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Review

Inositol supplementation in women with polycystic ovary syndrome undergoing intracytoplasmic sperm injection: a systematic review and meta-analysis of randomized controlled trials

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KEY MESSAGE
Myo-inositol supplementation is insufficient to improve the oocyte or embryo quality and pregnancy rates in women with polycystic ovary syndrome undergoing intracytoplasmic sperm injection. The role of d-chiro-inositol supplementation also remains controversial or unknown, and future research with different combinations of both inositol isoforms should properly address these concerns.

A B S T R A C T

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous disease that involves menstrual dysfunction and reproductive difficulty, as well as metabolic problems. The aim of this study was to assess the effectiveness of myo-inositol (MYO) and d-chiro-inositol (DCI) on improving oocyte or embryo quality and pregnancy rates for women with PCOS undergoing intracytoplasmic sperm injection (ICSI). We searched the *Web of Knowledge*, *MEDLINE*, *EMBASE*, *Pubmed*, *Scopus* and *Cochrane* databases for all articles published in any language up to March 2017. The selection criteria were as follows: (population) patients with PCOS; (intervention) treatment with inositol (MYO, DCI, or both, with any dose and any duration) in conjunction with an ovulation-inducing agent versus the ovulation-inducing agent alone; (outcome) oocyte and embryo quality; (study design) randomized controlled trials. Of 76 identified studies, eight RCTs were included for analysis comprising 1019 women with PCOS. MYO supplementation was insufficient to improve oocyte quality (OR 2.2051; 95% CI 0.8260 to 5.8868), embryo quality (OR 1.6231, 95% CI 0.3926 to 6.7097), or pregnancy rate (OR 1.2832, 95% CI 0.8692 to 1.8944). Future studies of appropriate dose, size and duration of DCI are vital to clarify its the role in the management of PCOS.

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Introduction

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous disease that involves menstrual dysfunction and reproductive difficulty, as well as metabolic problems. Use of the Rotterdam criteria will probably increase its already high prevalence, and currently, it is the most common endocrinopathy in women, affecting 7–14% of women of childbearing age worldwide (Bozdag et al., 2016).

It has been proposed that insulin resistance is the pathophysiological basis for this syndrome, and some women with PCOS suffer from metabolic problems (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004a, 2004b). For women with PCOS undergoing assisted reproduction techniques, improvements have been reported in women with hyperandrogenism or insulin resistance who are using drugs such as metformin or inositol in different forms, combinations or doses (Naderpoor et al., 2015). With the use of these drugs, endocrine–metabolic improvements have been observed, as have improvements in spontaneous ovulations and the quality of oocytes and embryos (Genazzani, 2016).

A recent systematic review (Unfer et al., 2016) and an International Consensus Conference (Facchinetti et al., 2015) noted that supplementation with inositol(s) could fruitfully affect different pathophysiological aspects of disorders pertaining to obstetrics and gynaecology. The aim of this study was to assess the effectiveness of the major inositol stereoisomers, myo-inositol (MYO) and d-chiro-inositol (DCI), in improving reproductive outcomes (oocyte or embryo quality and pregnancy rates) for women with PCOS undergoing ICSI.

Materials and methods

Selection of studies

We searched the Institute for Scientific Information *Web of Knowledge*, *MEDLINE*, *EMBASE*, *Pubmed*, *Scopus* and *Cochrane* databases for all articles (in any language) published in peer-reviewed journals up to March 2017 using the search strategy described in **Appendix S1**. Reference lists from papers identified by the search, as well as key reviews, were hand-searched to identify additional publications. Those that were in press in peer-reviewed journals and available online, ahead of publication, were also considered.

To guide the scope of the review and the search procedure, selection and synthesis of the literature, PICOS (population, interventions, comparators, outcomes, study design) criteria were formulated *a priori*. The selection criteria were as follows: (population) patients with PCOS; (intervention) treatment with inositol (MYO, DCI or both with any dose and any duration) in conjunction with an ovulation-inducing agent versus the ovulation-inducing agent alone; (outcome) oocyte and embryo quality; (study design) randomized controlled trials. Full articles that met the inclusion criteria were reviewed in detail. Other relevant papers were used for references.

The exclusion criteria were presence of other causes of hyperandrogenism or infertility, such as hypothyroidism, congenital adrenal hyperplasia, Cushing's syndrome, hyperinsulinaemia or endometriosis.

Assessment of study quality and data synthesis

We followed the PRISMA (http://www.prisma-statement.org/statement.htm) and MOOSE guidelines (Stroup et al., 2000) for systematic reviews and meta-analyses. Two authors (NM and LP) independently conducted the search and screened studies for inclusion, extracted and checked the data and synthesized the findings. Two authors (NM and LP) independently determined the adequacy of the study designs and main methodological characteristics to ascertain the validity of the research. Disagreements were resolved by discussion and consensus.

Data extraction

Data were extracted from included studies by two independent reviewers (NM and LP) using a specially developed data extraction form according to the selection criteria. The information extracted included description of the study, participants, intervention (dose and duration of MYO and DCI) and study results according to the outcomes outlined above. When the data of interest (methodology or results) were not available in the published paper, the authors were contacted by e-mail.

Data synthesis and meta-analysis

The available data on the outcome measures for all trials were extracted, pooled, and analysed. When the data were not present in the randomized controlled trials, the authors were contacted by e-mail. The odds ratio, risk ratio, mean difference, and their respective 95% confidence intervals were estimated with a fixed-effects or random-effects meta-analysis model. The fixed-effects model was used for variables with low heterogeneity, and the random-effects model was used for variables with moderate or high heterogeneity. R software (https://www.r-project.org) was used for all statistical analyses.

Results

The literature search identified 76 studies, but only eight publications met the criteria for final inclusion in the current systematic review (Artini et al., 2013; Ciotta et al., 2011; Colazingari et al., 2013; Isabella and Raffone, 2012; Pacchiarotti et al., 2016; Papaleo et al., 2009; Piomboni et al., 2014; Unfer et al., 2011) (**Figure 1** and **Table 1**). The inclusion or exclusion of each of eight studies for each outcome analysed (oocyte and embryo quality and pregnancy rate) are also

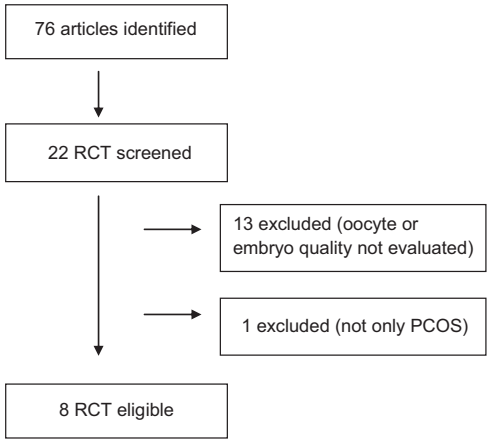

Figure 1 – Included studies.

Table 1 – Randomized controlled trials that evaluated oocyte and embryo quality in women with polycystic ovary syndrome undergoing intracytoplasmic sperm injection.

Authors	Method (randomization type)	Population	Intervention	Objectives (oocyte and embryo quality/pregnancy rate)	Outcomes
Piomboni et al., 2014	Computer-generated randomization	68 women with PCOS (Rotterdam criteria) Exclusion criteria: congenital adrenal hyperplasia; Cushing's syndrome and androgen-secreting tumours	Group A: 500 mg DCI plus gonadotrophins; group B: 1700 mg metformin plus gonadotrophins; control group: only gonadotrophins; 12 weeks	Yes/No	A higher number of good-quality metaphase II oocytes was observed in DCI ($P < 0.05$) and metformin ($P < 0.05$) groups comoared with control group
Colazingari et al., 2013	Computer-generated randomization (NCT1338844)	100 women with PCOS (Rotterdam criteria) Exclusion criteria: advanced endometriosis; poor responders; premature ovarian failure	Study group: 1.1 g MYO plus DCI 27.6 mg; control group: DCI 500 mg; 12 weeks	Yes/No	MYO plus DCI improve oocyte and embryo quality
Isabella et al., 2012	Computer-generated randomization	54 women with PCOS <40 years (Rotterdam criteria) Exclusion criteria: insulin resistance, hyperglycaemia, or both	Control group: placebo Study group A: DCI 300 mg; study group B: DCI 600 mg; study gruop C: DCI 1200 mg; study gruop D: DCI 2400 mg; 8 weeks	Yes/No	The oocyte and embryo quality was significantly reduced by DCI supplementation
Ciotta et al., 2011	Randomization not described	34 women with PCOS <40 years (Rotterdam criteria) Exclusion criteria: hypothyroidism; hyperthyroidism; diabetes Mellitus; androgen-secreting cancers, adrenal hyperplasia; Cushing's syndrome	Study group: MYO 2 g plus folic acid; control group: folic acid; 12 weeks	Yes/No	MYO improved oocyte and embryo quality
Unfer et al., 2011	Randomization not described	84 women with PCOS <40 years (Rotterdam criteria) Exclusion criteria: insulin resistance, hyperglycaemia, or both	Group A: MYO 4 g; group B: DCI 1.2 g; 8 weeks	Yes/Yes	MYO improved oocyte and embryo quality, and pregnancy rates
Papaleo et al., 2009	Randomization not described	60 women with PCOS <40 years (Rotterdam with hyperandrogenemia) Exclusion criteria: hyperinsulinemia, hyperprolactinaemia, hypothyroidism, adrenal hyperplasia; Cushing's syndrome	Study group: MYO 2 g twice a day plus folic acid; Control group: folic acid; time not described. One ICSI cycle	Yes/Yes	MYO reduced the mean number of germinal vesicles and degenerated oocytes with a trend for increased percentage of metaphase II oocytes; no differences in pregnancy rates nor in embryo quality
Artini et al., 2013	Computer-generated randomization	50 overweight women with PCOS (oligomenorrhoea, ultrasound for PCOS and hyperandrogenemia) Exclusion criteria: enzymatic adrenal deficiency; other endocrine disease; hyperprolactynaemia; hormonal treatment	Study group: MYO 2 g daily; control group: folic acid; 12 weeks	Yes/Yes	MYO improved oocyte quality and pregnancy rates
Pacchiarotti et al., 2016	Computer-generated randomization (NCT01540747)	569 women with PCOS aged 27–38 years (Rotterdam criteria) Exclusion criteria: tubal; uterine; genetics and male causes of infertility; FSH > 12 IU/l; BMI > 26	Study group A: MYO 4 g plus folic acid plus melatonin 3 mg; Study group B: MYO 4 g plus folic acid; control group: folic acid; time not described. One ICSI cycle	Yes/Yes	MYO improved oocyte and embryo quality

BMI, body mass index; DCI, D-Chiro-Inositol; MYO: Myo-Inositol; NCT: number clinical trial; PCOS: Polycystic ovary syndrome.

shown in **Table 1**. Although the study by Brusco and Mariani (2013) met the inclusion criteria, it was rejected because it also included patients diagnosed as 'poor responders', and the results were not separated from those with PCOS.

It was uncommon for studies to describe allocation concealment; only three randomized controlled trials included in that review (Artini et al., 2013; Ciotta et al., 2011; Colazingari et al., 2013) described if evaluators and participants were double-blinded. Dropout was described in most of the studies (Artini et al., 2013; Ciotta et al., 2011; Colazingari et al., 2013; Pacchiarotti et al., 2016; Piomboni et al., 2014; Unfer et al., 2011) and was mainly a result of cancelled cycles, most of them from increased risk of ovarian hyperstimulation syndrome.

Interventions included 1019 participants who were aged 18–39 years. Concerning type or dose of inositol, MYO was evaluated in four articles (Artini et al., 2013; Ciotta et al., 2011; Pacchiarotti et al., 2016; Papaleo et al., 2009). In two articles, DCI was evaluated (Isabella and Raffone, 2012; Piomboni et al., 2014), the combination of both was evaluated in one study (Colazingari et al., 2013), and they were compared with each other in another study (Unfer et al., 2011). The doses of MYO varied between 1.1 g and 4 g, with no reason for the differences. Studies assessing the effectiveness of DCI also had varying doses; Isabella and Raffone (2012) even used different doses within their study.

Author contact

Four authors were contacted by e-mail to request additional data regarding their publications, with responses received from the authors of three studies (Artini et al., 2013; Ciotta et al., 2011; Papaleo et al., 2009).

Risk of bias

All participants were selected from specialized outpatient clinic referrals. All studies adequately described PCOS diagnostic criteria, inclusion and exclusion criteria. Only Piomboni et al. (2014) and Isabella and Raffone (2012) excluded overweight women with PCOS. In fact, the mean BMI was over 25 in the remaining studies. Artini et al. (2013) included only overweight women with PCOS.

The duration of follow-up was 12 weeks in the studies by Artini et al. (2013), Ciotta et al. (2011), Colazingari et al. (2013) and Piomboni et al. (2014); 8 weeks in the studies by Ciotta et al. (2011) and Colazingari et al. (2013); and one cycle of ICSI in the studies by Artini et al. (2013) and Papaleo et al. (2009).

None of the authors had a conflict of interest. Baseline characteristics were not significantly different between intervention groups. Only one study did not report baseline characteristics (Colazingari et al., 2013).

Primary outcomes

Oocyte quality was the primary outcome in all randomized controlled trials; embryo quality was the primary outcome in all except in one (Piomboni et al., 2014). The eight randomized controlled trials defined oocyte quality as the presence of metaphase II (MII) oocytes, and all except Artini et al. (2013) also reported metaphase I oocytes, germinal vesicle or degenerated oocytes. Other parameters of oocyte quality were described by Piomboni et al. (2014) (oocyte morphology was evaluated according to Alpha Scientist in Reproductive Medicine and ESHRE Special Interest Group of Embriology, 2011). Individually, all randomized controlled trials, except those of Isabella and Raffone (2012) and Papaleo et al. (2009) showed oocyte quality improvement, but MYO supplementation did not improve quality of MII oocytes in the meta-analysis (OR 2.2051, 95% CI 0.8260 to 5.8868) of the four included studies (Artini et al., 2013; Ciotta et al., 2011; Pacchiarotti et al., 2016; Papaleo et al., 2009) (**Figure 2**).

The eight randomized controlled trials defined embryo quality as the presence of type I embryos. Three studies also reported type II and III embryos (Colazingari et al., 2013; Pacchiarotti et al., 2016; Papaleo et al., 2009). Four studies showed embryo quality improvement (Ciotta et al., 2011; Colazingari et al., 2013; Pacchiarotti et al., 2016; Unfer et al., 2011), whereas improvements were not shown in three studies (Artini et al., 2013; Isabella and Raffone, 2012; Papaleo et al., 2009). Three studies were included in the meta-analysis of the effect of MYO supplementation on embryo quality (Artini et al., 2013; Ciotta et al., 2011; Papaleo et al., 2009) (**Figure 3**). MYO supplementation did not increase the number of type I embryos (OR 1.6231, 95% CI 0.3926 to 6.7097). For both oocyte and embryo quality, a random-effects model was used because of the heterogeneity of both variables.

One study that was not included in the meta-analysis reported a significant difference between MYO and DCI in improving oocyte and embryo quality and pregnancy rates (Unfer et al., 2011). Another study not included in the meta-analysis reported a significant difference between MYO and DCI versus DCI alone in improving oocyte and embryo quality (Colazingari et al., 2013).

Secondary outcomes

Pregnancy rate was only measured in four randomized controlled trials without being the primary outcome in any of them (Artini et al., 2013; Pacchiarotti et al., 2016; Papaleo et al., 2009; Unfer et al., 2011). In the meta-analysis of three studies of three studies, MYO supplementation did not increase the clinical pregnancy rates (OR 1.2832, 95%

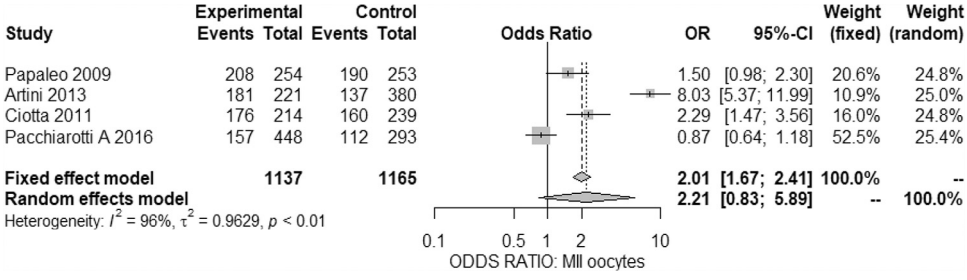

Figure 2 – Comparison: myo-inositol plus folic acid versus folic acid alone. Outcome: oocyte quality (metaphase II oocytes).

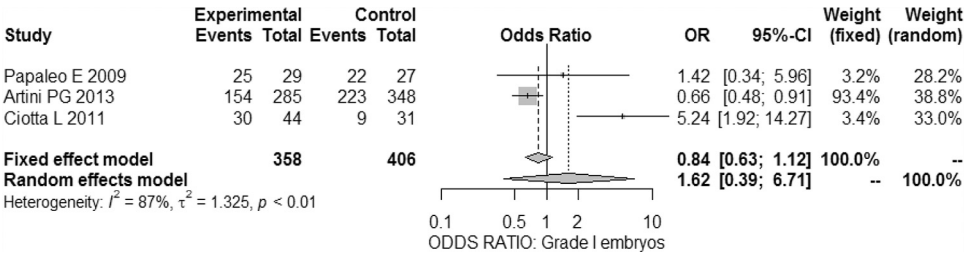

Figure 3 – Comparison: myo-inositol plus folic acid versus folic acid alone. Outcome: embryo quality (grade I embryos).

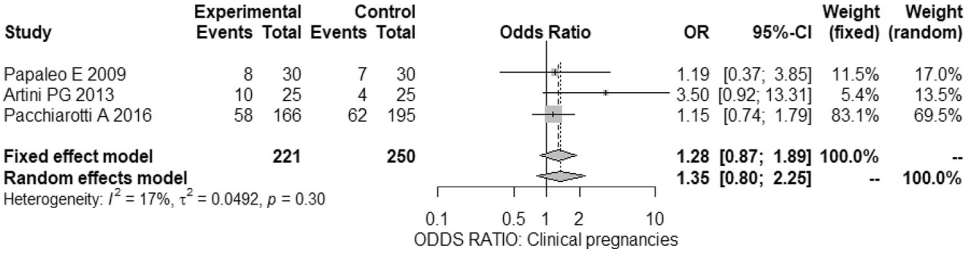

Figure 4 – Comparison: myo-inositol plus folic acid versus folic acid alone. Outcome: clinical pregnancy rates.

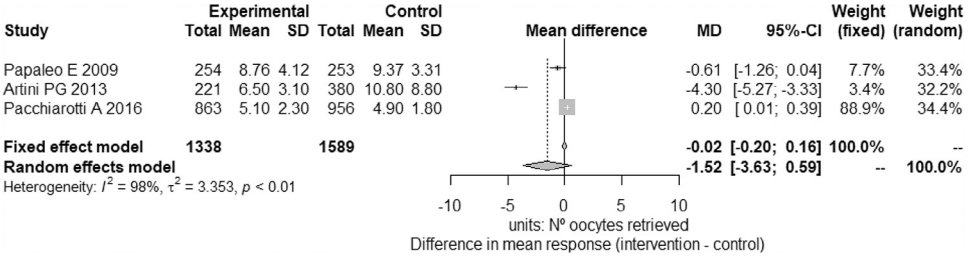

Figure 5 – Comparison: myo-inositol plus folic acid versus folic acid alone. Outcome: total number of oocytes retrieved.

CI 0.8692 to 1.8944) when using the meta-analysis fixed-effects model (Artini et al., 2013; Pacchiarotti et al., 2016; Papaleo et al., 2009) (**Figure 4**).

The total number of ocytes retrieved was higher in the control group compared with the MYO group (mean difference 1.5175, 95% CI –3.6263 to 0.59) in the meta-analysis of three studies (Artini et al., 2013; Pacchiarotti et al., 2016; Papaleo et al., 2009) (**Figure 5**). Data from Ciotta et al. (2011) could not be included as only median values for the total number of oocytes retrieved were available.

Discussion

We reported for the first time in a systematic review and meta-analysis of women with PCOS undergoing ICSI that MYO supplementation, compared with folic acid, is not associated with high oocyte and embryo quality or a high pregnancy rate. Assisted reproduction techniques have 30 years of history, and all of the studies conducted so far agree on the importance of determining the oocyte–embryo quality as the main predictors of positive results. Therefore, studies in recent years have focused on identifying substances that maintain or improve this quality, and it seems that both MYO and DCI are molecules that meet this function (Unfer et al., 2016). Some actions of insulin are mediated by inositolphosphoglycan, and studies have shown that a MYO or DCI deficiency can contribute to the development of insulin resistance (Croze and Soulage, 2013; Saltiel, 1991). At a reproductive level, inositol has been detected in the ovarian follicle and seems to influence oocyte meiosis (Mann et al., 2010). Although limited data are available on its deficit, it has been observed that supplementation of inositol increases ovulation and spontaneous pregnancy in women with PCOS, apart from improvements in lipid profile and weight (Minozzi et al., 2013; Unfer et al., 2016). Data have also been published on oxidative stress in the follicular fluid of women with PCOS undergoing assisted reproduction techniques (Piomboni et al., 2014), decreased FSH dose and the duration of ovulation induction required for follicular development (Emekçi Özay et al., 2017; Papaleo et al., 2009) and increased clinical pregnancy rates (Emekçi Özay et al., 2017). Higher concentrations of MYO in human follicular fluid seem to play a role in follicular maturity and provide a marker of good oocyte quality (Chiu et al., 2002).

The results of the present study, however, suggest that MYO supplementation is insufficient to improve the oocyte or embryo quality or the pregnancy rate. This is inconsistent with recent systematic reviews and international guidelines on the management of women with PCOS. These guidelines recognize that MYO improves the oocyte

and embryo quality of women with PCOS undergoing assisted reproduction techniques (Facchinetti et al., 2015; Unfer et al., 2016). The difference between our study and the systematic review published by Unfer et al. (2016) in oocyte quality was that Unfer et al. (2016) included RCTs with MYO alone or in conjunction with assisted reproduction techniques, whereas RCTs on PCOS women undergoing ICSI were involved in our study. In addition, two new RCTs have been integrated (Artini et al., 2013; Pacchiarotti et al., 2016).

The main limitation of the present meta-analysis was undoubtedly the small number of randomized controlled trials and the high heterogeneity that existed between them for any of the outcomes. The most relevant weaknesses in the systematic review were limitations in the research designs. Data on the effect size were often lacking. In many studies, the sample sizes were small, and no information was available on power calculations to estimate the appropriate sample size. Furthermore, outcome measures were diverse, which made it difficult to compare findings. The results were so different from those offered by separate studies and reported in other systematic reviews that it was important to note them.

MYO supplementation increased the MII oocytes and reduced the metaphase I, germinal vesicles and degenerated oocytes when analysed separately. These effects are similar to those observed with melatonin (Pacchiarotti et al., 2016). With embryo quality, which is generally assessed as an amount or percentage of type I embryos, four of the six studies that analysed embryo quality showed improvements (Ciotta et al., 2011; Colazingari et al., 2013; Pacchiarotti et al., 2016; Unfer et al., 2011). Concerning pregnancy rate, which was only measured in four studies, improvements were found in pregnancy rates in two of the studies (Artini et al., 2013; Unfer et al., 2011). In relation to dose and duration of use, although heterogeneity in both directions was observed, it seems that the results were independent of the dose (Unfer et al., 2016). In the present meta-analysis, however, none of these outcomes were improved. One limitation is that heterogeneity was high in some of the analyses, but that reinforces the hypothesis that more than MYO supplementation is needed to enhance reproductive outcomes.

A combination of metaphase I and DCI has been shown to be an efficient and safe alternative in the management of PCOS, especially to contain the effects of insulin resistance in a synergistic way (Sun et al., 2002). MYO is the most abundant inositol in the body and the precursor to DCI. DCI contributes to mediating insulin activity mainly in non-ovarian tissues. Conversion levels are organ-specific, making the relationship between MYO and DCI variable between organs (Sun et al., 2002). It has also been shown that insulin can stimulate enzymatic activity in the ovaries, leading to an increase in the DCI/MYO conversion rate (Carlomagno et al., 2011; Minozzi et al., 2013; Monastra et al., 2017).

Studies analysing the effect of DCI on oocyte and embryo quality in women with PCOS undergoing ICSI, have reported contradictory results. A study comparing both inositol forms observed that MYO supplementation rather than DCI was able to improve oocyte and embryo quality during ovarian stimulation protocols (Unfer et al., 2011). In addition, Isabella and Raffone (2012) showed that increasing DCI dosage progressively worsened oocyte quality and total r-FSH units. Piomboni et al. (2014), however, observed a higher number of good-quality MII oocytes in DCI and metformin groups compared with controls. In the study by Colazingari et al. (2013), only the MYO-DCI treated group (physiological ratio: 1.1 g + 27.6 mg) was characterized by an increase in embryo quality and less need for FSH in the ICSI cycle.

Interestingly, in all studies analysed, no side-effects were reported at any dose of MYO or DCI, which resulted in a high degree of patient compliance.

In conclusion, the data obtained from this systematic review and meta-analysis indicate a lack of arguments to justify that MYO supplementation is sufficient to improve the oocyte or embryo quality and pregnancy rates. The role of DCI supplementation also remains controversial or unknown, and future research with different combinations of both inositol isoforms should properly address these concerns.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.rbmo.2017.07.005.

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