination with other drugs, could improve CPR and LBR in PCOS women undergoing IVF.^{15,18,22}

In studies comparing metformin and MYO, there is no difference in hormonal parameters. No between group difference in ovarian stimulation outcomes including duration and dosage of gonadotropins, E2, P4 levels, number of follicles >14 mm on day of trigger. While metformin is traditionally used to restore ovulation and reduce OHSS risk during IVF, however, it does not improve pregnancy or live birth rates. MYO led to higher CPR in women with PCOS compared with metformin (2 RCTs, n=220; RR=1.52, 95% CI: 1.05 to 2.18; p=0.03, I²=3%; low certainty evidence.²⁰ Thus, MYO has shown more successful results in terms of CPR than metformin in IVF. OHSS is an important iatrogenic complication in IVF and that PCOS patients are at an extreme risk for the development of OHSS. Recent trials point out that MYO is effective in preventing OHSS in a way similar to metformin. Metformin may lower OHSS risk in agonist protocol, reduce estradiol levels on trigger day and increase mature oocytes but cause more side effects, while MYO may shorten gonadotropin duration with fewer side effects. MYO decreases estradiol levels on the day of ovulation trigger, reduces the number of intermediate-sized follicles, thereby contributing to a reduction of the risk of OHSS. Overall, according to results, metformin and MYO, showed potential in reducing OHSS risk. A metaanalysis by Unanyan et al.²⁰ CPR were higher in the inositol group than in the metformin group (RR=1.52, 95% CI: 1.05 to 2.18, p=0.03). In the same meta-analysis, the combination of metformin and MYO provided higher success in terms of both CPR and LBR. Prabhakar et al.²¹ randomized study to evaluate the benefits of MYO plus metformin versus MYO alone in women with PCOS undergoing ovulation induction cycles. Group I (n=57): metformin (1500 mg) plus MYO (4 g) per day; Group II (n=59): MYO 4g per day. According to the results of this study, 4g MYO alone gave more effective results than the combination of 4g/day MYO and metformin.

From a metabolic perspective, in studies comparing metformin and inositol, there is no difference in hormonal and metabolic effects or inositol is effective in metformin. MYO and metformin have equal effects on body mass index, waist-hip ratio, menstrual irregularities, and HOMA-IR. Overall, MYO led to a statistically significant improvement in the metabolic profile of PCOS patients as metformin. Moreover, MYO use is safe and patient compliance is high. Therefore, it can justify the addition of MYO for PCOS management. Combining MYO with lower doses of metformin may enhance tolerance

for patients intolerant to full-dose metformin. It is unclear whether there is any benefit from using a combination of metformin and MYO. Based on some current results, MYO alone appears to be better than metformin in terms of both metabolic effect and ovulation induction and IVF outcomes in women with PCOS.⁴¹⁻⁴³

There is still controversy regarding the phenotypic classification of PCOS. The characteristics of non-hyperandrogenic phenotype D PCOS appear in a separate group within the syndrome. Unfer et al.⁴⁶ showed that the administration of MYO induced a significant improvement in metabolic and endocrine parameters in H-PCOS (group A-B_C), while the effects on NH-PCOS (group D) were negligible. Based on this results, inositol treatment controversial in the non-hyperandrogenic D group. Therapy with inositols is not appropriate for patients exhibiting phenotype D PCOS, since they are not affected by hyperandrogenism and do not always experience dysmetabolism. The effect of inositol treatment on the different PCOS phenotypes remains an outstanding question. There are no studies yet on Rotterdam phenotypic groups (A-B-C-D) in women with PCOS undergoing IVF patients. It is clear that randomized prospective studies are needed on this subject.⁴⁷⁻⁴⁸

As a result, PCOS remains the most common endocrine disorder in women worldwide. Position statement from the expert group on inositol in basic clinical research and on PCOS (EGOI-PCOS) and the Polish Society of Andrology recommends that MYO be considered as a potential pretreatment strategy prior to OHSS.⁴⁸ In non-PCOS and PCOS populations, it is advised that MYO (4 g)+folic acid (400 µg) or MYO/DCI (40:1 ratio) supplementation be started three months prior to the start of ovarian stimulation. Lastly, MYO and/or DCI may be effective in ICSI procedures for male factor infertility. These recommendations are in line with the recently published guidelines from the Italian Society of Human Reproduction.⁴⁹ More recently, similar recommendations have been made by the Club of the Italian Society of Endocrinology (SIE).^{48,49}

CONCLUSION

Metformin and MYO are recommended by international guidelines for improving metabolic profiles in PCOS. Although many studies have shown positive effects of MYO, MYO plus DCI use on IVF outcomes in PCOS and non-PCOS patient groups, the effects on CPR and LBR appear to be limited according to current meta-analysis results. Randomized prospective studies are not yet available comparing according to Rotterdam classifications in PCOS and non-PCOS patient groups. Further evaluations by large multicentre randomized controlled trials are needed to assess the CPR and LBR in PCOS and non-PCOS patients undergoing with IVF.

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This review was externally peer-reviewed.

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