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REVIEW ARTICLE

Effects of myo-inositol in women with PCOS: a systematic review of randomized controlled trials

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Polycystic ovary syndrome (PCOS) affects 5%–10% of women in reproductive age, and it is the most common cause of infertility due to ovarian dysfunction and menstrual irregularity. Several studies have reported that insulin resistance is common in PCOS women, regardless of the body mass index. The importance of insulin resistance in PCOS is also suggested by the fact that insulin-sensitizing compounds have been proposed as putative treatments to solve the hyperinsulinemia-induced dysfunction of ovarian response to endogenous gonadotropins. Rescuing the ovarian response to endogenous gonadotropins reduces hyperandrogenemia and re-establishes menstrual cyclicity and ovulation, increasing the chance of a spontaneous pregnancy. Among the insulin-sensitizing compounds, there is myo-inosiol (MYO). Previous studies have demonstrated that MYO is capable of restoring spontaneous ovarian activity, and consequently fertility, in most patients with PCOS. With the present review, we aim to provide an overview on the clinical outcomes of the MYO use as a treatment to improve ovarian function and metabolic and hormonal parameters in women with PCOS.

Keywords: Infertility, insulin resistance, IVF, myo-inositol, oocyte quality, PCOS

Introduction

Polycystic ovary syndrome (PCOS) is the most common cause of infertility, ovarian dysfunction and menstrual irregularity, affecting 5%–10% of women in reproductive age [1]. Both the aetiology and diagnosis of the syndrome are controversial. Indeed, the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine sponsored a Consensus Meeting in Rotterdam (2003) [2,3], in order to reach a general agreement of the scientific community on diagnostic criteria for this syndrome.

Although nowadays the criteria established in Rotterdam are widely accepted, they leave out a crucial condition related to PCOS: insulin resistance.

Several studies have reported that insulin resistance is common in PCOS women, regardless of the body mass index (BMI). Indeed, hyperinsulinaemia due to insulin resistance occurs in approximately 80% of women with PCOS and central obesity, as well as in 30%–40% of lean women diagnosed with PCOS [4,5].

The exact cause of the insulin resistance observed in PCOS women is unknown, although a post-receptor defect, that could affect glucose transport, has been proposed [6,7]. Insulin resistance is significantly exacerbated by obesity, and it is a key factor in the pathogenesis of anovulation and hyperandrogenism [5,8]. The importance of insulin resistance in PCOS is also suggested by the fact that insulin-sensitizing compounds, such as metformin, pioglitazone and troglitazone, have been proposed as treatment to solve the hyperinsulinemia-induced dysfunction of ovarian response to endogenous gonadotropins. Rescuing the ovarian response to endogenous gonadotropins reduces hyperandrogenemia, re-establishes menstrual cyclicity and ovulation, increasing the chance of a spontaneous pregnancy [9–11].. In particular, metformin induces reduction of total and free testosterone concentrations [12]. However, commonly used insulin-sensitizing drugs, like metformin, can induce gastrointestinal side effects [13], possibly resulting in reduced patients' compliance [13].

Further studies have suggested that impairment in the insulin pathway could be due to a defect in the inositolphosphoglycans (IPGs) second messenger [14,15]. IPGs are known to have a role in activating enzymes that control glucose metabolism [16,17]. In PCOS women, a defect in tissue availability or altered metabolism of inositol or IPGs mediators may contribute to insulin resistance [18].

Inositol belongs to the vitamin B complex. Epimerization of the six hydroxyl groups of inositol leads to the formation of up to nine stereoisomers, including myo-inositol (MYO) and D-chiro-inositol (DCI); both stereoisomers were used, as insulin sensitizer drugs, in the treatment of PCOS treatments [19–23]. Human adults consume approximately 1 g of inositol (mainly MYO) per day in different biochemical forms [18]. Circulating free MYO is taken up by most tissues by a membrane-associated sodium-dependent inositol co-transporter; inositol uptake is inhibited by glucose [24]. In particular, it was shown that MYO had 10 times more affinity for the transporter compared to DCI [25].

Data from other groups have shown that DCI is synthesized by an epimerase that converts MYO into DCI, with each tissue having its own particular conversion rate, likely due to the specific needs for the two different molecules [26,27]. In particular, it was shown that the DCI to mass index (MI) ratio was itself insulin dependent. In fact, in subjects suffering from type 2 diabetes, the DCI/MI ratio was reduced [14,15,27,28], and less DCI was synthesized due to a reduction in epimerase activity [14,15,27,28].

All of these studies were performed on insulin sensitive tissues, such as muscle and liver. However, unlike tissues such as muscle and liver, ovaries do not become insulin resistant [29–31].

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Furthermore, elevated concentrations of MYO in human follicular fluid play a role in follicular maturity and provide a marker of good-quality oocytes [32,33].

Previous studies have demonstrated that MYO is capable of restoring spontaneous ovarian activity, and consequently fertility, in most patients with PCOS [21].

Here, we aim to provide an overview on the clinical outcomes of MYO as a treatment to improve ovarian function and metabolic and hormonal parameters in women with PCOS.

Methods

Systematic literature search was performed in December 2010 in the following electronic databases: Medline, Amed, and The Cochrane Library. We performed a search over the period January 1999 to November 2010 and only randomized controlled clinical trials (RCT) were included.

Search terms were as follows: "myo-inositol," "inositol," "polycystic ovary syndrome," "oocyte quality," "ovarian stimulation," "in vitro fertilization," "ovarian function," "insulin resistance."

No language restrictions were imposed. Further relevant papers were located by hand-searching the reference lists of recent systematic reviews. Only human studies were included. Data from treatments with myo-inositol in combination with other drugs as well as animal and *in vitro* investigations were excluded.

We obtained hard copies of all the papers listed through our own university library or interlibrary loans. All sources of information obtained were read and evaluated by one of us (G.D.), and successively checked independently by the other authors (V.U.).

Results of the literature search

Decision tree is reported in Figure 1. A total of 70 studies were identified; 49 out of 70 were excluded because of not involving MYO treatment in women with PCOS. The remaining 21 trials were considered eligible for this review. Six of them [20,22,34–37] were RCTs (level of evidence Ib) and met the selection criteria for this review and are presented in Table I. Four trials [22,34–36] evaluated the effect of MYO administration on hormonal levels. In one trial, it evaluated the effects of MYO on oocyte quality [20], and in another one [37] data on ovarian function improvement after MYO administration were reported.

All the subjects analysed in these studies were PCOS patients. Among the six studies that were RCTs, one trial was a randomized controlled MYO vs. folic acid [34]; two were double-blind randomized controlled trial MYO vs. folic acid [22,35]; one was a prospective randomized controlled MYO vs. folic acid [20]; one was a randomized controlled MYO vs. metformin [36] and in four of these trials [20,22,35,36] the dosage of 4 g of MYO was used; in one trial [34] 2 g of MYO were used.

The last paper [37] described in Table I is not considered in our discussion because it was performed on patients who were treated with a multivitamin complex.

In the study of Genazzani et al. [34], 20 PCOS patients were recruited, five patients were amenorrheic and 15 oligomenorrheic. Ten of the 20 patients (Group A) were randomly assigned to be treated with MYO 2 g plus folic acid 200 μg every day (Inofolic®, LO.LI. Pharma, Rome, Italy). The other patients (Group B, control group) were administered only folic acid at the daily dosage of 200 μg. No changes of life style or diet were required from the patients.

Endocrine profile was evaluated after treatment, on day 7 of the first menstrual cycle occurring after the 10–12th week of treatment. Consistent and significant changes were observed in Group A. Indeed, plasma luteinizing hormone (LH), prolactin (PRL), LH/follicle-stimulating hormone (FSH) ratio and insulin levels significantly decreased; furthermore, the homeostatic model assessment (HOMA) index that measures insulin resistance was also reduced. On the other hand, the index of insulin sensitivity glucose/insulin ratio significantly increased. Furthermore, after oral glucose load, both insulin response and the area under the curve (AUC) were significantly lower ($p < 0.01$ and $p < 0.05$, respectively).

Ferriman-Gallway score decreased after 12 weeks of MYO administration although the reduction was not statistically significant (22.7 + 1.4 to 18 + 0.8). Ovarian volumes were significantly reduced (12.2 + 0.6 to 8.7 + 0.8 ml, $p < 0.05$). No changes were observed in Group B.

Furthermore, as long as the patients were treated with MYO, the normal menstrual cycles was restored, while patients assigned to the Group B remained oligomenorrheic throughout the study.

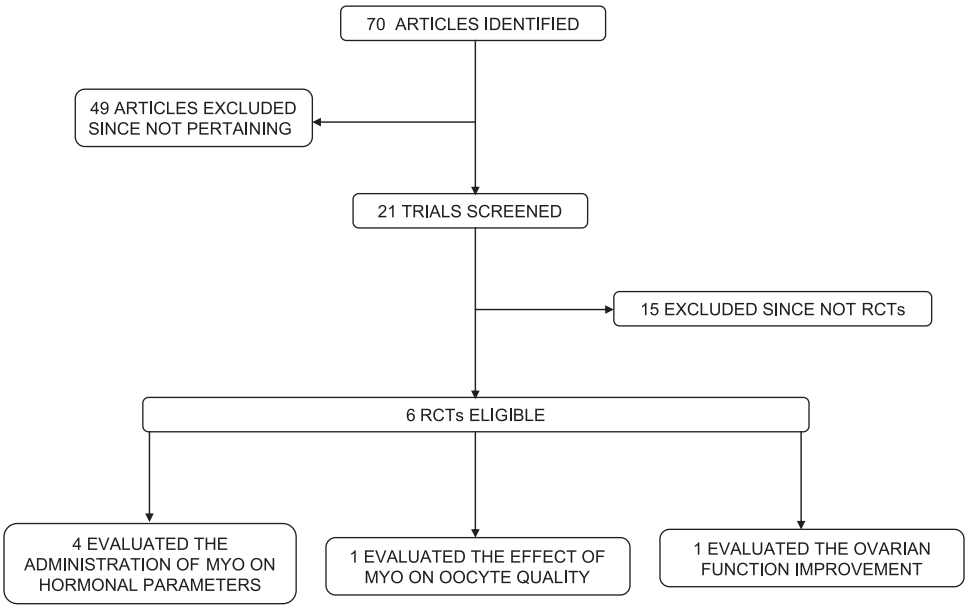

Figure 1. Flow chart of studies

Table I. Eligible RCTs where MYO have been evaluated for the treatment of PCOS patients.

Reference	Study design	Duration	Intervention	N° of subjects	Inclusion criteria	Exclusion criteria	Assessment of the response	Results
34	Randomized, controlled vs. folic acid	12 weeks	MYO 2 g FA 200 mg/day	N°= 20 Treatment: 10 Placebo: 10	Presence of micropolycystic ovaries at ultrasound; mild-to-severe hirsutism and/or acne; oligomenorrhea or amenorrhoea; absence of enzymatic adrenal deficiency and/or other endocrine disease; normal PRL levels (range 5–25 ng/ml); no hormonal treatment for at least 6 months before the study.	Not described	LH, FSH, PRL, E2, A, 17OHP, T, insulin, cortisol, OGTT[a] for insulin, glucose, C-peptide determinations, vaginal ultrasound examination Feriman-Gallway score, BMI, HOMA	LH, PRL, T, insulin levels, LH/FSH results weresignificantly reduced. Insulin sensitivity results were significantly improved. Menstrual cyclicity was restored in all amenorrheic and oligomenorrheic subjects.
35	Double-blind, randomized, controlled vs. folic acid	12–16 weeks	MYO 4 g FA 400 mg/day	N° = 42 Treatment: 23 Placebo: 19	Presence of oligomenorrhea, high serum-free testosterone level and/or hirsutism presence of micropolycystic ovaries at ultrasound	Not described	Systolic/diastolic blood pressure, triglycerides, cholesterol, BMI, waist-to-hip ratio, plasma glucose and insulin sensitivity, total/free T, DHEAS, SHBG, A, progesterone peak value	MI increased insulin sensitivity, improved glucose tolerance and decreased glucose-stimulated insulin release. There was a decrement in serum total T and serum-free T concentrations. In addition, there was a decrement in systolic and diastolic blood pressure. Plasma triglycerides and total cholesterol concentration decreased.
21	Prospective, randomized, controlled vs. folic acid	During ovulation induction for ICSI	MYO 4 g FA 200 mg/day	N° = 60 Treatment: 30 Placebo: 30	Age: <40 years PCOS women diagnosed byoiligo amenorrhea,hyperandroge nism orhyperandrogenemia andtypical features of ovarieson ultrasound scan	Other medical conditions causing ovulatory disorders: hyperinsulinemia, hyperprolactinemia, hypothyroidism, or androgen excess, such as adrenal hyperplasia or Cushing syndrome	Number of morphologically mature oocytes retrieved, embryo quality, pregnancy and implantation rates. Total number of days of FSH stimulation, total dose of gonadotropin administered, E2 level on the day of hCG administration, fertilization rate per number of retrieved oocytes, embryo cleavage rate, live birth and miscarriage rate, cancellation rate, and incidence of moderate or severe ovarian hyperstimulation syndrome	Total r-FSH units and number of days of stimulation were significantly reduced in the myo-inositol group. Peak E2 levels at hCG administration were significantly lower in patients receiving myo-inositol. The mean number of oocytes retrieved did not differ in the two groups, whereas in the group cotreated with myo-inositol the mean number of germinal vesicles and degenerated oocytes was significantly reduced, with a trend for increased percentage of oocytes in metaphase II
22	Double-blind, randomized, controlled vs. folic acid	16 weeks	MYO 4 g FA 200 mg/day	N° = 92 Treatment: 45 Placebo: 47	Age: <35 years women with oiligoamenorrhea, amenorrhea and PCOS ovaries. Ovaries were described as polycystic (PCOs) about the criteria of Adams et al.[**]	Patients with significant hyperprolactinemia, abnormal thyroid function tests and congenital adrenal hyperplasia.	Ovarian activity was monitored using serum E2, P and LH. Ovulation frequency was calculated using the ratio of luteal phase weeks to observation weeks. Inibin-b, fasting glucose, fasting insulin, or insulin AUC, VLDL, LDL, HDL, total cholesterol, triglycerides, BMI.	Beneficial effect of MYO treatment upon ovarian function, anthropometric measures and lipid profiles
36	Randomized, controlled vs. metformin	Until the end of the study or positive pregnancy test	MYO 4 g FA 400 mg/day	N° = 120 Treatment: 60Placebo: 60	Age: <35 years Women with PCOS defined by Rotterdam Criteria	Other medical condition causing ovulatory dysfunction, tubal defects, semen parameters defects.	Restoration of spontaneous ovarian activity by weekly serum P dosage and a transvaginal ultrasound scan documenting the presence of follicular growth or luteal cyst	Both metformin and MYO can be considered as first-line treatment for restoring normal menstrual cycles in most patients with PCOS, even if MI treatment seems to be more
37	Double-blind, randomized, controlled vs. placebo	16 weeks	Inositol 200 mg/day	N° = 283 Treatment: 136 Placebo: 147	Age: <35 years Women with oligomenorrhea, amenorrhea and PCOS ovaries. Ovaries weredescribed as polycystic(PCOs) about the criteria ofAdams et al.**	Patients with significant hyperprolactinemia, abnormal thyroid function tests and congenital adrenal hyperplasia.	Ovarian activity was monitored using serum E2, P and LH. Ovulation frequency was calculated using the ratio of luteal phase weeks to observation weeks. Inibin-b, fasting glucose, fasting insulin, or insulin AUC, VLDL, LDL, HDL, total cholesterol, triglycerides, BMI.	effective than metformin

FA, folic acid; PRL, prolactin; E2, oestradiol; A, androstenedione; 17OHP, 17-hydroxy-progesterone; T, testosterone; P, progesterone; OGTT, oral glucose tolerance; BMI, body mass index; LH, luteinizing hormone; FSH, follicle stimulating hormone; DHEAS, dehydroepiandrosterone; SHBG, sex hormone binding globulin; AUC, area under the curve of OGTT; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[a]OGTT performed sampling 15 minutes before and 30, 60, 90, 120 and 240 minutes after the oral assumption of 75 g of glucose.

[b]Adams J, Polson JW, Franks S. Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. Br Med J 1986;293:355–359.

Costantino et al. [35] recruited 42 patients; after randomization, 23 received 2 g of MYO plus 200 μg of folic acid (Inofolic®, LO.LI. Pharma) twice a day and 19 received 400 μg folic acid alone as placebo. Among the 42 women, seven had impaired glucose tolerance and were assigned as follows: four of them received MYO and three received placebo.

The study started when patients were in the follicular phase of the menstrual cycle; no changes in usual habits for food, sport and lifestyle were required.

During the present study, patient treated with MYO showed a reduction in both systolic and diastolic pressure values (131 ± 2 to 127 ± 2 mmHg and 88 ± 1 to 82 ± 3 mmHg, respectively), while these values increased in the placebo group (128 ± 1 to 130 ± 1 mmHg; $p = 0.002$ and 86 ± 7 to 90 ± 1 mmHg; $p = 0.001$, respectively).

Furthermore, in the MYO treatment group, plasma triglycerides decreased from 195 ± 20 to 95 ± 17 mg/dl and total cholesterol significantly decreased from 210 ± 10 to 171 ± 11 mg/dl. Although there was no change in the fasting plasma insulin and glucose concentration in either group, AUC, for both insulin and glucose, decreased during the oral glucose tolerance test (8.54 ± 1.149 to 5.535 ± 1.792 μU/ml/min; $p = 0.03$ and 12.409 ± 686 to 10.452 ± 414 mg/dl/min; $p = 0.04$, respectively) for MYO-treated patients. No changes were observed in the placebo group.

Consequently, the composite whole body insulin sensitivity index (ISI) significantly increased from 2.80 ± 0.35 to 5.05 ± 0.59 mg/dl in the MYO group, while it did not change in the placebo group. Ovulation was restored in 16 (69.5%) women belonging to the MYO group and four(21%) belonging to the placebo group ($p = 0.001$). After treatment, the progesterone (P) peak was higher in the MYO group (15.1 ± 2.2 ng/ml) compared to placebo. Furthermore, a significant reduction in total serum T (99.5 ± 7 to 34.8 ± 4.3 ng/dl, $p = 0.003$) and in free T (0.85 ± 0.11 to 0.24 ± 0.03 ng/dl, $p = 0.01$) was observed.

Testosterone reduction was accompanied by an increase in serum sex hormone binding globulin. Furthermore, there was reduction of more than 50% in the serum dehydroepiandrosterone sulphate in the MYO group (366 ± 47 to 188 ± 24 μg/dl; $p = 0.003$), while it was not significant in the placebo group.

Papaleo et al. [20] broaden the clinical use of MYO by evaluating its effect on oocyte quality and the ovarian stimulation protocol for PCOS women. Sixty women were enrolled in the study; after randomization, 30 were assigned to receive 2 g MYO and 200 μg folic acid (Inofolic®, LO.LI. Pharma) twice a day (Group A); 30 received 400 μg folic acid only (Group B).

In the Group A (Inofolic®), the stimulation protocol was milder and shorter. Indeed, both the total recombinant FSH (r-FSH units) (1958 ± 695 vs. 2383 ± 578; $p = 0.01$) and number of stimulation days (11.4 ± 0.9 vs. 12.4 ± 1.4; $p < 0.01$) were significantly reduced. Furthermore, oestradiol (E2) levels (2232 ± 510 vs. 2713 ± 595 pg/ml; $p < 0.02$) after human chorionic gonadotropin administration were significantly lower in the Group A. These resulted in significant lower number of cancelled cycles because of hyperstimulation risk (E2 > 4000 pg/ml). The number of oocytes retrieved did not differ between the two groups, whereas in the group treated with MYO the number of immature oocytes and degenerated oocytes was significantly reduced (1.0 ± 0.9 vs. 1.6 ± 1.0; $p = 0.01$), with a trend for increased percentage of metaphase II stage oocytes (0.82 ± 0.11% vs. 0.75 ± 0.15%).

No differences were reported in fertilization and cleavage rates, the number of transferred embryos, and the number of top-quality transferred embryos and pregnancy rate.

Gerli et al. [22] enrolled 92 patients to evaluate MYO effects on ovarian and metabolic factors; 45 received 2 g MYO combined with 200 μg folic acid twice a day (Inofolic®, LO.LI. Pharma), 47 received 400 μg folic acid as placebo.

There were eight conceptions and one miscarried in the first trimester. However, only 42 of the patients declared before the study that they wished to conceive. Among these, the distribution of pregnancy was: placebo one out of 19 patients, while in the MYO group it was four out of 23 patients.

An intention to treat analysis revealed that eight of 45 MYO patients failed to ovulate during treatment, compared with 17 out of 47 placebo-treated patients ($p = 0.04$); the MYO-treated group had a significantly increased frequency of ovulation compared with the placebo group. According to these data, the concentrations of P recorded during monitoring of ovarian function indicated that most of the ovulations showed normal endocrine profiles during both MYO and placebo treatment. All patients started treatment outside the luteal phase, and the delay to the first ovulation after starting the program was significantly shorter in the MYO-treated group (24.5 vs. 40.5, $p = 0.02$).

The analysis of E2, inhibin-B, and T concentrations on the first and eighth day of treatment showed that the MYO-treated group had a significant ($p = 0.03$) increase in E2 levels, whereas the control group showed no change. There was no change in circulating levels of inhibin-B or T concentrations.

The BMI decreased significantly in the MYO group ($p = 0.04$). No change was observed in the waist-to-hip ratio in either group. Circulating leptin concentration declined in the MYO group, in contrast to the control group, but there was no change recorded in the fasting glucose, fasting insulin or insulin AUC in response to the glucose challenge in either group.

The very-low-density lipoprotein showed little change during the treatment period, but the low-density lipoprotein (LDL) showed a trend toward reduction, and the high-density lipoprotein (HDL) increased significantly in the MYO group.

Raffone et al. [36] performed a study aiming to compare the effects of metformin and MYO on PCOS patients: 120 women were recruited; 60 patients were treated with metformin 1500 mg/day (Glucophage®, Merck Pharma, Rome, Italy), while 60 received 4 g MYO plus 400 μg folic acid (Inofolic®).

Among the patients treated with metformin, 50% restored spontaneous ovulation activity; in these patients, ovulation occurred after 16.7 (+2.5) days from the day 1 of the menstrual cycle. Pregnancy occurred spontaneously in 11 of these patients; seven women dropped out. The remaining 42 patients were treated with 1500 mg of metformin plus r-FSH for a maximum of three cycles. Pregnancy occurred in 11 women, nine of these pregnancies occurred in the metformin-resistant patients (n = 23), two in the group which had ovulation restored with metformin alone. The total pregnancy rate was 36.6%, five of the 22 pregnancies (22.7%) evolved in spontaneous abortion at 9 weeks of gestation.

Seven subjects in the metformin group dropped out because of the development of side effects and loss of follow-up.

In the MYO group, 65% of patients restored spontaneous ovulation activity, ovulation occurred after a mean of 14.8 (+1.8) days from the day 1 of the menstrual cycle. Pregnancy occurred spontaneously in 18 of these patients and four women dropped out. The remaining 38 patients were treated with 4 g/day MYO, 400 μg/day folic acid and r-FSH in small doses (37.5 U/day for three cycles). Pregnancy occurred in a total of 11 women, eight of these pregnancies occurred in the MYO-resistant patients (n = 17), three in the group which had ovulation restored with MYO alone.

The total pregnancy rate was 48.4%, six of the 29 pregnancies (20.6%) evolved in spontaneous abortion. The efficacy in restoring regular ovulation was evaluated by comparing both the percentage of patients who responded to the treatment and the median length of follicular phase in metformin and in MYO group: ovulation occurred after a mean 16.7 (+2.5) days from the day 1 of the menstrual cycle in the metformin group and after a mean 14.8 (+1.8) in the MYO group. The median between metformin and MYO differed significantly ($p < 0.003$). Inclusion, exclusion criteria and the main outcome measures for all studies are described in Table I.

Conclusions

PCOS is one of the most common endocrine disorders affecting women, it is the most common cause of female infertility and it is characterized by a combination of hyperandrogenism, chronic anovulation and irregular menstrual cycle [38,39]. Several patients affected by PCOS are also affected by insulin resistance although they do not show signs of diabetes [4,10]; furthermore, insulin resistance is not linked to the BMI [7,40]. PCOS-induced insulin resistance determines a higher risk for the development of type 2 diabetes, hypertension and dyslipidemia, all elements of the metabolic syndrome [41].

MYO is an important constituent of follicular microenvironment, playing a determinant role in both nuclear and cytoplasmic oocyte development. Indeed, inositol 1,4,5-triphosphate modulates intracellular Ca^{2+} release.

Calcium signaling in oocytes has been extensively studied in various species because of its putative role in oocyte maturation and the early stages of fertilization [42,43]. It has been demonstrated that fully grown mammalian germinal vesicles (GV), that exhibit spontaneous intracellular calcium oscillations, are associated with a higher incidence of GV breakdown. MYO supplementation was suggested to promote meiotic progression of these GV. Indeed, high concentration of MI in the fluids of the human follicles strongly associates with good-quality oocytes [44].

Despite the relatively high number of reports evaluating clinical studies that used MYO as a treatment in women with PCOS, only few of them were designed as RCTs (level of evidence Ib).

Four articles [22,34–36] evaluated the effects of MYO administration on hormonal and metabolic parameters in patients with PCOS. The results of these studies support the hypothesis of a primary role of IPG as second messenger of insulin signal and demonstrate that MYO administration significantly affects the hormonal milieu in PCOS patients.

There are specific positive effects of MYO treatment on insulin plasma levels and on insulin response to oral glucose load. Indeed, MYO decreased insulin plasma levels, glucose/insulin, HOMA index as well as other hormonal parameters such as LH, LH/FSH, testosterone and PRL. Furthermore, MYO inositol is able to induce normal menstrual cycles. These trials supported the hypothesis that MYO supplementation induces the reduction of insulin levels probably by inducing an increase of IPG levels; therefore, higher IPG levels could be able to amplify insulin signal.

In particular, in two studies [20,34] the authors suggest that a deficiency in the precursors of IPG such as MYO and/or DCI might be an additional cofactor contributing to the pathophysiology of the insulin resistance of PCOS patients [18].

All the PCOS patients showed a significant improvement of typical hormonal parameters: indeed, after MYO treatment LH levels, LH/FSH ratio, T and HOMA index were decreased. Furthermore, the insulin AUC after glucose load was reduced, being a clear signal of the improved peripheral sensitivity. Interestingly, PRL plasma levels also resulted significantly lower under MYO administration.

In addition to this, Gerli et al. demonstrated a significant reduction in weight in the patients treated with MYO, in contrast to the placebo group where the BMI increased. Associated with the weight loss, it was possible to observe a significant reduction in circulating leptin and an increase in HDL concentrations, while LDL showed a trend toward reduction.

These data on HDL cholesterol were the first evidence showing that MYO treatment could be useful in reducing the risk of cardiovascular diseases in PCOS women.

Several trials showed that insulin sensitizer agents, such as metformin and MYO, are the first-line treatment to restore normal menstrual cycles in women suffering from PCOS [9–13], suggesting that an endocellular defect of the precursor of IPG such as MYO and/or DCI might trigger the compensatory hyperinsulinemia in most PCOS subjects.

Moreover, Raffone et al. showed that MYO slightly improves pregnancy rate compared to metformin.

These findings further support the hypothesis that the reduction of insulin levels induced by MYO oral supplementation depends on the increased availability of the main precursor of IPG insulin second messenger.

Furthermore, in one trial [20] it has been shown that MYO is effective in ovarian stimulation protocols in women with PCOS.

PCOS women have an increased risk of hyperstimulation syndrome [45]. Indeed, high levels of serum ovarian androgens are implicated in production of elevated serum E2 levels after gonadotropin ovarian stimulation. PCOS patients treated with MYO + gonadotropin showed a significant reduction in E2 levels after hGC administration. This was reflected on the lower number of in vitro fertilization (IVF) cycles cancelled because of high E2 levels (sign of hyperstimulation syndrome [20]).

Literature studies already suggested that MYO has positive effect on developmental competence of maturing oocytes [46].

In line with this evidence, a recent clinical trial aiming to compare the effect of MYO or DCI supplementation on oocyte quality of PCOS patients showed that only MYO rather than DCI is able to improve oocyte quality [47]. Based on these data, we developed a theory that identified a "DCI paradox [48]," where we suggest that ovaries in PCOS patients likely present an enhanced MI to DCI epimerization that leads to a MI tissue depletion; this, in turn, could eventually be responsible for the poor oocyte quality characteristic of these patients [49].

Remarkably, in all the studies analysed, no side effects were reported at the doses of both 2 and 4 g/day, thus resulting in a high patient compliance. The 4 g/day treatment regimen is useful to treat all the symptom spectrum, resulting in a more complete and effective treatment.

In conclusion, by analyzing different studies focused on MYO supplementation to improve several of the hormonal disturbances of PCOS, we provide a level Ia evidence of MYO effectiveness. MYO mechanism of action appears to be mainly based on improving insulin sensitivity of target tissues, resulting in a positive effect on the reproductive axis (MYO restores ovulation and improves oocyte quality) and hormonal functions (MYO reduces clinical and biochemical hyperandrogenism and dyslipidemia) through the reduction of insulin plasma levels.

***Declaration of Interest*:** The authors report no conflict of interest.

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