Archives of Gynecology and Obstetrics
https://doi.org/10.1007/s00404-018-4861-y

REVIEW

Myo-inositol supplementation reduces the amount of gonadotropins and length of ovarian stimulation in women undergoing IVF: a systematic review and meta-analysis of randomized controlled trials

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Received: 22 March 2018 / Accepted: 28 July 2018

Abstract

Purpose To evaluate whether oral myo-inositol supplementation (MI) is able to reduce the amount of gonadotropins (GA) and the length of controlled ovarian hyperstimulation (SL) in both Polycystic Ovarian Syndrome (PCOS) and non-PCOS women undergoing in vitro fertilization (IVF).

Methods We performed a systematic review (PROSPERO ID: CRD42017069439) of randomized controlled trials (RCTs). We searched articles published in English between January 1985 to August 2017, using the combination of the Medical Subject Headings "Inositol" with "Ovulation Induction", "follicle-stimulating hormone, human, with HCG C-terminal peptide", "Reproductive Techniques, Assisted", and "Fertilization in Vitro". We collected data about GA and SL comparing MI to no treatment or D-Chiro-Inositol (DCI) supplementation (controls). A subgroup analysis was performed to evaluate selected outcomes in PCOS and non-PCOS women.

Results We included 8 studies embedding 812 participants. We found a reduction in GA ($p < 0.00001$) and SL ($p = 0.0007$) in patients receiving MI with respect to controls. MI was effective in both PCOS ($p < 0.00001$) and non-PCOS women ($p = 0.02$) in reducing GA; conversely, MI supplementation decreased the SL only in PCOS women ($p < 0.00001$).

Conclusion During IVF, MI is effective in both PCOS and non-PCOS women in saving gonadotropins, but reduces efficiently SL only in PCOS women.

Keywords Myo-inositol · In vitro fertilization · Recombinant follicle-stimulating hormone · Controlled ovarian hyperstimulation

Introduction

Inositols belong to a sugar alcohol family involved in the regulation of a plethora of metabolic pathways and hormonal signaling in human body [1, 2]. These molecules take part to a variety of function and signaling pathways that include cell growth, survival, and reproduction [3, 4].

Inositols are naturally found under nine chemical stereoisomers (cyclohexane-1,2,3,4,5,6-hexol), two of which, D-Chiro-Inositol (DCI—*cis*-1,2,4-*trans*-3,5,6-cyclohexanehexol) and Myo-Inositol (MI—*cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol), are the most common in eukaryotic cells [5, 6]. In last years, different studies stressed the importance of insulin-sensitizing properties of inositols. Indeed, both MI and DCI seem able to activate key enzymes involved in glucose metabolism and uptake [7–9]. Starting from these data, the role of MI and/or DCI supplementation in Polycystic Ovary Syndrome (PCOS) women undergoing in vitro fertilization (IVF) to improve oocytes quality, embryos and chances to achieve pregnancy have been investigated with some interesting results [10–12]. However, evidence on this topic is still poor, and a recent meta-analysis focusing on PCOS women undergoing ICSI found inconclusive evidence on MI and DCI efficacy in improving IVF outcome [13]. Nevertheless, the results provided in this meta-analysis are

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Published online: 04 August 2018

potentially limited by different sources of bias, such as the poor number of events described (especially for clinical pregnancy rate). In addition, authors did not evaluate the effects of Inositols on COH (controlled ovarian hyperstimulation) parameters, such as gonadotropins consumption, duration of ovarian stimulation, and number of cancelled cycles. Finally, the analysis was limited to PCOS patients.

Based on this scenario, the aim of our work was to summarize the available evidence from randomized controlled trials (RCTs) about the effects of MI supplementation on COH variables (gonadotropins consumption, duration of ovarian stimulation, and number of cancelled cycles), including both PCOS and non-PCOS patients undergoing IVF cycles.

Materials and methods

Study design and registration

This is a systematic review and meta-analysis of all RCTs investigating the effects of MI on COH outcomes. The review protocol was registered in PROSPERO international prospective register of systematic reviews (registration number: CRD42017069439) before data extraction. The review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement [14] and the Cochrane Reviewers' Handbook. Outcomes were defined, screened, selected, and reported following the recommendations of the Core Outcome Sets in Women's and Newborn Health (CROWN) initiative.

Inclusion criteria

- Language: we included only studies reported in English language.
- Study designs: RCTs.
- Population: infertile women undergoing IVF.
- Intervention: MI supplementation.
- Timing of intervention: during the course of COH.
- Comparator: infertile women undergoing IVF not receiving intervention or receiving DCI.
- Outcomes:
  - primary outcome: to compare the COH variables (gonadotropins consumption, duration of ovarian stimulation, and number of cancelled cycles) in patients receiving oral MI with respect to patients not receiving intervention (controls) during IVF.
  - Secondary outcomes: to compare the COH variables (gonadotropins consumption, duration of ovarian stimulation, and number of cancelled cycles) in PCOS with respect to non-PCOS women who underwent oral MI supplementation during IVF.
  - Tertiary outcome: to estimate the effect of intervention on IVF outcomes (total and mature oocytes retrieved, clinical pregnancy rate).
- Outcomes' measures:
  - gonadotropins' amount [per cycle (GA)]: defined as the number (mean ± SD) of international units (IU) of drug used until ovulation induction.
  - Stimulation length [per cycle (SL)]: defined as the number of days (mean ± SD) in which gonadotropins were administered.
  - Cancelled cycles [CC]: defined as the percentage of cycles cancelled due to inadequate (poor or exaggerate) ovarian response.
  - Total oocytes [per cycle (TO)]: defined as the number of oocytes (mean ± SD) retrieved at pick-up.
  - Mature oocytes [per cycle (MO)]: defined as the amount (mean ± SD) of MII oocytes obtained.
  - Clinical pregnancy rate [per cycle (CPR)]: defined as the presence of a gestational sac on transvaginal ultrasound or other definitive clinical signs (positive urine or serum β-human chorionic gonadotropin test).

Search strategy

A systematic literature search was conducted from January 1985 to August 2017 in the following electronic bibliographic databases: MEDLINE, EMBASE, Global Health, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register), Health Technology Assessment Database and Web of Science. The search strategy included the combination of the Medical Subject Heading (MeSH) "Inositol" (MeSH Unique ID: D007294) with "Ovulation Induction" (MeSH Unique ID: D010062), "follicle-stimulating hormone, human, with HCG C-terminal peptide" (MeSH Unique ID: C437186), "Reproductive Techniques, Assisted" (MeSH Unique ID: D027724), and "Fertilization in Vitro" (MeSH Unique ID: D005307).

Study selection and data extraction

Titles and/or abstracts of studies retrieved using the search strategy, and those from additional sources were screened independently by two review authors (A.V., M.N.) to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies was retrieved and independently assessed for eligibility by other two review team members (A.S.L., R.D.A.). Any

disagreement between them over the eligibility of particular studies was resolved through discussion with a third external collaborator. A standardized, pre-piloted form was used to extract data from the included studies for assessment of study quality and evidence synthesis. Two authors (A.V., M.N.) independently extracted data from studies about study features and included populations (participant number and inclusion criteria), type of intervention (duration of therapy and drug posology), and pregnancy rates. Any discrepancies were solved through a discussion with a third external collaborator.

Quality assessment

Two review authors (A.S.L., R.D.A.) independently assessed the risk of bias in included studies according to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [15], considering the following characteristics: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias. Disagreements between the review authors over the risk of bias in particular studies were resolved by discussion, with involvement of a third external collaborator where necessary.

Data synthesis

The statistical analysis was performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, London).

Dichotomous variables were analysed using the odds ratio (OR) with 95% confidence interval (95% CI). Continuous data were compared using the means and standard deviations of outcome measures and expressed as mean differences (MD) with 95% CI. Significance level was set at $p < 0.05$. To assess heterogeneity, the I^2 statistics was used. We considered the degree of heterogeneity as low when I^2 was < 30%, moderate if between 30 and 50% and high if I^2 was > 50%. When the heterogeneity was moderate or high, data were compared using the "random model". When the heterogeneity was low, the results were reported only in a fixed effects model.

Moreover, the influence of individual studies on the overall results was explored by serially excluding each study and different study subgroups (according to methodological quality judgment of authors) in a sensitivity analysis when more than three studies were included in the meta-analysis. In addition, a subgroup analysis was performed to measure the different outcomes in different subclass of patients (PCOS and non-PCOS).

We aimed to assess Publication Bias (related to size of the trials) with the use of Funnel plot (plot of the effect estimate from each study against the standard error) if at least ten studies were included in the meta-analysis, according to Cochrane Handbook Recommendations [15]. Nevertheless, not enough studies were included.

Results

Study selection

As detailed in Fig. 1, the search of the above-mentioned electronic bibliographic databases retrieved 238 items. After duplicates removed ($n = 150$), the screening of retrieved items leads to the exclusion of other 76 articles, because out of purpose for the current systematic review. The remaining 12 studies [10–12, 16–24] were assessed, checking carefully the full text. Thus, we excluded two studies [16, 17], because they did not report data about the primary outcomes of the current systematic review. One additional study [19] was excluded because in abstract form. Moreover, one study [23] was also excluded due to non-RCT study design.

Finally, we included eight RCTs [10–12, 18, 20–22, 24] in this review.

Included studies

The trials included a total number of 812 patients, ranging from 29 [21] to 361 [12]. In six studies [10, 12, 20–22], intervention group received MI and control group received folic acid. One study [18] compared MI and DCI administration, while another one [11] compared the effects MI plus DCI vs. DCI alone.

Type of intervention

In all included studies, MI, DCI, or placebo was administered as oral supplements. Intervention group received 4 g of MI in six studies [10, 12, 18, 20, 21, 24], 2 g of MI in the study by Artini et al. [22], and 1.1 g MI + 27.6 mg DCI in the study by Colazingari et al. [11]. Comparator was placebo in six studies (400 µg of folic acid in five studies [10, 12, 20–22] and not specified in the study by Lesoine and Regidor [24]), 1.2 g of DCI in the study by Unfer et al. [18], and 1 g of DCI in the study by Artini et al. [22].

The period of administration was extremely variable among the included studies: Papaleo et al. [10] started on the day of gonadotropin-releasing hormone (GnRH) administration, and administrated continuously; Unfer et al. [18] 8 weeks before recombinant follicle-stimulating hormone (rFSH) administration; Lisi et al. [20] the 3 months before and during rFSH administration; Schillaci et al. [21] at least 1 month before GnRH-agonist; Pacchiarotti et al. [12] from the first day of the cycle until 14 days after embryo transfer;

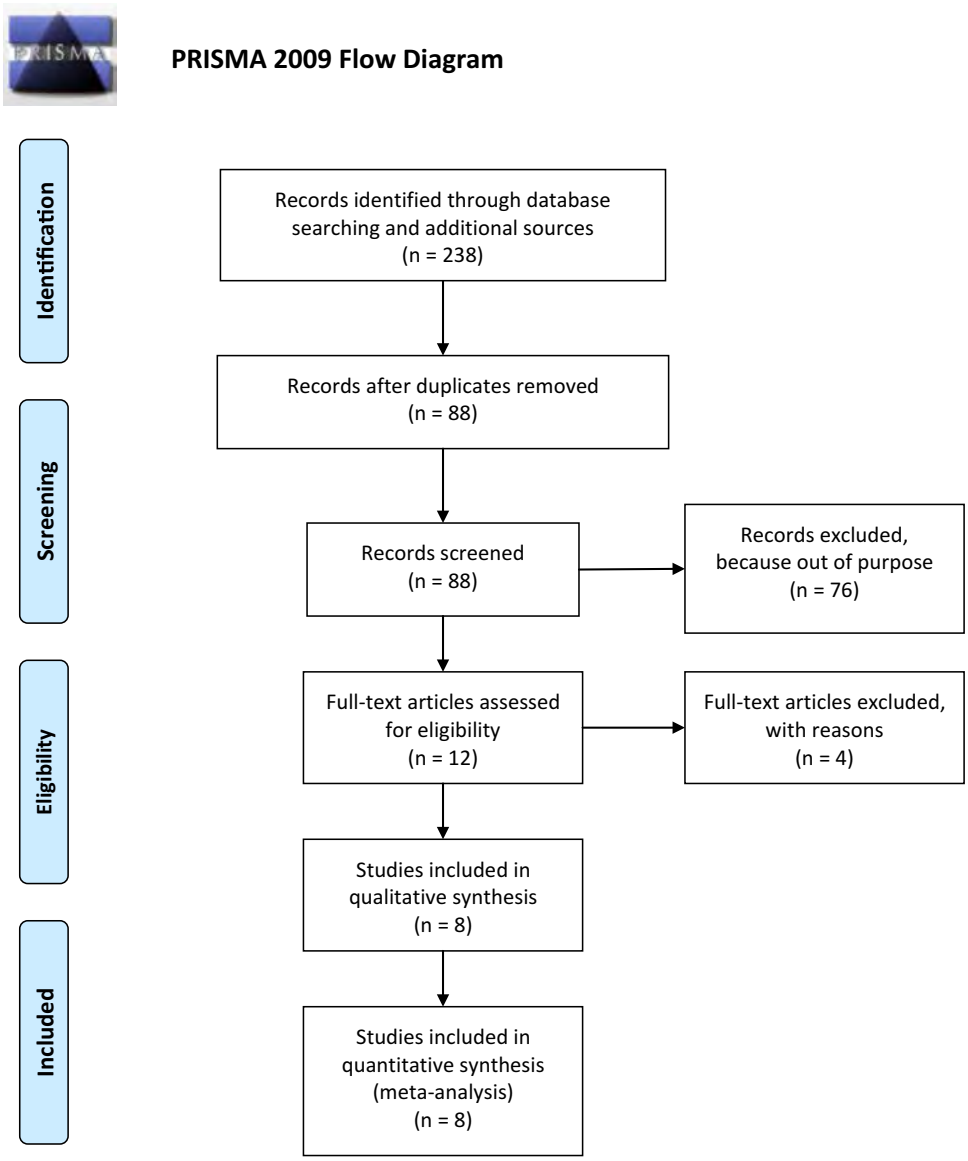

Fig. 1 PRISMA flow diagram for study selection and inclusion From the Ref. [14]

two studies [11, 12] 12 weeks before rFSH administration; and finally, one study [24] did not report clear information about this point.

Type of patients

Six studies [10–12, 18, 22, 24] included only PCOS patients, one study [20] included only patients without PCOS, and another study [21] included both PCOS and non-PCOS patients, reporting data separately. In all the studies focusing on PCOS patients [10–12, 18, 21, 22, 24], PCOS was diagnosed according to Rotterdam criteria [25].

Regarding non-PCOS patients, one study [20] included women < 40 years and basal FSH level < 10 mUI/mL; another study [21] included "poor responders", defined as patients having < 3 follicles and estradiol levels < 600 pg/mL at human chorionic gonadotropin (hCG) day.

Type of ovarian stimulation

All the included studies, but one [24], used long-stimulation protocols with GnRH agonists (starting from the midluteal phase of the previous cycle). Otherwise, in the study by Lesoine and Regidor [24], pituitary desensitization was obtained using GnRH antagonists (from the 6th day of gonadotropins administration).

Ovarian stimulation consisted in a single daily administration of 150 IU rFSH in six studies [10, 11, 18, 20, 22, 24]. Schillaci et al. [21] administered 150 UI rFSH per day in PCOS patients, whereas for "poor responders" rFSH starting dosage was 300 IU/day, until a maximum dose of 450 UI (on

the basis of folliculometry). Pacchiarotti et al. [12] administered 225 IU of human menopausal gonadotrophins (HMG) for the first 6 days, followed by 225 IU of less-acidic rFSH until hCG administration.

Ovulation induction was obtained in five studies [10–12, 18, 21] using 10,000 IU urinary hCG i.m and in one study [24] using 5000 IU urinary hCG. One study [20] used 250 µg recombinant hCG and another study [22] did not report the dosage of hCG.

In four studies [10, 11, 18, 22], ovulation was triggered when serum 17β-estradiol (E_2) exceeded 200 pg/mL per follicle and there were at least three follicles with a minimum diameter of 18 mm. In one study [20], the only condition was the presence of three follicles with a mean diameter ≥ 17 mm. In another study [12], the ovulation induction was performed when 50% of the follicles had reached 20 mm of diameter and E_2 level was 250 pg/mL per follicle. The remaining two studies [21, 23] did not describe criteria for ovulation induction.

Assessment of the risk of study bias

- Selection bias: three studies [10, 12, 20] used an adequate method of random sequence generation, while three studies [18, 21, 24] did not report detailed information. In one study [22], the randomization schedule was prepared by one of the authors, and in another study [11], the pharma company prepared and kept it. Four studies [10, 18, 21, 24] did not report allocation strategy. One study [12] declared a double-blind procedure, without to add other details about allocation concealment. All the other studies [11, 20, 22] used adequate allocation technique.
- Performance bias: information about blinding of participants and personnel was clearly reported and adequate in three studies [11, 12, 20], whereas it was unclear (not adequately detailed) in one study [22] and inadequate in the remaining four studies [10, 18, 21, 24].
- Detection bias: blinding of outcome assessment was not performed in four studies [10, 18, 21, 24], unclear (not adequately detailed) in three studies [11, 12, 22], and adequate in only one study [20].
- Attrition bias: only one study [24] could be considered at high risk of incomplete outcome data, and another [21] reported unclear information about this point. All the other six studies [10–12, 18, 20, 22] adequately reported outcome data.
- Reporting bias: one study [21] did not report data about MO in the PCOS subgroup analysis, so it could be considered at medium risk of bias. Another study [24] was judged at high risk of selective data reporting, since it did not report quantitative data about NO, MO, and CPR. All the other six studies [10–12, 18, 20, 22] clearly reported all the data about primary and secondary outcomes.
- Other sources of bias: considering as other sources of bias trial registration (on national/international data registries), baseline imbalance, blocked randomization in open-label trials, we judged only one study at the high risk [24], whereas all the others were at low risk [10, 12, 18, 20, 22] or unclear risk [11, 21].

The assessment of the risk of study bias is summarized in Fig. 2.

Effects of intervention

Myo-inositol vs. no intervention

- GA: analysis included 600 patients from five studies [10, 12, 20–22], of which 288 received MI and 312 did not receive intervention. As reported in Fig. 3, GA was significantly lower in patients receiving MI (MD = −493.66,

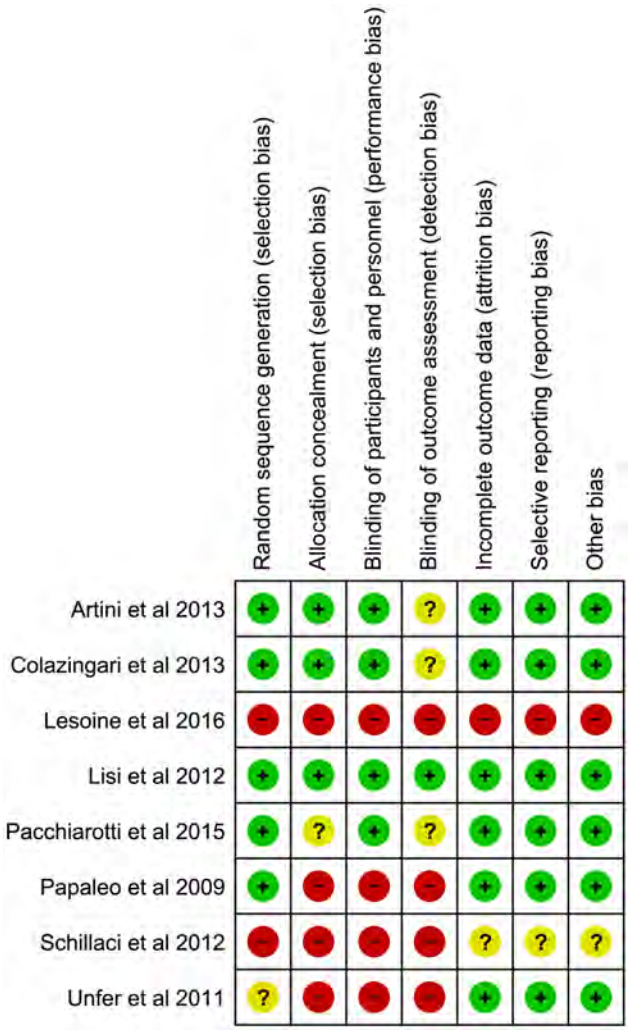

Fig. 2 Assessment of risk of bias for included studies

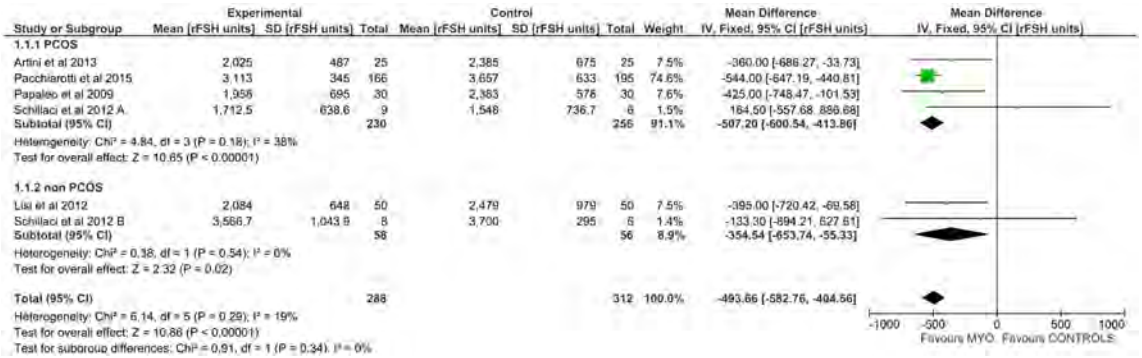

Fig. 3 Meta-analysis of randomized controlled trials to assess gonadotropin amount for ovarian stimulation in myo-inositol group vs. no treatment group (controls)

[95% CI − 582.76, − 404.56], $p < 0.00001$), with low heterogeneity among studies ($I^2 = 19\%$).

- SL: six studies [10, 12, 20–22, 24] with 629 participants were included, of which 302 in MI group and 327 in control group. As reported in Fig. 4, SL resulted significantly shorter in MI group in comparison with controls (MD = − 0.71, [95% CI − 1.12, − 0.30], $p = 0.0007$). A moderate inconsistency was present among studies ($I^2 = 39\%$).
- CC: analysis of 125 patients from three studies [10, 21, 22] did not show differences among groups (OR 0.50, 95% CI 0.14–1.70, $I^2 = 9\%$, $p = 0.26$).
- TO: five studies [10, 12, 20–22] with 600 participants were analysed (288 in MI group and 312 in control group). No difference among groups were observed in terms of TO (MD = − 0.13, [95% CI − 1.71, − 1.44], $I^2 = 80\%$, $p = 0.87$).
- MO: analysis of 160 patients (80 in MI group and 80 in control group) from two studies [10–20] did not found statistical differences in terms of MO (MD = − 0.87, [95% CI − 2.36, 0.61], $I^2 = 59\%$, $p = 0.25$).
- CPR: five studies [10, 12, 20–22] with 600 participants were included (288 in MI group and 312 in control group). No difference among groups were observed in terms of CPR (OR 0.81, 95% CI 0.57–1.15, $I^2 = 0\%$, $p = 0.99$).

Myo-inositol vs. D-chiro-inositol

A meta-analysis was not possible, because one study analysed the present comparison [18]. In detail:

- GA: total rFSH units (1953.6 ± 397.5 vs. 2360.5 ± 301.9) were significantly reduced ($p < 0.01$) in the MI group with respect to DCI group.
- SL: number of days of stimulation (11.1 ± 0.8 vs. 12.7 ± 1.1) was significantly reduced ($p < 0.01$) in the MI group with respect to DCI group.
- CC: no cycle was cancelled in MI group, while in DCI group, four cycles were cancelled due to estradiol peak > 4000 pg/mL ($p = 0.05$).

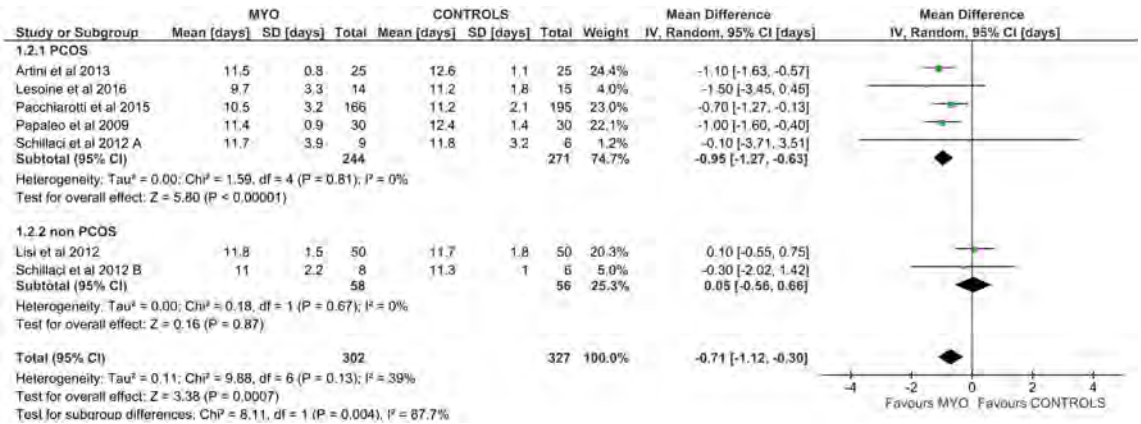

Fig. 4 Meta-analysis of randomized controlled trials to assess days of ovarian stimulation in myo-inositol group vs. no treatment group (controls)

- TO: the total number of oocytes retrieved did not differ significantly between the two groups.
- MO: the number of MO was significantly higher ($p < 0.05$) in MI group (8.21 ± 2.39) than DCI group (7.08 ± 2.67).
- CPR: CPR was significantly higher ($p < 0.05$) in MI group (22) than DCI group (10).

Myo-inositol plus D-chiro-inositol vs. D-chiro-inositol

A meta-analysis was not possible, because only one study included the present comparison [11]. In detail:

- GA: for ≤ 35-year-old patients, the GA was significantly lower in MI + DCI group in respect to DCI alone (1569.02 ± 497.12 vs. 1899.21 ± 618.17, $p = 0.03$). Differently, no statistical significance was observed in patients older than 35 years among groups (p = ns).
- SL: this parameter was not reported in the study.
- CC: this parameter was not reported in the study.
- TO: no differences were found in the number of oocytes retrieved between the groups in the ≤ 35 age category. On the contrary, in the > 35 age category, the number of oocytes retrieved was higher in the DCI group (10.75 ± 5.23) with respect to MI + DCI group (8.35 ± 3.21), but not significant ($p = 0.05$).
- MO: for ≤ 35-year-old patients, the number of MO was higher in the DCI group (8.00 ± 4.92) with respect to MI + DCI group (7.91 ± 4.51). Similarly, in the > 35 age category, the number of MO was higher in the DCI group (8.35 ± 5.19) with respect to MI + DCI group (6.91 ± 2.26). However, data were not significant.
- CPR: this parameter was not reported in the study.

Sensitivity analysis

The serial exclusion of each study from meta-analysis did not produce significant changes in GA (from MD = − 509.07 [95% CI − 599.49, − 418.64; $I^2 = 0\%$, $p < 0.00001$] to MD = − 354.54 [95% CI − 522.77, − 169.43; $I^2 = 0\%$, $p < 0.00001$] with the exclusion of Schillaci et al. [21] and Pacchiarotti et al. [12]), SL (from MD = − 0.93 [95% CI − 1.24, − 1.61; $I^2 = 0\%$, $p < 0.00001$] to MD = − 0.58 [95% CI − 1.04, − 0.12; $I^2 = 32\%$, $p = 0.01$] with the exclusion of Artini et al. [22] and Lisi et al. [20]), TO (from MD = − 0.82 [95% CI − 2.24, − 0.60; $I^2 = 74\%$, $p < 0.26$] to MD = 0.32 [95% CI − 1.23, − 1.86; $I^2 = 79\%$, $p = 0.69$] with the exclusion of Schillaci et al. [21] and Artini et al. [22]), CPR (from OR 0.88 [95% CI 0.61–1.28] to OR 0.71 [95% CI 0.39–1.29] with the exclusion of Artini et al. [22] and Pacchiarotti et al. [12]). Similarly, the exclusion of studies with high/unclear risk of bias in at least three domains [10, 18, 21, 24], when possible, did not provide significant changes in meta-analysis results for all of the outcomes evaluated.

A sensitivity analysis for the outcomes MO and CC was not possible due to the small number of included studies [10, 21, 22].

Effects of intervention in PCOS and non-PCOS patients

A subgroup analysis was possible only for the comparison "Myo-inositol vs. no intervention". Differently, concerning the remaining comparisons ("Myo-inositol vs. D-chiro-inositol", "Myo-inositol plus D-chiro-inositol vs. D-chiro-inositol"), two studies (one for each comparison) focusing only on PCOS women were included (data reported in "Effects of intervention") and subgroup analysis was not possible. Studies were split in two subgroups: PCOS and non-PCOS. Schillaci et al. [21] provided separate data about the two subgroups of interest. Those data were extracted and used for subgroups analysis separately (Schillaci et al. A: PCOS patients; Schillaci et al. B: non-PCOS patients). Differently, all the other studies focused only on PCOS women [10, 12, 22, 24] or non-PCOS women [20]. Finally, information from five studies was included in PCOS subgroup [10, 12, 21, 22, 24] and additional data from two studies [20, 21] was included in non-PCOS subgroup.

The total number of PCOS patients was 515 ($n = 244$ in MI group and $n = 271$ in control group), while the total number of non-PCOS patients was 114 ($n = 58$ in MI group and $n = 56$ in control group).

Concerning GA (Fig. 3), a major saving of gonadotropins was observed in PCOS patients (MD = − 507.20, [95% CI − 600.54, − 413.86], $p < 0.00001$) in comparison with non-PCOS patients (MD = − 354.54, [95% CI − 653.74, − 55.33], $p = 0.02$), even if not statistically significant ($p = 0.34$). Differently, concerning the outcome SL (Fig. 4), a significant difference was observed between PCOS and non-PCOS patients ($p = 0.004$), with a considerable reduction in the first subgroup (MD = − 0.95, [95% CI − 1.27, − 0.63], $p < 0.00001$) and no effect in the second subgroup (MD = − 0.05, [95% CI − 0.56, − 0.66], $p = 0.87$).

Finally, regarding MO, TO, CC, and CPR, no significant difference in MI effect was found between PCOS and non-PCOS patients (tests for subgroup differences: $p = 0.87$, $p = 0.57$, $p = 0.69$, and $p = 0.99$).

Discussion

Main findings

To the best of our knowledge, this is the first systematic review and meta-analysis investigating the effects of MI

supplementation on COH parameters in both PCOS and non-PCOS patients. Intriguingly, the analysis of data from six studies [10, 12, 20–22] showed a significant reduction in SL ($p = 0.0007$), as well as in gonadotropin dose ($p < 0.00001$) in patients receiving MI in comparison with respect to controls, without differences in CC rate, TO, MO, and CPR ($p =$ ns). In detail, subgroup analysis showed that MI was effective in both PCOS ($p < 0.00001$) and non-PCOS women ($p = 0.02$) in saving gonadotropins, but it was efficient only in PCOS women in reducing the length of COH ($p < 0.00001$). Our results about PCOS women are fully in line with two previously published systematic reviews of RCTs [26, 27], which highlighted the positive effects of MI supplementation for ovarian function and metabolic and hormonal parameters, key elements to improve IVF outcomes.

No difference was observed concerning the other endpoints (TO, MO, and CPR), confirming what was recently found by Mendoza et al. [13] for PCOS women. In particular, this group pooled data from eight RCTs comprising 1019 women with PCOS: according to their data analysis, MI supplementation was insufficient to improve oocyte quality (OR 2.2051; 95% CI 0.8260–5.8868), embryo quality (OR 1.6231, 95% CI 0.3926–6.7097), or pregnancy rate (OR 1.2832, 95% CI 0.8692–1.8944).

Conversely, another recent systematic review and meta-analysis [28] found a significant association of MI supplementation with improved clinical pregnancy rate [95% confidence interval (CI), 1.04–1.96; $p = 0.03$] and reduced abortion rate (95% CI, 0.08–0.50; $p = 0.0006$). Although these authors found grade 1 embryos proportion (95% CI, 1.10–2.74; $p = 0.02$), germinal vesicle and degenerated oocytes retrieved (95% CI, 0.11–0.86; $p = 0.02$), and total amount of ovulation drugs (95% CI, −591.69 to −210.39; $p = 0.001$) improved in favour of MI, there were no significant difference in TO and MO retrieved, SL, and estradiol peak level. The partial disagreement of these results with respect to our and Mendoza's group findings may be due to different inclusion/exclusion criteria and, most important, to the different methodology applied for data analysis.

Finally, no modifications in pooled results were observed after applying a sensitivity analysis, confirming the consistency of our results.

Strengths and limitations

The results of the present study are original and they were achieved following a rigorous methodology. However, they are not exempt from limitations. First, the overall methodological quality of included studies was limited. In addition, some of the outcomes of the meta-analysis, including GA and SL, were not primary outcomes of the original studies. Nonetheless, a certain heterogeneity between patients in terms of baseline characteristics, as well as in terms of COH management, are implicit when performing a pooled analysis of published data: notably, the subgroup of non-PCOS patients included only a small number ($n = 114$) of heterogeneous patients. In addition, included studies showed very different methods regarding timing and duration of MI supplementation, as well as type of COH. Finally, we found very limited data on PCOS patients [11, 18] regarding the comparisons between MI and DCI and between MI + DCI vs. DCI alone.

Interpretation

From the clinical point of view, ovarian stimulation during IVF procedures is associated with high costs, especially for the so-called "poor responders" [29], and with a higher risk of ovarian hyperstimulation syndrome (OHSS) for PCOS patients with respect to the general population [30]. In this scenario, the possible reduction of the GA used, as well as the duration of COH, may significantly reduce the costs of the procedure: on the one hand, the reduction of GA and days of stimulation necessary for ovulation induction can directly decrease the costs (lower number of gonadotropin vials, reduced number of outpatient accesses for the follow-up); on the other hand, the reduction of the above-mentioned parameters may significantly decrease the risk of OHSS and, in this way, avoid all the costs related to its management and hospitalization of the patient [31].

Conclusion

Despite the flaw of available evidence, our data analysis suggests that oral MI supplementation is able to reduce GA used in both PCOS and non-PCOS women undergoing IVF. Conversely, this supplement seems able to reduce COH length only in PCOS population.

Author contributions ASL: designed the systematic review and lead its development. AV and MN: performed the meta-analysis of retrieved data. GA: edited the manuscript. RD: supervised the development of the systematic review and meta-analysis and gave the final approval. All the authors concurred to screen the literature, include relevant data and write the manuscript. All the authors fulfil the International Committee of Medical Journal Editors (ICMJE) criteria.

Funding The work was not supported by any grant/fund.

Compliance with ethical standards

Conflict of interest The authors have no proprietary, financial, professional, or other personal interest of any nature in any product, service, or company. The authors alone are responsible for the content and writing of the paper.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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