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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

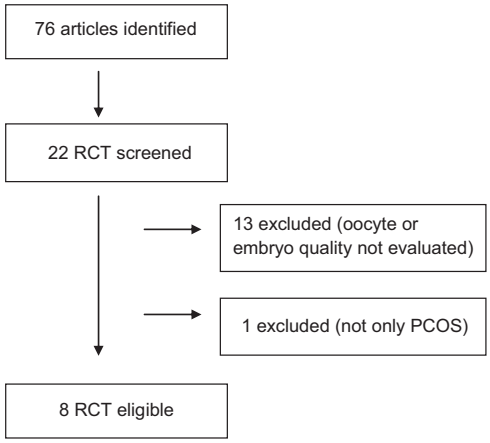

Figure 1 – Included studies.

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