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Inositol for subfertile women with polycystic ovary syndrome (Review)

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[Intervention Review]

Inositol for subfertile women with polycystic ovary syndrome

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ABSTRACT

Background

Subfertile women are highly motivated to try different adjunctive therapies to have a baby, and the widespread perception is that dietary supplements such as myo-inositol (MI) and D-*chiro*-insoitol (DCI) are associated with only benefit, and not with harm. Many fertility clinicians currently prescribe MI for subfertile women with polycystic ovary syndrome (PCOS) as pre-treatment to in vitro fertilisation (IVF) or for ovulation induction; however no high-quality evidence is available to support this practice. This review assessed the evidence for the effectiveness of inositol in subfertile women with a diagnosis of PCOS.

Objectives

To evaluate the effectiveness and safety of oral supplementation of inositol for reproductive outcomes among subfertile women with PCOS who are trying to conceive.

Search methods

We searched the following databases (to July 2018): Cochrane Gynaecology and Fertility Group (CGFG) Specialised Register, CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, and AMED. We also checked reference lists and searched the clinical trials registries.

Selection criteria

We included randomised controlled trials (RCTs) that compared any type, dose, or combination of oral inositol versus placebo, no treatment/standard treatment, or treatment with another antioxidant, or with a fertility agent, or with another type of inositol, among subfertile women with PCOS.

Data collection and analysis

Two review authors independently selected eligible studies, extracted data, and assessed risk of bias. The primary outcomes were live birth and adverse effects; secondary outcomes included clinical pregnancy rates and ovulation rates. We pooled studies using a fixed-effect model, and we calculated odds ratios (ORs) with 95% confidence intervals (CIs). We assessed the overall quality of the evidence by applying GRADE criteria.

Main results

We included 13 trials involving 1472 subfertile women with PCOS who were receiving myo-inositol as pre-treatment to IVF (11 trials), or during ovulation induction (two trials). These studies compared MI versus placebo, no treatment/standard, melatonin, metformin, clomiphene citrate, or DCI. The evidence was of 'low' to 'very low' quality. The main limitations were serious risk of bias due to poor reporting of methods, inconsistency, and lack of reporting of clinically relevant outcomes such as live birth and adverse events.

We are uncertain whether MI improves live birth rates when compared to standard treatment among women undergoing IVF (OR 2.42, 95% CI 0.75 to 7.83; P = 0.14; 2 RCTs; 84 women; I^2 = 0%). Very low-quality evidence suggests that for subfertile women with PCOS undergoing pre-treatment to IVF who have an expected live birth rate of 12%, the rate among women using MI would be between 9% and 51%.

We are uncertain whether MI may be associated with a decrease in miscarriage rate when compared to standard treatment (OR 0.40, 95% CI 0.19 to 0.86; P = 0.02; 4 RCTs; 535 women; I^2 = 66%; very low-quality evidence). This suggests that among subfertile women with PCOS with an expected miscarriage rate of 9% who are undergoing pre-treatment to IVF, the rate among women using MI would be between 2% and 8%; however this meta-analysis is based primarily on one study, which reported an unusually high miscarriage rate in the control group, and this has resulted in very high heterogeneity. When we removed this trial from the sensitivity analysis, we no longer saw the effect, and we noted no conclusive differences between MI and standard treatment.

Low-quality evidence suggests that MI may be associated with little or no difference in multiple pregnancy rates when compared with standard treatment (OR 1.04, 95% CI 0.63 to 1.71; P = 0.89; 2 RCTs; 425 women). This suggests that among subfertile women with PCOS who are undergoing pre-treatment to IVF, with an expected multiple pregnancy rate of 18%, the rate among women using inositol would be between 12% and 27%.

We are uncertain whether MI may be associated with an increased clinical pregnancy rate when compared to standard treatment (OR 1.27, 95% CI 0.87 to 1.85; P = 0.22; 4 RCTs; 535 women; I^2 = 0%; very low-quality evidence). This suggests that among subfertile women with PCOS who are undergoing pre-treatment to IVF, with an expected clinical pregnancy rate of 26%, the rate among women using MI would be between 24% and 40%. Ovulation rates were not reported for this comparison.

Other comparisons included only one trial in each, so for the comparisons MI versus antioxidant, MI versus an insulin-sensitising agent, MI versus an ovulation induction agent, and MI versus another DCI, meta-analysis was not possible.

No pooled evidence was available for women with PCOS undergoing ovulation induction, as only single trials performed comparison of the insulin-sensitising agent and the ovulation induction agent.

Authors' conclusions

In light of available evidence of very low quality, we are uncertain whether MI improves live birth rate or clinical pregnancy rate in subfertile women with PCOS undergoing IVF pre-treatment taking MI compared to standard treatment. We are also uncertain whether MI decreases miscarriage rates or multiple pregnancy rates for these same women taking MI compared to standard treatment. No pooled evidence is available for use of MI versus placebo, another antioxidant, insulin-sensitising agents, ovulation induction agents, or another type of inositol for women with PCOS undergoing pre-treatment to IVF. No pooled evidence is available for use of MI in women undergoing ovulation induction.

PLAIN LANGUAGE SUMMARY

Inositol for women with a diagnosis of polycystic ovary syndrome and subfertility

Review question

We looked at whether women who have polycystic ovary syndrome (PCOS) and were having difficulty getting pregnant would benefit from taking supplements of inositol.

Background

Women with PCOS who are trying to get pregnant are more likely to face difficulties as a result of their condition. These women who are finding it difficult to get pregnant can be offered different treatments. One of the treatments that can be offered is supplements. Inositol is one of the supplements thought to increase the chance of getting pregnant. At the moment, we are unsure whether taking inositol will actually help these women get pregnant, and whether any harms are associated with taking these supplements.

Search date

We searched for studies published up to July 2018.

Study characteristics

In total, we found 13 randomised controlled trials involving 1472 subfertile women with PCOS. All of these studies included women with PCOS who were having difficulty conceiving. All of the women included in these studies were receiving usual prenatal care. In addition to this, women were given myo-inositol (a form of inositol) and then were compared to women who were receiving no treatment or were receiving melatonin, metformin, clomiphene citrate, or D-*chiro*-inositoI (another form of inositol). In 11 studies, all women were also having in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI), and in the remaining two studies, women were undergoing ovulation induction.

Key results

Myo-inositol plus folic acid versus folic acid (standard treatment) as pre-treatment to IVF (low- or very low-quality evidence)

Few studies on this comparison are available, and the quality of these studies is low to very low. Based on currently available evidence, we were unable to show that taking myo-inositol increases the chances of becoming pregnant or having a baby among women with PCOS. Our findings suggest that if the chance of having a baby, for women undergoing pre-treatment to IVF, with standard treatment (folic acid alone) was 12%, the chance among women using myo-inositol could be as low as 9%, or could be as high 51%. We are unclear on whether myo-inositol could lower miscarriage rates, as these results are based on only two studies, one of which reported unusually high rates of miscarriage among women who were not receiving myo-inositol; therefore, we are not confident that this is the true effect of this treatment. MI may produce little or no difference in multiple pregnancy rates.

We were unable to assess the benefit or harm of taking myo-inositol for women with PCOS undergoing ovulation induction, as we had identified only two trials, and each performed a different comparison.

Quality of the evidence

We assessed the quality of the evidence as ranging from low to very low due to poor explanations of how these trials were run and the small number of trials that we could include. Also, reporting on issues that are important for subfertile couples was poor; these include the chance of having a baby when taking myo-inositol, and whether its use leads to harmful effects.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Myo-inositol compared to placebo, no/standard treatment in women undergoing IVF treatment for subfertile women with polycystic ovary syndrome

Patient or population: subfertile women with polycystic ovary syndrome
Setting: clinic
Intervention: myo-inositol
Comparison: placebo, no/standard treatment in women undergoing IVF treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo, no/standard treatment in women undergoing IVF treatment	Risk with myo-inositol			
Live birth	Study population		OR 2.42 (0.75 to 7.83)	84 (2 RCTs)	⊕◯◯◯ VERY LOW[a,b]
	116 per 1000	242 per 1000 (90 to 507)			
Adverse event - miscarriage	Study population		OR 0.40 (0.19 to 0.86)	535 (4 RCTs)	⊕◯◯◯ VERY LOW[c,d]
	88 per 1000	37 per 1000 (18 to 77)			
Adverse event - multiple pregnancy	Study population		OR 1.04 (0.63 to 1.71)	425 (2 RCTs)	⊕⊕◯◯ LOW[e,f]
	179 per 1000	185 per 1000 (121 to 272)			
Clinical pregnancy	Study population		OR 1.27 (0.87 to 1.85)	535 (4 RCTs)	⊕◯◯◯ VERY LOW[c,g]
	264 per 1000	313 per 1000 (238 to 399)			
Ovulation	Not reported in this comparison				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; IVF: in vitro fertilisation; PCOS: polycystic ovary syndrome; OR: odds ratio; RCT: randomised controlled trial

GRADE Working Group grades of evidence.
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Downgraded one level due to risk of bias, as unclear blinding in one study and unclear selective reporting in both studies.
[b] Downgraded two levels due to imprecision, as both studies has small sample sizes and confidence intervals are wide.
[c] Downgraded two levels due to risk of bias, as one study has unclear allocation concealment, three have unclear blinding, and one is at high risk for selective reporting, when live birth was stated as an outcome but no data were reported, and the study author communicated that none were available.
[d] Downgraded one level due to inconsistency of results, as heterogeneity was moderately high.
[e] Downgraded one level due to risk of bias, as allocation concealment and blinding were unclear in one study.
[f] Downgraded one level due to imprecision, as the size criterion is met but the 95% CI overlaps no effect, thereby failing to exclude important benefit or harm.
[g] Downgraded one level due to imprecision, as only two studies and one small study reported no events in either arm.

BACKGROUND

Description of the condition

Polycystic ovary syndrome (PCOS) is associated with no single clinical symptom, that is, it is typically characterised by irregular menstrual cycles (including amenorrhoea (absence of cycles) and oligomenorrhoea (infrequent cycles), excess androgen (male hormone) production, obesity, and polycystic ovary morphology on ultrasound) (Rotterdam 2004). PCOS is the most common endocrine abnormality among reproductive women (Abu Hashim 2012); it is thought to affect 6% to 10% of women in the reproductive age group, although this rate could be as high as 15% when the broader Rotterdam criteria are applied (Fauser 2012). The pathophysiology of PCOS is unclear; however insulin resistance and its effects on metabolic and reproductive features seem to be important factors, and genetic and environmental causes also play a role (Facchinetti 2015; Franks 1995). A study of Indian women with PCOS shows genetic differences between women with PCOS and a matched control group (Shaikh 2016). Women with PCOS are at greater risk of developing diabetes mellitus, obesity, cardiovascular disease, and endometrial hyperplasia/cancer (Fauser 2012). Approximately 50% of women with PCOS are obese, but this rate is thought to differ regionally, with the highest prevalence of obesity observed in the USA and Australia, where 61% to 76% of women with PCOS are considered obese (Azziz 2009; Ching 2007; Glueck 2005).

Diagnostic criteria are based on the *Revised 2003 Consensus* (Rotterdam 2004), which was jointly proposed by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine. For a diagnosis of PCOS, a woman must exhibit at least two of the following three criteria.

- Oligo-ovulation (infrequent ovulation) or anovulation (absence of ovulation), or both.
- Hyperandrogenism (high levels of male hormones), either clinically with excessive hair growth, or biochemically with raised blood serum androgen levels.
- Polycystic ovary, defined as the "presence of 12 or more follicles in each ovary measuring 2 mm to 9 mm in diameter and/or increased ovarian volume (> 10 mL)", in one or both ovaries.

PCOS is diagnosed on the basis of these criteria only after other disorders such as congential adrenal hyperplasia, androgen-secreting tumours, or Cushing syndrome have been excluded (Vause 2010), although more recently it has been proposed that the definition should be based on anti-mullerian hormone (AMH) levels > 5 ng/mL (Dewailly 2011).

Anovulation is the reason that approximately one-third of couples seek fertility advice, and about 90% of women with this condition have PCOS (Balen 2002). Anovulation is probably due to the effects of PCOS - numerous antral follicles, elevated androgen secretion from the ovaries, a surge in luteinising hormone (LH), and hyperinsulinaemia - although the underlying aetiology (cause) remains unknown (Brown 2009). Hypersecretion of LH is found only in women with PCOS, and this is thought to impact fertility and miscarriage by disturbing the timing of oocyte (fertilised egg) maturation (Balen 1993).

Change in lifestyle is an important management choice for overweight women with PCOS; this includes dietary energy restriction and exercise in an attempt to restore ovulation and reproductive functions (Moran 2009; Moran 2011). Current leading treatments for ovulation induction include clomiphene citrate (an anti-oestrogen agent) and letrozole (Galazis 2011; Seyedoshohadaei 2016). A recent Cochrane Review showed improved live birth and pregnancy rates with the use of letrozole (an aromatase inhibitor) when compared to clomiphene citrate, although the quality of the evidence was low (Franik 2014). Other treatments include insulin-sensitising drugs (metformin), gonadotrophins (Tarlatzis 2008), and laparoscopic ovarian drilling (Abu Hashim 2012).

Women with PCOS experiencing fertility problems often have some degree of insulin resistance, which is defined as decreased insulin-mediated glucose utilisation by cells in the body that results in raised blood sugar levels. It is thought that up to 50% of both obese and non-obese women with PCOS have insulin resistance, whereas in the general population, its prevalence is thought to be between 10% and 25% (Rotterdam 2004). Burghen 1980 first demonstrated the positive correlation between hyperandrogenism and hyperinsulinism in women with PCOS. A negative effect on insulin action is associated with having both PCOS and obesity, and the resulting hyperinsulinaemia contributes to reproductive problems in women with PCOS (Fauser 2012). The combination of obesity with metabolic, inflammatory, and endocrine disorders may lead to problems in ovulatory function, oocyte quality, and endometrial receptivity. Many women with PCOS undergoing medically assisted cycles face an increased rate of cycle cancellation and potentially life-threatening complications due to ovarian hyperstimulation syndrome (OHSS) (Fischer 2016). Among pregnant women with PCOS, the incidence of gestational diabetes is increased, and when it occurs, this may result in foetal macrosomia, gestational hypertensive disorders, and small-for-gestational-age babies (Fauser 2012).

Description of the intervention

Inositol is a chemical compound (a sugar alcohol) with nine forms. Two of these are myo-inositol (MI) and D-*chiro*-inositol (DCI); both play an important biological role in mediating different actions of insulin and are known as insulin-sensitising agents. Inositol is found in fruits, nuts, and beans; can be produced in the body from glucose (Unfer 2014); and can be taken as a dietary supplement. We consume approximately one gram a day in a regular diet, but absorption of this free inositol can be inhibited by glucose (Beemster 2002). Inositol also acts as an antioxidant - a group of vitamins, minerals, and fatty acids that reduce oxidative

damage stress by scavenging free radicals. Free radicals are released in the body as a result of oxidative stress and cause harmful reactions within the cells (Ruder 2008).

Inositol has been proposed as treatment for PCOS and is critical for many biological pathways: the concentration is much higher in reproductive organs than in serum, perhaps indicating the importance of this substance in reproduction (Unfer 2014). The MI form is largely responsible for glucose uptake, and DCI is responsible for glycogen synthesis (Kamenov 2015). Inositol is available in tablet and powder forms and has been given at a dose of 2 grams/d to 4 grams/d (Lisi 2016); however the literature provides no clear information on the appropriate therapeutic dose nor on associated adverse effects. Inositol can also be given as Inofolic®, a supplement that contains 2 grams of MI and 200 micrograms of folic acid (Papaleo 2011).

Inositol has been used in conjunction with fertility treatments in women undergoing ovulation induction and in those undergoing in vitro fertilisation (IVF) (Regidor 2018). For women with ovulatory disorders such as PCOS, less invasive options such as controlled ovarian stimulation (ovulation induction) are usually recommended before more invasive artificial reproductive techniques such as IVF are proposed (Melo 2015).

Medical options for ovulation induction include gonadotrophins, which directly stimulate the ovaries; aromatase inhibitors (letrozole); oestrogen receptor modulators (tamoxifen and clomiphene citrate); and insulin-sensitising drugs such as metformin (Melo 2015; Wang 2017).

IVF is a more invasive fertility treatment. It involves stimulation of the ovaries by gonadotrophins (and in some cases, adjuncts) to create oocytes, collect these oocytes, and fertilise them with sperm to create embryos. Fertilisation can be natural or can occur with intracytoplasmic sperm injection (ISCS), whereby embryos are transferred into the uterus and the uterine lining is maintained with hormones.

How the intervention might work

Studies show altered metabolic parameters and reduced availability of inositol in the tissues of women with PCOS (Iuorno 2002). This inability to synthesise or metabolise inositol adequately may contribute to insulin resistance and hyperinsulinaemia (Facchinetti 2015). Inositols are thought to be therapeutic for PCOS because they act as insulin-sensitising agents and free radical scavengers, helping to regulate metabolism while promoting ovulation (Nestler 2015; Ruder 2008). MI has also been shown to help regulate hormones (LH surge), menstrual cycles, ovulation, androgen levels, and hirsutism (excessive hair growth) (Facchinetti 2015; Minozzi 2008).

Kamenov 2015, an experimental study, showed that MI is well tolerated and may be effective for ovulation induction and metabolic balance in women with PCOS. Genazzani 2014a studied MI in women of normal weight with PCOS and showed a modulating effect on hormones including androstenedione, plus a decrease in insulin response after 12 weeks of treatment. Another study by the same researchers - Genazzani 2014 - assessed effects of DCI in obese women with PCOS and demonstrated a positive effect on insulin resistance and hormonal balance. Minozzi 2013, a longitudinal study, found that a combination of MI and DCI led to improved glucose metabolism. Simi 2017 found that inositol as pre-treatment and as stimulation therapy in IVF reduces insulin resistance, thereby improving ovarian function, oocyte quality, and embryo and pregnancy rates while reducing the amount of gonadotrophin needed during stimulation. MI is often given three months before an IVF cycle as pre-treatment (Simi 2017).

A systematic review of randomised controlled trials showed that MI supplementation in women with PCOS may lead to improvement in insulin sensitivity, restoration of ovulation, improvement in oocyte quality, and reduction in hyperandrogenism through reduction of insulin plasma levels, which may, in turn, help to increase fertility (Unfer 2012).

Why it is important to do this review

Subfertile women are highly motivated to try different adjunctive therapies to have a baby, and the widespread perception is that dietary supplements such as MI and DCI are associated only with benefit - not with harm. Inositol is widely available on the Internet for purchase, and many fertility clinicians are currently prescribing MI for subfertile women with PCOS. Some evidence indicates that higher doses of DCI may lead to greater numbers of immature oocytes of lower quality (Carlomagno 2011). Although DCI is widely used to treat PCOS, it has not been approved by the US Food and Drug Administration (FDA). One review article provided limited evidence to support the use of inositol for improving fertility in women with PCOS, as the trials were small and very few included a placebo control (Vitek 2015). A Cochrane Review found that two trials that used DCI for women with PCOS did not report the important outcomes of live birth and clinical pregnancy and provided no evidence of effect for improved ovulation rate (Morley 2017). This Review included only DI and excluded women who were undergoing IVF or ICSI. We are conducting this systematic review to provide evidence of any benefit or harm, or both, associated with use of MI and DCI for women undergoing pre-treatment to IVF, and for those undergoing ovulation induction.

OBJECTIVES

To evaluate the effectiveness and safety of oral supplementation of inositol for reproductive outcomes among subfertile women with PCOS who are trying to conceive.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs) were eligible for inclusion. We considered cross-over trials as eligible, but we included only data from the first phase (Dias 2006).

Types of participants

Subfertile women with PCOS (as defined by criteria used in the Rotterdam consensus workshop) who were trying to become pregnant were eligible for inclusion (Rotterdam 2004). These included subfertile women undergoing expectant management, timed intercourse, ovulation induction, intrauterine insemination (IUI), in vitro fertilisation (IVF), or intracytoplasmic sperm injection (ICSI). For the purposes of analysis, we separated participants into two population groups - women undergoing ovulation induction (OI), and women using inositol as pre-treatment to IVF. We defined 'subfertility', or 'infertility', as failure to achieve a successful pregnancy after 12 months of timed, unprotected intercourse (ASRM 2013).

Types of interventions

Inclusion criteria

- Oral inositol versus:
  - placebo or no treatment; or
  - any active intervention (e.g. another antioxidant, an insulin-sensitising agent, an ovulation induction agent).
- One type (stereoisomer) of oral inositol versus another type (e.g. myo-inositol (MI), D-*chiro*-inositol (DCI)). We included any of the following inositol compounds: myo-inositol, D-*chiro*-inositol, or L-*chiro* inositol.

We analysed any fertility agent (i.e. metformin, clomiphene citrate, or any antioxidant) given in addition to inositol and appearing in both intervention and comparator arms as inositol versus no treatment (e.g. metformin + inositol vs metformin).

Types of outcome measures

Primary outcomes

- Live birth or ongoing pregnancy: we reported live birth by preference, but if data were unavailable, we reported ongoing pregnancy. Live birth is defined as delivery of a live foetus after 20 completed weeks of gestation, and ongoing pregnancy as evidence of a gestational sac with foetal heart motion at 12 weeks, confirmed by ultrasound
- Any adverse event (including miscarriage, multiple birth, ectopic pregnancy, foetal abnormalities, drug side effects, ovarian hyperstimulation syndrome) as reported by trial investigators. We subgrouped these events according to the type of adverse event reported

Secondary outcomes

- Clinical pregnancy, defined as evidence of a gestational sac, confirmed by ultrasound, at six to eight weeks of gestation
- Number of women undergoing ovulation induction who have achieved ovulation during the study period (as determined by ultrasound or mid-luteal phase serum progesterone level > 3 ng/mL)
- Gestational diabetes mellitus per woman (as defined by trials)

Search methods for identification of studies

We searched from inception of the databases to 30 July 2018, for all published and unpublished RCTs of inositol, without language restrictions and in consultation with the Cochrane Gynaecology and Fertility Group (CGFG) Information Specialist.

Electronic searches

We searched the following electronic databases, trial registers, and websites.

- Cochrane Gynaecology and Fertility Group (CGFG) Specialised Register of Controlled Trials (Procite platform; searched July 2018) (Appendix 1).
- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, via the Cochrane Central Register of Studies Online (web platform; searched July 2018) (Appendix 2).
- MEDLINE (OVID platform; searched from 1946 to July 2018) (Appendix 3).
- Embase (OVID platform; searched from 1980 to July 2018) (Appendix 4).
- PsycINFO (OVID platform; searched from 1806 to July 2018) (Appendix 5).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO platform; searched from 1946 to July 2018) (Appendix 6).
- Allied and Complementary Medicine Database (AMED) (OVID platform; searched from 1985 to July 2018) (Appendix 7).

We combined the MEDLINE search with the Cochrane highly sensitive search strategy for identifying randomised trials, which appears in Chapter 6 of the *Cochrane Handbook for Systematic*

Reviews of Interventions (Lefebvre 2011). We combined Embase, PsycINFO, and CINAHL searches with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (Scottish Intercollegiate Network).

Other electronic sources of trials (web platforms; all searched March 2018) included the following.

- Trial registers for ongoing and registered trials.
    - Clinicaltrials.gov (www.clinicaltrials.gov) (a service of the US National Institutes of Health).
    - World Health Organization International Trials Registry Platform search portal (www.who.int/trialsearch/Default.aspx) (Appendix 8).
- Latin American Caribbean Health Sciences Literature (LILACS) and other Spanish/Portuguese databases via the Virtual Health Library Regional Portal (VHL) (regional.bvsalud.org/php/index.php?lang=en) (Appendix 9).
- PubMed and Google Scholar (for recent trials not yet indexed in the major databases) (Appendix 10).
- OpenGrey (www.opengrey.eu/) for unpublished literature from Europe (Appendix 11).
- Web of Science (wokinfo.com/) (another source of trials and conference abstracts) (Appendix 12).

Searching other resources

We handsearched the reference lists of articles retrieved by the search and contacted experts in the field to obtain additional studies.

We used ENDNOTE bibliographic management software to manage the search output.

Data collection and analysis

Selection of studies

We used COVIDENCE software for selection of studies (COVIDENCE), data extraction, and assessment of risk of bias of included studies.

Two review authors (MS and RMP) conducted an initial screen of titles and abstracts retrieved by the search; we then retrieved the full texts of all potentially eligible studies. Independently, two review authors (MS and RMP) examined these full-text articles for compliance with the inclusion criteria and selected studies that were eligible for inclusion in the review. We have recorded the reason for exclusion of any study that we excluded following a review of full texts. We corresponded with study investigators as required to clarify study eligibility. We resolved disagreements regarding study eligibility by discussion or by consultation with a third review author (VJ). We documented the study selection process using a PRISMA flow chart.

Data extraction and management

Independently, two review authors (MS and RMP) extracted data from eligible studies using a data extraction form in COVIDENCE. We resolved disagreements by discussion or by consultation with a third review author (VJ). Data extracted included study characteristics and outcome data. When studies had multiple publications, review authors collated multiple reports of the same study, so that each study - rather than each report - was the unit of interest in the review; these studies have a single study ID with multiple references.

We corresponded with study investigators to ask for further information about methods and results, as required.

Assessment of risk of bias in included studies

Independently, two review authors (MS and RMP) used the Cochrane tool to assess risk of bias for the following domains (Higgins 2011): selection (random sequence generation and allocation concealment); performance (blinding of participants and personnel); detection (blinding of outcome assessors); attrition (incomplete outcome data); reporting (selective reporting); and other bias. We resolved disagreements by discussion or by consultation with a third review author (VJ). We described all judgements fully and presented our conclusions in the 'Risk of bias' table, which we incorporated into our interpretation of review findings by performing sensitivity analyses (see below).

We took care to search for within-trial selective reporting, as in trials failing to report obvious outcomes or reporting them in insufficient detail. We searched for published protocols and compared the outcomes specified in the protocol versus those reported in the final published study.

Random sequence generation (possible selection bias; biased allocation to the intervention due to inadequate generation of a randomised sequence)

Criteria included:

- low risk of bias (e.g. coin toss, random number table; computer random number generator); and
- unclear risk of bias (e.g. studies providing insufficient information or not describing the methods used for randomisation).

We excluded from the review any study deemed to be at high risk of bias (i.e. quasi-randomised).

Allocation concealment (possible selection bias; biased allocation to interventions due to inadequate concealment of allocations before assignment)

Criteria included:

- low risk of bias (e.g. telephone, web-based or central randomisation; sequentially numbered sealed opaque envelopes);

- high risk of bias (e.g. open allocation, unsealed or see-through envelopes, alternation, date of birth, medical record number); and
- unclear risk of bias (e.g. no description of how allocation was concealed, insufficient information provided).

Blinding of participants and personnel (possible performance bias due to knowledge of allocated interventions by participants and personnel during the study) and blinding of outcome assessors (possible detection bias due to knowledge of allocated interventions by outcome assessors)

We considered that studies were at low risk of bias if they were blinded, or if we judged that lack of blinding would be unlikely to affect study results. Lack of blinding of outcome assessors is unlikely to introduce detection bias with objective outcomes such as live birth, clinical pregnancy, and multiple pregnancy; however lack of blinding may influence outcomes for other adverse events such as skin irritation or digestive problems.
Criteria for participants and personnel included:
- low risk of bias, if study authors report no blinding of personnel or outcome assessment and review authors judge that the outcome was unlikely to be affected by lack of blinding; or if the study was blinded and it was unlikely that the blinding could have been broken;
- high risk of bias, if study authors report no blinding and the outcome was likely to be influenced by lack of blinding, or if blinded and blinding was likely to be broken); and
- unclear risk of bias, if study authors provide insufficient information, or if the study did not address this outcome.

Incomplete outcome data (possible attrition bias due to quantity, nature, and handling of incomplete outcome data)

Criteria included:
- low risk of bias (e.g. no missing outcome data, missing outcome data balanced across groups, missing data imputed by appropriate methods);
- high risk of bias (e.g. the reason for missing outcome data was likely to be related to the true outcome with either an imbalance in numbers or reasons for missing data across intervention groups; 'as treated' analysis was done with substantial departure of the intervention received from that assigned at randomisation); and
- unclear risk of bias (e.g. insufficient reporting of attrition to permit judgement of low or high risk (i.e. the number randomised was not stated), no reasons for missing data given).

Selective reporting (possible reporting bias)

We attempted to find protocols of the included studies and to compare outcomes between the protocol and the final published study to assess within-trial selective reporting. If no protocol was available, we assessed reporting of outcomes from the Methods section of the paper and also assessed whether an outcome was likely to have been planned or measured but not reported in the paper.
Criteria included:
- low risk of bias, when it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported and evidence suggests that the trial has been registered;
- high risk of bias, when not all of the study's pre-specified outcomes have been reported, one or more reported primary outcomes were not pre-specified, or outcomes of interest were reported incompletely and so cannot be entered into a meta-analysis; or when the study fails to report results of a key outcome that would have been expected to have been reported; and
- unclear risk of bias, when insufficient information is available to permit a judgement of high or low risk.

Other bias (possible bias due to problems not covered in the previously discussed biases)

Criteria included:
- low risk of bias, when the study appears to be free of any other source of bias;
- high risk of bias, when a specific study design is used or when a study is fraudulent; and
- unclear risk of bias, when study authors provided insufficient information.

Measures of treatment effect

For dichotomous data (e.g. live birth rates), we used numbers of events in the control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (ORs). We reported no continuous data. We presented 95% confidence intervals (CIs) for all outcomes. When data needed to calculate ORs were not available, we utilised the most detailed numerical data available that facilitated similar analyses of included studies (e.g. test statistics, P values).

Unit of analysis issues

The primary analysis was per woman randomised. We briefly summarised in an additional table data that did not allow valid analysis (e.g. 'per cycle' data) and were not to be pooled or used in quantitative synthesis. However, we analysed 'per cycle' data when the trial provided data for only one cycle per woman. We counted multiple live births (e.g. twins, triplets) as one live birth event. We included only first-phase data from cross-over trials (Dias 2006).

Dealing with missing data

We analysed the data on an intention-to-treat basis as far as possible and attempted to obtain missing data from the trial authors. When

these were unobtainable, we undertook imputation of individual values for live birth and pregnancy. We assumed that live births and pregnancies did not occur in participants without a reported outcome. For other outcomes, we analysed only available data. We subjected to sensitivity analysis any imputation undertaken.

Assessment of heterogeneity

We considered whether clinical and methodological characteristics of included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We assessed statistical heterogeneity using the I^2 statistic, taking a value greater than 50% as indicative of substantial heterogeneity (Higgins 2003; Higgins 2011).

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, review authors aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by staying alert for duplication of data. As we included only four studies in the largest analysis, it was not possible to create a funnel plot to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies) (Higgins 2011).

Data synthesis

As the included studies were sufficiently similar, we combined the data using a fixed-effect model for the following comparisons while stratifying for ovulation induction or pre-IVF treatment.

- Myo-inositol versus placebo, no treatment, or folic acid (we assumed that all women were given folic acid as standard treatment, i.e. folic acid was given to both intervention and control arms).
- Myo-inositol versus another type of antioxidant.
- Myo-inositol versus D-*chiro*-inositol (DCI).
- Myo-inositol versus an insulin-sensitising agent.
- Myo-inositol versus an ovulation induction agent.

We analysed any fertility agent (i.e. metformin, clomiphene citrate, or another antioxidant) given in addition to inositol and appearing in both intervention and comparator arms as inositol versus no treatment (e.g. metformin + inositol vs metformin).
We pooled the data for these comparisons.
We displayed an increase in the odds of a particular outcome, which may be beneficial (e.g. live birth) or detrimental (e.g. adverse effects), graphically in meta-analyses to the right of the centre-line, and a decrease in the odds of a particular outcome to the left of the centre-line.
We performed statistical analysis using Review Manager 5.3 (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

To answer questions of clinical interest, we conducted subgroup analyses to examine separate evidence within the following subgroups, if data were available for the outcomes of live birth and clinical pregnancy.

- Type of inositol: myo-inositol (MI) or D-*chiro*-inositol (DCI).
- Type of comparator.

For the outcome of adverse events, we subgrouped data on the basis of the type of event.
In addition to visually inspecting subgroup differences, we performed a significance test to determine the percentage of variability in effect estimates from different subgroups that was due to genuine subgroup differences rather than to sampling error (chance) (Higgins 2011). We took statistical heterogeneity into account when interpreting the results, especially if we noted variation in the direction of effect.

Sensitivity analysis

We conducted sensitivity analyses (if we identified at least three studies) for live birth and clinical pregnancy to determine whether conclusions were robust to different decisions made regarding eligibility and analysis. These analyses included consideration of whether review conclusions would have differed if:

- we had restricted eligibility to studies at low risk of bias (i.e. studies with low risk of bias in the domains of randomisation and allocation concealment);
- we had restricted analysis to studies of inositol only versus placebo or no treatment only (i.e. by excluding studies with a co-intervention in both arms);
- we had restricted analyses to studies without imputed data;
- we had restricted the primary outcome to live birth only; or
- identified studies had failed to report the primary outcome of live birth but did report interim outcomes such as pregnancy. We undertook an assessment as to whether interim values (e.g. clinical pregnancy rates) were similar to those reported in studies that also reported live birth.

Overall quality of the body of evidence: 'Summary of findings' table

We prepared a 'Summary of findings' table using GRADEproGDT software and Cochrane methods (GradePro). In this table, we evaluated the overall quality of the body of evidence for the main review outcomes (live birth, adverse events (miscarriage and multiple pregnancy), clinical pregnancy, and ovulation rates) for the main review comparison (inositol vs placebo or no treatment). We prepared additional 'Summary of findings' tables for these outcomes for other important comparisons (inositol vs another type of inositol, inositol vs another type of antioxidant, inositol vs an insulin-sensitising agent, and inositol vs an ovulation induction

agent). We assessed the quality of the evidence using GRADE criteria (risk of bias, consistency of effect, imprecision, indirectness, and publication bias). Two review authors working independently made judgements about evidence quality (high, moderate, low, or very low) and resolved disagreements by discussion. We justified, documented, and incorporated these judgements into reporting of results for each outcome.

RESULTS

Description of studies

Results of the search

Through database and reference list searches and by handsearching, we retrieved 397 abstracts and titles, which we screened to identify trials that met our inclusion criteria. We retrieved the full texts of 50 trials for appraisal. All studies were published in English. Of the 50 studies assessed, we included 13, excluded 35, and placed two in the 'Awaiting assessment' category. Please see Characteristics of included studies and Characteristics of excluded studies for study details.

Included studies

Thirteen studies met the criteria for inclusion. Eleven trials were based in Italy (Artini 2013; Brusco 2013; Ciotta 2011; Colazingari 2013; Pacchiarotti 2015; Papaleo 2008; Papaleo 2009; Piomboni 2014; Raffone 2010; Rosalbino 2012; Unfer 2011), one in Albania (Hoxha 2016), and one in Germany (Lesoine 2016).

We tried to contact the authors of all included trials to obtain further details and clarification. However, we could not obtain data for meta-analysis from six trials (Brusco 2013; Colazingari 2013; Hoxha 2016; Lesoine 2016; Piomboni 2014; Rosalbino 2012). Brusco 2013 provided data for clinical pregnancy for women with PCOS, together with women with poor response to stimulation; however, we could not separate the data for these two groups; Colazingari 2013 reported clinical pregnancy in the narrative but provided no data. The remaining four trials reported on required stimulation dose, oocyte and embryo quality, and fertilisation rates.

Participants

The included trials randomly assigned 1472 subfertile women with PCOS who were trying to become pregnant.

Eleven studies included women undergoing pre-treatment to in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) (Artini 2013; Brusco 2013; Ciotta 2011; Colazingari 2013; Hoxha 2016; Lesoine 2016; Pacchiarotti 2015; Papaleo 2009; Piomboni 2014; Rosalbino 2012; Unfer 2011). The pre-treatment period extended from eight to twelve weeks before IVF/ICSI. The treatment period for Pacchiarotti 2015 lasted from the first day of the cycle to 14 days after embryo transfer, and Papaleo 2009 started treatment on the first day of gonadotrophin-releasing hormone (GnRH) administration.

Two studies enrolled women who were undergoing ovulation induction (Papaleo 2008; Raffone 2010).

The ages of women enrolled in the studies varied. Raffone 2010 enrolled only women who were younger than 35 years. Colazingari 2013 enrolled two different age groups: women who were younger than 35 years and women who were 35 years of age and older; we analysed these two groups separately. The remaining studies stated that they enrolled women who were younger than 40 years of age.

Three trials enrolled mostly overweight women (Artini 2013; Colazingari 2013; Papaleo 2009); Artini 2013 enrolled women with a mean body mass index (BMI) of 26.5 ± 6.1 in the treatment group, and women with a BMI of 26.3 ± 7 in the control group; Papaleo 2009 enrolled women with a mean BMI of 26.7 ± 7.5 in the treatment group, and women with a BMI of 26.3 ± 6.8 in the control group; Colazingari 2013 enrolled women who had a BMI less than 28 kg/m².

Further details of inclusion and exclusion criteria are available in the Characteristics of included studies table.

Interventions

Most included trials used myo-inositol as treatment. Comparisons covered inositol (myo-inositol (MI) or D-*chiro*-inositol (DCI)) versus placebo, no treatment, or standard treatment (folic acid < 1 mg); inositol (MI) versus antioxidant (melatonin); MI versus an insulin-sensitising agent (metformin); MI versus an ovulation induction agent (clomiphene citrate); and inositol (MI) versus another inositol (DCI). No trials looked at L-*chiro* inositol.

Duration of treatment ranged from approximately six weeks - 'first day of cycle to embryo transfer' in Pacchiarotti 2015 - to six months - in Raffone 2010.

The comparison 'myo-inositol versus placebo or no treatment/standard treatment (folic acid) as a pre-treatment to IVF' included:

- four trials looking at myo-inositol (MI) (Artini 2013; Ciotta 2011; Lesoine 2016; Papaleo 2009). Lesoine 2016 was the only trial to use placebo as a control. Also included were arms two (MI) and three (standard treatment) of Pacchiarotti 2015 (a three-arm trial) and arms one (DCI) and three (no treatment) of Piomboni 2014 (a three-arm trial); and
- three trials looking at DCI (Brusco 2013; Hoxha 2016; Rosalbino 2012). Hoxha 2016 and Rosalbino 2012 compared different doses of DCI against each other and placebo, and Brusco 2013 looked at MI plus DCI versus no treatment.

For the comparison 'inositol versus antioxidant':

- Pacchiarotti 2015 looked at melatonin; this trial contained three arms - (1) MI plus melatonin, (2) MI, and (3) folic acid. Investigators analysed arms one and two for this comparison and arms two and three for the inositol versus placebo/no treatment comparison.

The comparison 'inositol versus an insulin sensitising agent' included:

- two trials (Piomboni 2014; Raffone 2010). Piomboni 2014 was a three-arm trial that provided (1) DCI, (2) metformin, and (3) no treatment. We included arms one and two here, and arms one and three in the inositol versus placebo/no treatment comparison. Raffone 2010 looked at MI versus metformin.

The comparison 'inositol versus an ovulation induction agent' included:

- one trial that compared MI versus clomiphene citrate (Papaleo 2008).

The comparison 'inositol versus another inositol' included:

- two trials (Colazingari 2013; Unfer 2011). Colazingari 2013 compared MI plus DCI plus folic acid versus DCI, and Unfer 2011 looked at MI versus DCI.

Outcomes

Primary outcomes

Live birth

The primary outcome for this review was live birth. Two trials reported on live birth (Artini 2013; Ciotta 2011). Papaleo 2008 reported on ongoing pregnancy, which we used as a surrogate for live birth. We sent emails and letters to authors of all other included trials to ask whether they had collected data on live birth.

Adverse events

Six trials reported miscarriage (Artini 2013; Ciotta 2011; Pacchiarotti 2015; Papaleo 2008; Papaleo 2009; Unfer 2011). Papaleo 2008, an abstract, did not provide miscarriage data - only a narrative to say there was no difference between groups. Three trials reported multiple pregnancy (Ciotta 2011; Pacchiarotti 2015; Papaleo 2008).

Secondary outcomes

Clinical pregnancy

Seven trials reported on clinical pregnancy (Artini 2013; Brusco 2013; Ciotta 2011; Pacchiarotti 2015; Papaleo 2009; Raffone 2010; Unfer 2011). We tried to contact the authors of all trials that did not report clinical pregnancy rates. Brusco 2013 reported clinical pregnancy but did not separate data for women with PCOS from data for women who were poor responders, so we could not use these data in the meta-analysis. Colazingari 2013 reported in the narrative that investigators measured the effect of MI + DI versus DI alone for the outcome of clinical pregnancy but provided no data and did not respond to emails.

Ovulation rate

Two trials reported on ovulation rate (Papaleo 2008; Raffone 2010).

Gestational diabetes mellitus

We found no studies that looked at gestational diabetes mellitus.

Design

All 13 trials were of parallel-group design. Two trials included five arms and looked at four different doses of D-*chiro*-inositol (DCI) versus placebo (Hoxha 2016; Rosalbino 2012). Pacchiarotti 2015 and Piomboni 2014 each included three arms.

The sample size ranged from 29 women in Lesoine 2016 to 569 women in Pacchiarotti 2015. Only one of the seven trials included in the meta-analysis reported that investigators had performed a sample size calculation (Pacchiarotti 2015).

Funding

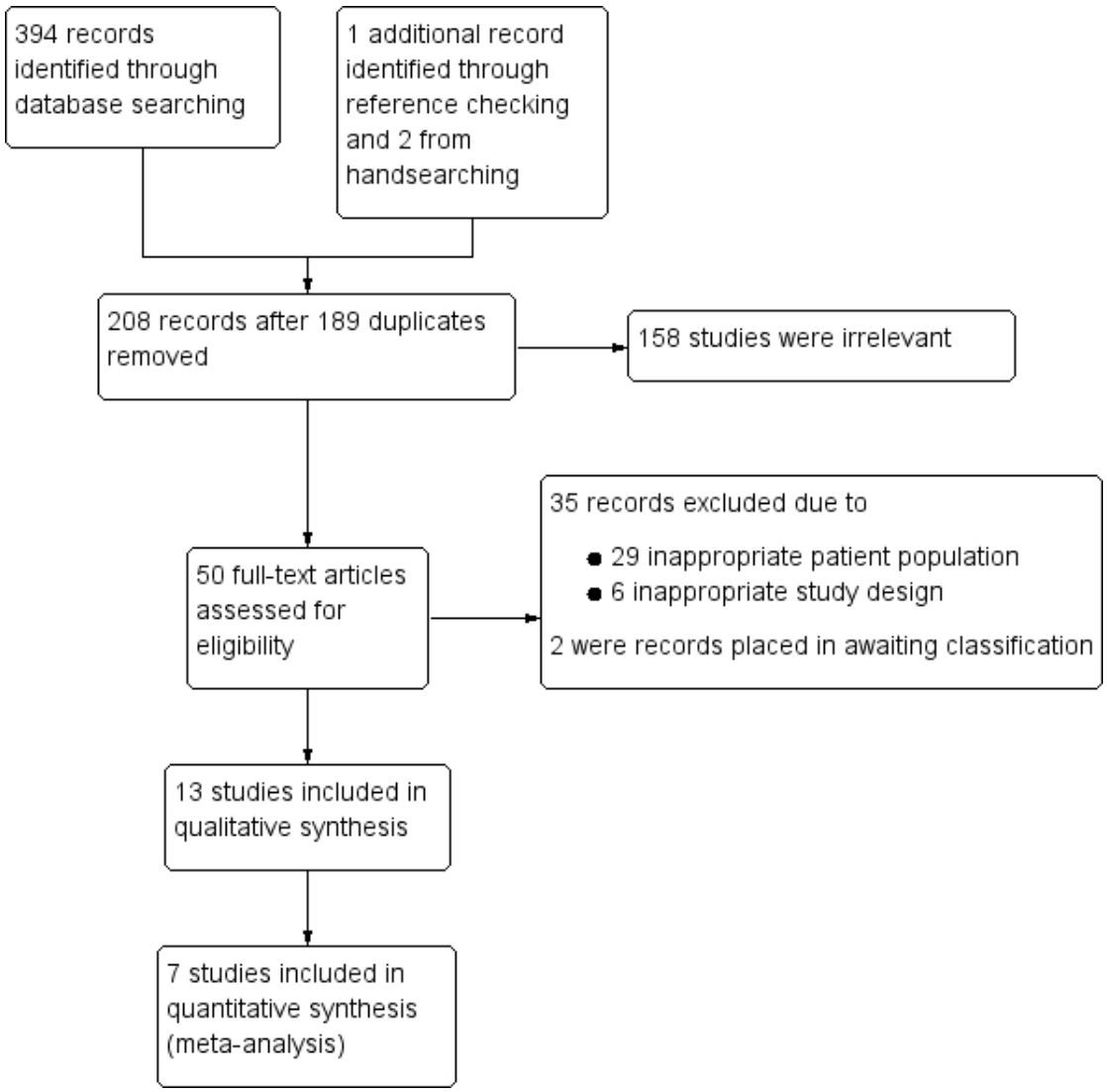
Most trials did not report funding. Papaleo 2009 replied by email that "LoLi Pharma provided the product to the patients for free". Unfer 2011 replied by email that the trial did not receive funding.

Excluded studies

We retrieved the full texts of trials identified as potentially eligible for inclusion (Figure 1). We excluded 35 studies, 29 of these because the population did not meet the review criteria (Agarwal 2015; Benelli 2016; Cappelli 2013; Cheang 2008; Cianci 2015; Ciotta 2012; Ciotta 2012a; Costantino 2009; Don 2012; Formuso 2015; Fruzzetti 2017; Genazzani 2008; Gerli 2003; Gerli 2007; Immediata 2014; Iuorno 2002; Jamilian 2017; LeDonne 2012; Lisi 2012; Moretti 2016; Morgante 2015; Nehra 2017; Nestler 1999; Nestler 2001; Nordio 2012; Orbetzova 2016; Ozay 2016; Pizzo 2014; Tagliaferri 2017). Many of these trials recruited women with PCOS who were not attending a subfertility clinic, and whose main concern was not pregnancy but rather ways to control their symptoms of PCOS. Six trials were not randomised

and therefore used a study design that we could not include (DeLeo 2012; DeLeo 2014; Emekci Ozay 2017; Nazzaro 2011; Papaleo 2007; Wdowiak 2016).

Figure 1. Study flow diagram.



Ongoing trials

We found 11 ongoing trials through searches of trial registries (IRCT2017021432525N2; IRCT2017070234845N1; NCT01514942; NCT01540747; NCT01555190; NCT02221154; NCT02385396; NCT02630485; NCT03059173; NCT03177122; NCT03201601).

Studies awaiting classification

We identified two studies that are awaiting classification (Llaneza 2018; Mahey 2018).

Risk of bias in included studies

See Figure 2 for a summary of risk of bias in individual trials, and see Figure 3 for a summary of each risk of bias item across all included trials. Further information may be found in the risk of bias sections of the Characteristics of included studies.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

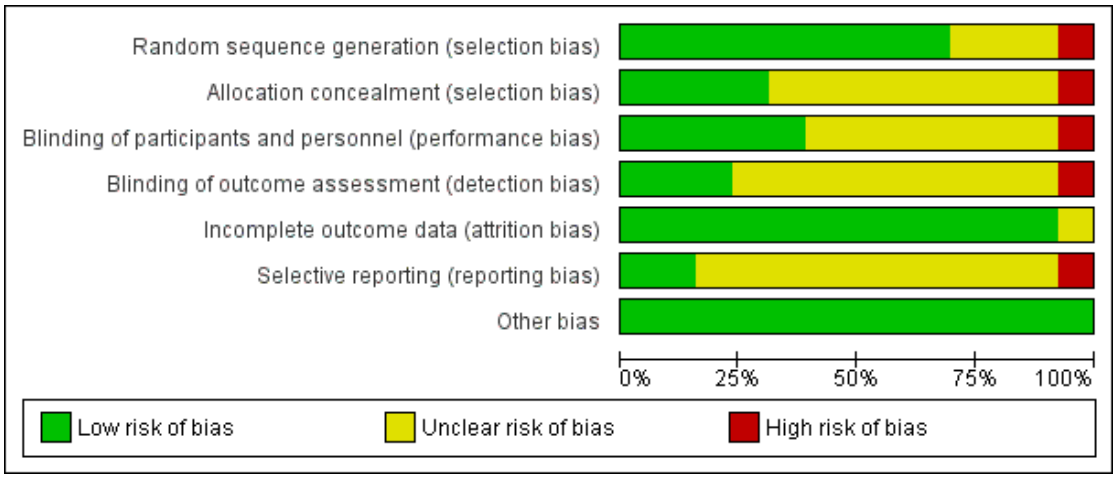
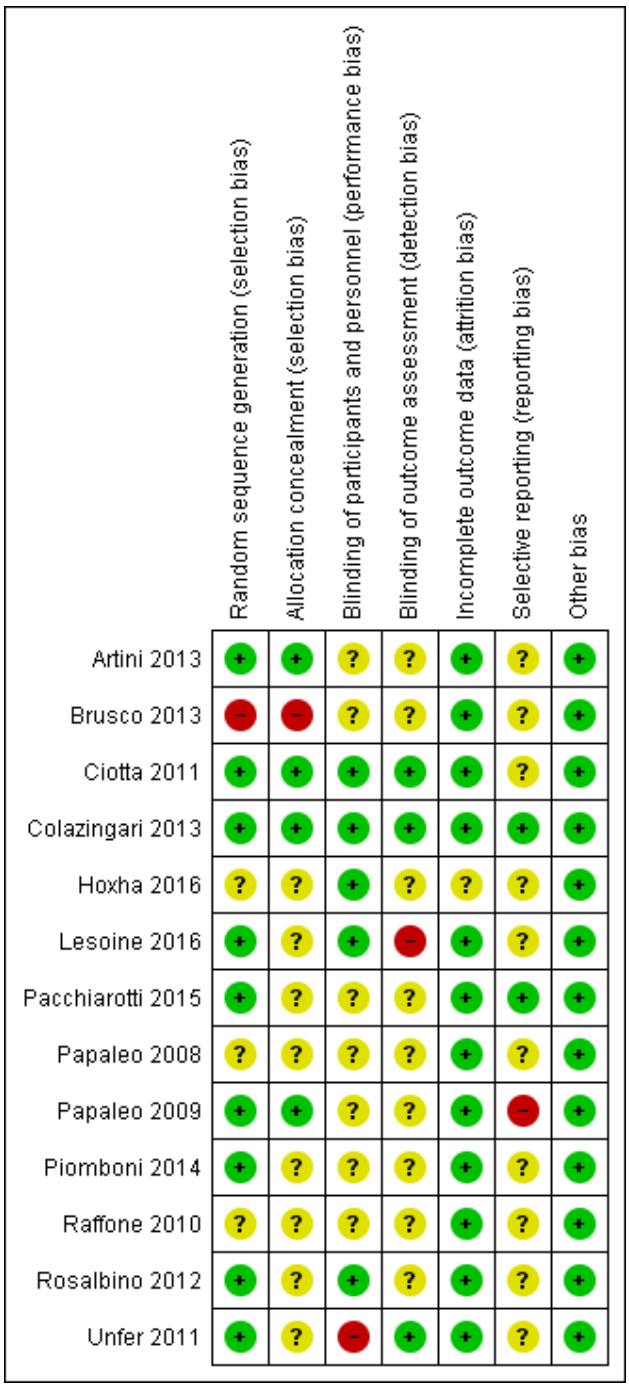


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Sequence generation

All 13 included trials were randomised and used a parallel design. Nine trials had low risk of bias for this domain as methods of randomisation were explained; typically these methods involved computer-generated or random numbers tables (Artini 2013; Ciotta 2011; Colazingari 2013; Lesoine 2016; Pacchiarotti 2015; Papaleo 2009; Piomboni 2014; Rosalbino 2012; Unfer 2011). Three trials simply reported that the women were randomised but did not explain the methods used in the study report nor in follow-up emails (Hoxha 2016; Papaleo 2008; Raffone 2010). Randomisation methods were seen as unclear for risk of bias in these trials. We determined that Brusco 2013 had high risk of bias, as study authors reported that randomisation was done in part by minimisation and in part by closed envelopes, and the number of women in study groups was unequal (i.e. 58 in the treatment group and 91 in the control group).

Allocation

We determined that four trials were at low risk of bias for allocation concealment (Artini 2013; Ciotta 2011; Colazingari 2013; Papaleo 2009). Artini 2013 and Colazingari 2013 used centralisation of the sequence of randomisation, and both Papaleo 2009 and Ciotta 2011 stated in emails that they used a sequentially numbered envelope method. We assigned one trial high risk of bias due to partial randomisation by minimisation and partial randomisation by envelopes (Brusco 2013). We judged that the remaining eight trials were at unclear risk for this domain, as study authors provided no explanation of allocation concealment in study articles or by email correspondence (Hoxha 2016; Lesoine 2016; Pacchiarotti 2015; Papaleo 2008; Piomboni 2014; Raffone 2010; Rosalbino 2012; Unfer 2011).

Blinding

Blinding of participants and personnel (performance bias)

We considered that the blinding status of participants could influence findings for the outcomes of live birth, pregnancy, and adverse effects, as myo-inositol (MI) is easily available, and it would be possible for participants to self-medicate, possibly causing any difference in effect to be underestimated. Therefore if participants were not blinded or the trial was not placebo-controlled, or both, we considered the trial to be at high risk. We considered five trials to be at low risk in this domain (Ciotta 2011; Colazingari 2013; Hoxha 2016; Lesoine 2016; Rosalbino 2012). Ciotta 2011 and Colazingari 2013 were double-blind (participants and personnel). Hoxha 2016, Lesoine 2016, and Rosalbino 2012 were placebo-controlled. Unfer 2011 was assigned high risk after study authors replied in an email that only the outcome assessors were blind. We classified the remaining 10 trials as having unclear risk as study authors provided no explanation (Artini 2013; Brusco 2013; Hoxha 2016; Lesoine 2016; Pacchiarotti 2015; Papaleo 2008; Papaleo 2009; Piomboni 2014; Raffone 2010; Rosalbino 2012).

Blinding of outcome assessors (detection bias)

We classified three trials as having low risk for this domain (Ciotta 2011; Colazingari 2013; Unfer 2011). Unfer 2011 stated that the outcome assessor was the only personnel to be blinded in the trial, and review authors assumed blinding of the outcome assessor for Colazingari 2013, when the study author stated that both participants and research team members were blinded. We classified Lesoine 2016 as high risk because only the scientist carrying out the procedure was blinded. We considered the remainder of the trials to be at unclear risk of bias, as we were unable to obtain the necessary information (Artini 2013; Brusco 2013; Hoxha 2016; Pacchiarotti 2015; Papaleo 2008; Papaleo 2009; Piomboni 2014; Raffone 2010; Rosalbino 2012).

Incomplete outcome data

We classified 12 trials as having low risk of bias for this domain, as researchers accounted for all dropouts and performed an intention-to-treat analysis (Artini 2013; Brusco 2013; Ciotta 2011; Colazingari 2013; Lesoine 2016; Pacchiarotti 2015; Papaleo 2008; Papaleo 2009; Piomboni 2014; Raffone 2010; Rosalbino 2012; Unfer 2011). We deemed that Hoxha 2016 was at unclear risk as the report was a conference abstract that provided only a description of effect - no data.

Selective reporting

We judged that eight trials were at low risk of bias for this domain, as it is clear that all of the studies' pre-specified outcomes had been reported (Artini 2013; Brusco 2013; Ciotta 2011; Colazingari 2013; Pacchiarotti 2015; Papaleo 2008; Raffone 2010; Unfer 2011). We classified four trials as having unclear risk, as study authors provided insufficient information (Hoxha 2016; Lesoine 2016; Piomboni 2014; Rosalbino 2012). We considered Papaleo 2009 to be at high risk, as study authors stated in the paper that live birth was a secondary outcome but provided no live birth data in the results. We emailed the study author, who replied by saying that no live birth data were available.

Other potential sources of bias

We classified all studies as having low risk; no other source of bias is apparent.

Effects of interventions

See: **Summary of findings for the main comparison** Myo-inositol compared to placebo, no/standard treatment as pre-treatment to IVF in women with PCOS; **Summary of findings 2** Myo-inositol compared to antioxidant (melatonin) as pre-treatment to IVF in women with PCOS; **Summary of findings 3** Myo-inositol compared to D-*chiro*-inositol as pre-treatment to IVF in women with PCOS; **Summary of findings 4** Myo-inositol compared to an insulin-sensitising agent (metformin) in women with PCOS undergoing ovulation induction; **Summary of findings 5** Myo-inositol compared to an ovulation induction agent (clomiphene) in women with PCOS undergoing ovulation induction

1. Myo-inositol versus placebo, no treatment, or standard treatment as pre-treatment to IVF for women with PCOS

All trials included in the following meta-analyses enrolled women who were taking myo-inositol (MI) versus standard treatment (folic acid) and were undergoing in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI), so subgrouping on type of control, type of inositol, type of comparator, or IVF/ICSI was not appropriate.

Primary outcomes

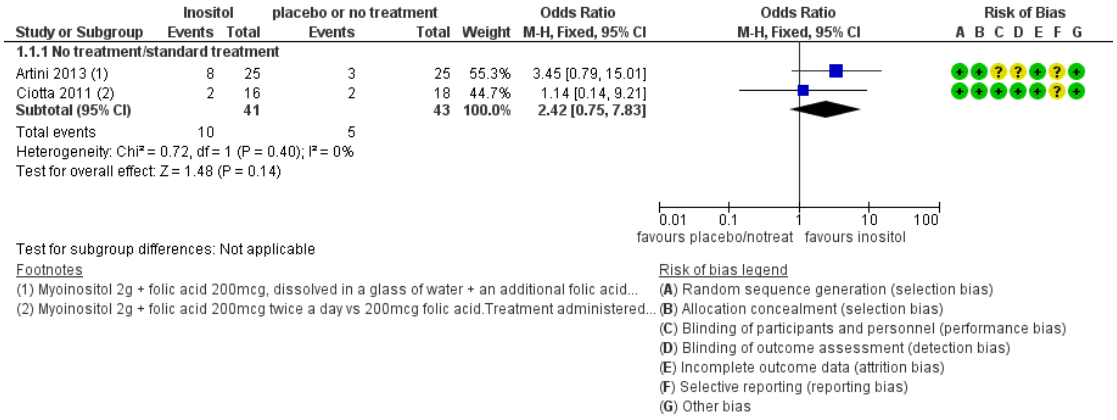
1.1 Live birth

See Analysis 1.1.

1.1.1 No treatment/standard treatment

We are uncertain whether MI improves live birth rates when compared to standard treatment (folic acid) (odds ratio (OR) 2.42, 95% confidence interval (CI) 0.75 to 7.83; P = 0.14; 2 RCTs; 84 women; I^2 = 0%; very low-quality evidence) (Figure 4). This suggests that among subfertile women with PCOS, using inositol as pre-treatment to IVF with an expected live birth rate of 12% would lead to a rate among women using inositol between 9% and 51% (Summary of findings for the main comparison). The wide confidence intervals indicate that we cannot be certain of any increase, small reduction, or no difference in live birth rates for women taking MI or no treatment.

Figure 4. Forest plot of comparison: 1 Inositol versus placebo, no treatment/standard treatment, outcome: 1.1 Live birth.



This result was based on only two trials. We performed a sensitivity analysis on studies that reported live birth and clinical pregnancy, and on those that failed to report the primary outcome of live birth but did report on clinical pregnancy; we found that evidence of a difference between these two subgroups was insufficient, as evidenced by overlapping confidence intervals of effect estimates of the two subgroups (see sensitivity analysis of clinical pregnancy 1.4 for a graphical display of this sensitivity analysis).

1.2 Adverse events

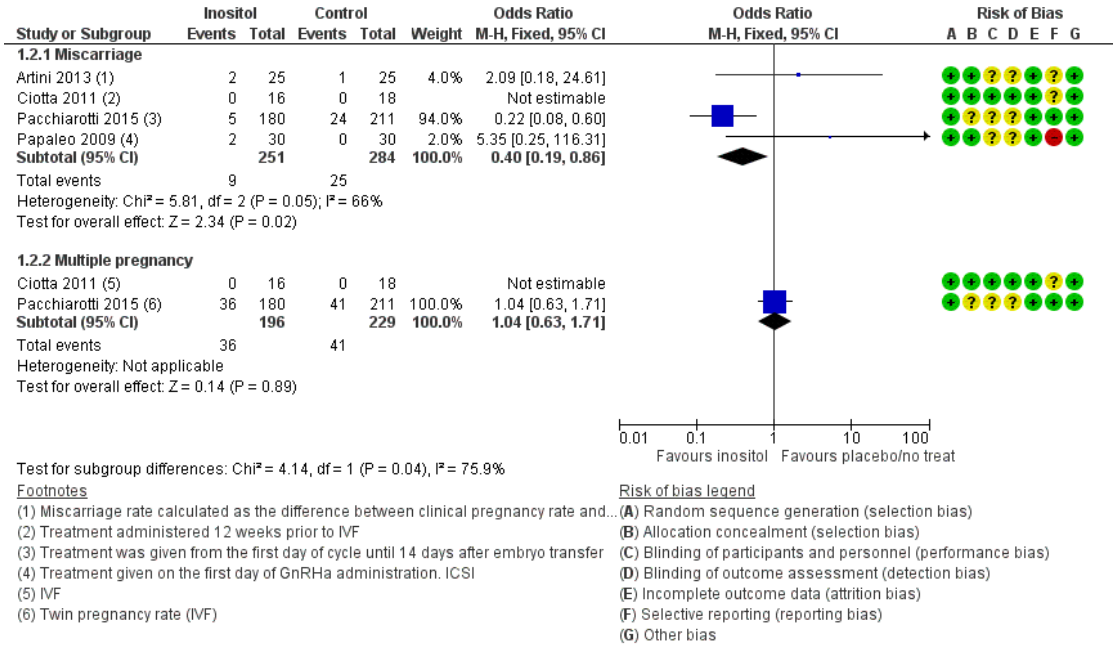
See Analysis 1.2.

We subgrouped adverse event data according to types of events that occurred, as reported by the included trials. These included miscarriage and multiple pregnancy.

1.2.1 Miscarriage

We are uncertain whether MI may be associated with a decrease in miscarriage rates when compared to standard treatment (OR 0.40, 95% CI 0.19 to 0.86; P = 0.02; 4 RCTs; 535 women; I^2 = 66%; very low-quality evidence); this suggests that among subfertile women with PCOS with an expected miscarriage rate of 9%, the rate among women using MI would be between 2% and 8% (Figure 5) (Summary of findings for the main comparison). Pacchiarotti 2015 reported an unusually large number of miscarriages in the control group compared to the myo-inositol group and was responsible for 94% of the weight in the meta-analysis; heterogeneity in this study was very high.

Figure 5. Forest plot of comparison: 1 Inositol versus placebo, no treatment, outcome: 1.2 Adverse event.



Sensitivity analyses

We restricted eligibility to studies at low risk of bias in the domains of randomisation and allocation concealment. We removed Pacchiarotti 2015 from the analysis, as we had classified it as having 'unclear' risk for allocation concealment. When we removed this trial from the analysis, we found no conclusive evidence of a difference in effect between myo-inositol and standard treatment groups and no heterogeneity (OR 3.17, 95% CI 0.48 to 20.97; P = 0.23; 3 RCTs; 144 women; I^2 = 0%).

Ciotta 2011 reported no miscarriages in either treatment or standard care groups.

1.2.2 Multiple pregnancy

Low-quality evidence suggests that MI may make little or no difference in multiple pregnancy rates when compared with standard treatment (OR 1.04, 95% CI 0.63 to 1.71; P = 0.89; 2 RCTs; 425 women) (Figure 5). This suggests that among subfertile women with PCOS with an expected multiple pregnancy rate of 18%, the rate among women using inositol would be between 12% and 27%. Only two trials in this comparison reported on multiple pregnancy (Ciotta 2011; Pacchiarotti 2015); Ciotta 2011 reported no events in either intervention or control arms (Summary of findings for the main comparison).

Sensitivity analyses

We were unable to perform a sensitivity analysis on studies with unclear risk of bias in the multiple pregnancy analysis, as we had included only two trials here.

Secondary outcomes

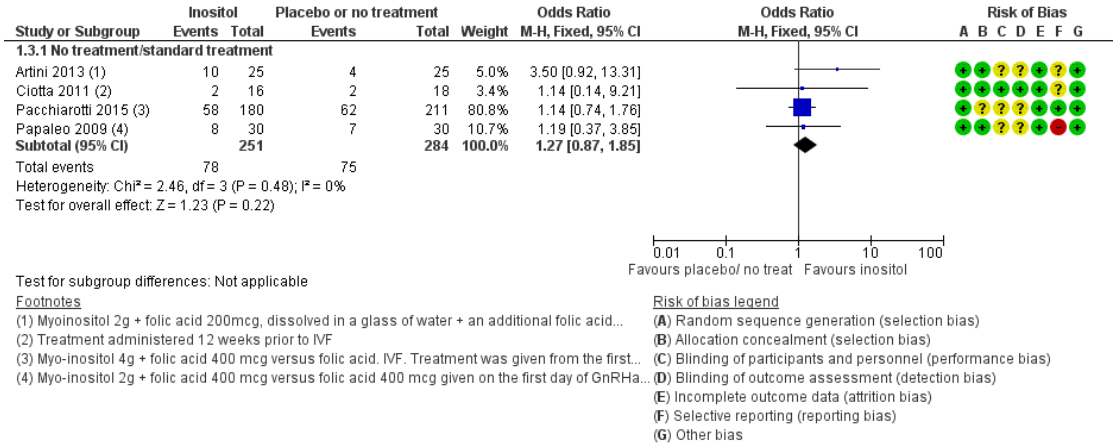
1.3 Clinical pregnancy

See Analysis 1.3.

1.3.1 No treatment/standard treatment

We are uncertain whether MI may be associated with an increased clinical pregnancy rate when compared to standard treatment (OR 1.27, 95% CI 0.87 to 1.85; P = 0.22; 4 RCTs; 535 women; I^2 = 0%; very low-quality evidence) (Figure 6). This suggests that among subfertile women with PCOS with an expected clinical pregnancy rate of 26%, the rate among women using MI would be between 24% and 40%.(Summary of findings for the main comparison). The wide confidence intervals indicate that we cannot be certain of any increase, small reduction, or no difference in clinical pregnancy rates for women taking MI or no treatment.

Figure 6. Forest plot of comparison: 1 Myo-inositol versus placebo, no/standard treatment in women undergoing IVF treatment, outcome: 1.3 Clinical pregnancy.



Sensitivity analyses for studies with unclear or high risk of bias

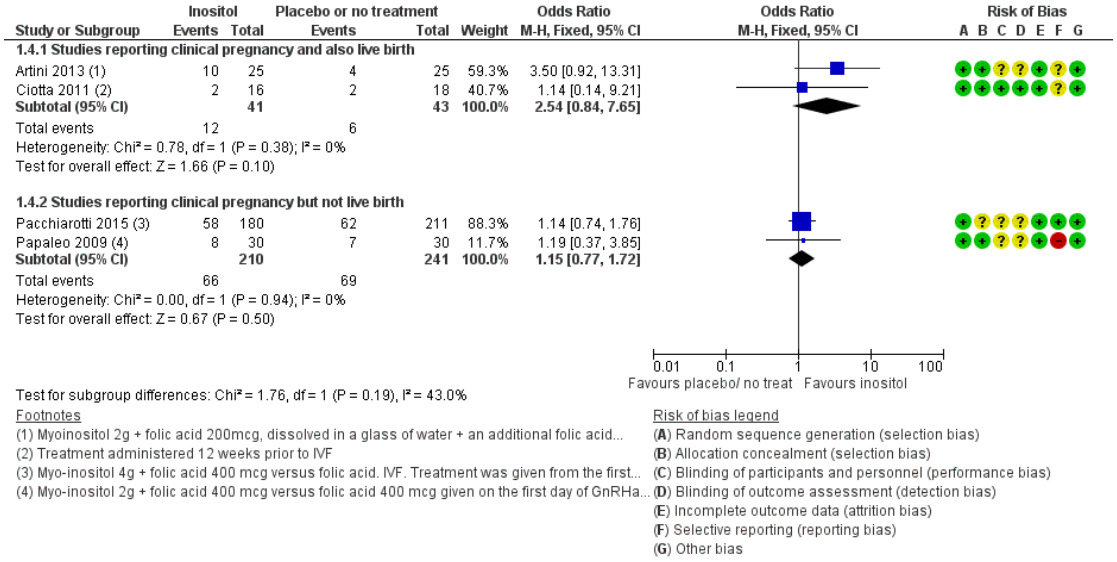
We removed Pacchiarotti 2015 from the analysis, as we had classified this study as having 'unclear' risk of bias for the allocation concealment domain. On removal from the analysis, we noted no difference in effect between inositol and no treatment groups (OR 1.79, 95% CI 0.81 to 3.96; P = 0.15; 3 RCTs; 144 women; I^2 = 0%).

Brusco 2013 provided data for clinical pregnancy, but we could not separate the combined population of women with PCOS and women with poor response to stimulation. This trial found an association in increased clinical pregnancy rate between use of MI plus folic acid versus folic acid alone (standard treatment).

Sensitivity analysis on clinical pregnancy (Analysis 1.4)

As reported for the live birth outcome, the clinical pregnancy result for Artini 2013 and Ciotta 2011 (studies that reported both live birth and clinical pregnancy) was OR 2.54; comparison of this with the two studies reporting only clinical pregnancy (i.e. not live birth) revealed that the OR was 1.15 (Figure 7) (Pacchiarotti 2015; Papaleo 2009), and data show no difference between these two subgroups, as evidenced by overlapping confidence intervals of effect estimates.

Figure 7. Forest plot of comparison: 1 Myo-inositol versus placebo, no/standard treatment as pre-treatment to IVF in women with PCOS, outcome: 1.4 Sensitivity analysis on clinical pregnancy.



These studies did not report the outcomes of ovulation rate and gestational diabetes mellitus.

2. Myo-inositol versus antioxidant (melatonin) as pre-treatment to IVF for women with PCOS

Primary outcomes

We included only Pacchiarotti 2015 in this comparison, and study authors did not report live birth.

2.1 Adverse event

See Analysis 2.1.

2.1.1 Miscarriage

Only Pacchiarotti 2015 reported on miscarriage for this comparison. We are uncertain whether inositol reduces or increases miscarriage rates when MI + folic acid is compared to melatonin (OR 0.70, 95% CI 0.22 to 2.24; P = 0.55; 358 women; very low-quality evidence) (Summary of findings 2).

2.1.2 Multiple pregnancy

Pacchiarotti 2015 reported on multiple pregnancy for this comparison. We are uncertain whether inositol reduces or increases multiple pregnancy when MI + folic acid is compared to melatonin (OR 0.95, 95% CI 0.57 to 1.59; P = 0.85; 358 women; very low-quality evidence) (Summary of findings 2).

Secondary outcomes

2.2 Clinical pregnancy

See Analysis 2.2.

Pacchiarotti 2015 reported on clinical pregnancy for this comparison. We are uncertain whether inositol increases clinical pregnancy rates when MI + folic acid is compared to melatonin (OR 0.83, 95% CI 0.53 to 1.28; P = 0.39; 358 women; very low-quality evidence) (Summary of findings 2).

Pacchiarotti 2015 did not report on ovulation rates nor on gestational diabetes mellitus.

3. Myo-inositol versus D-chiro-inositol as pre-treatment to IVF for women with PCOS

Primary outcomes

Unfer 2011 did not report on live birth.

3.1 Adverse event

See Analysis 3.1.

3.1.1 Miscarriage

Unfer 2011 reported on miscarriage rate for this comparison. We were uncertain whether inositol reduced the miscarriage rate when MI was compared to D-*chiro*-inositol (DCI) (OR 1.30, 95% CI 0.27 to 6.20; P = 0.74; 84 women; very low-quality evidence) (Summary of findings 3).
This trial did not report on multiple pregnancy.

Secondary outcome

3.2 Clinical pregnancy

See Analysis 3.2.
Unfer 2011 reported on clinical pregnancy rate for this comparison. We were uncertain whether inositol increased clinical pregnancy when MI was compared to DCI (OR 3.86, 95% CI 1.25 to 11.89; P = 0.02; 84 women; very low-quality evidence) (Summary of findings 3). Colazingari 2013 reported an improved clinical pregnancy rate in the MI + DI group when compared to the DI group. However, study authors provided no data for this outcome.
This trial did not report on ovulation rate nor on gestational diabetes mellitus.

4. Myo-inositol versus an insulin-sensitising agent (metformin) for women with PCOS undergoing ovulation induction

Primary outcomes

This study did not report on live birth.
This trial did not report on miscarriage or multiple pregnancy rate nor on any other adverse events.

Secondary outcomes

4.1 Clinical pregnancy

Raffone 2010 reported on clinical pregnancy for this comparison. We are uncertain whether MI improves clinical pregnancy rate when MI + folic acid is compared to metformin (OR 1.91, 95% CI 0.81 to 4.49; P = 0.14; 120 women; very low-quality evidence) (Summary of findings 4).

4.2 Ovulation

Raffone 2010 reported on ovulation rate for this comparison. We are uncertain whether MI improves ovulation rate when MI + folic acid is compared to metformin (OR 1.86, 95% CI 0.89 to 3.87; P = 0.10; 120 women; very low-quality evidence) (Summary of findings 4).
This study did not report on gestational diabetes mellitus.

5. Myo-inositol versus an ovulation induction agent (clomiphene) for women with PCOS undergoing ovulation induction

Primary outcomes

5.1 Live birth

See Analysis 5.1.
Papaleo 2008 reported on live birth with ovulation induction for this comparison. We are uncertain whether MI improved live birth rate when MI + folic acid was compared to clomiphene citrate (OR 1.27, 95% CI 0.48 to 3.40; P = 0.63; 75 women; very low-quality evidence) (Summary of findings 5).

5.2 Adverse events

This trial did not report on miscarriage rate.
See Analysis 5.2.

5.2.1 Multiple pregnancy

Papaleo 2008 reported on multiple pregnancy for this comparison. We are uncertain whether inositol decreased multiple pregnancy rates when MI + folic acid was compared to clomiphene citrate (OR 0.21, 95% CI 0.01 to 4.43; P = 0.31; 75 women; very low-quality evidence) (Summary of findings 5).

5.2.2 Miscarriage

The conference abstract Papaleo 2008 did not provide miscarriage data but provided a narrative to say there was no difference between groups.

Secondary outcomes

This trial did not report on clinical pregnancy rate.

5.3 Ovulation rate

See Analysis 5.3.

Papaleo 2008 reported on ovulation rate for this comparison. We are uncertain whether inositol improved ovulation rates when MI + folic acid was compared to clomiphene citrate (OR 0.59, 95% CI 0.20 to 1.68; P = 0.32; 75 women; very low-quality evidence) (Summary of findings 5).

This trial did not report on gestational diabetes.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Myo-inositol compared to antioxidant in women undergoing IVF treatment for subfertile women with polycystic ovary syndrome

Patient or population: subfertile women with polycystic ovary syndrome
Setting: clinic
Intervention: myo-inositol
Comparison: antioxidant (melatonin) in women undergoing IVF treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with antioxidant in women undergoing IVF treatment	Risk with myo-inositol			
Live birth	Not reported in this comparison				
Adverse event - miscarriage	Study population		OR 0.70 (0.22 to 2.24)	358 (1 RCT)	⊕◯◯◯ VERY LOW[a,b]
	39 per 1000	28 per 1000 (9 to 84)			
Adverse event - multiple pregnancy	Study population		OR 0.95 (0.57 to 1.59)	358 (1 RCT)	⊕◯◯◯ VERY LOW[a,b]
	208 per 1000	200 per 1000 (130 to 294)			
Clinical pregnancy	Study population		OR 0.83 (0.53 to 1.28)	358 (1 RCT)	⊕◯◯◯ VERY LOW[a,b]
	365 per 1000	323 per 1000 (234 to 424)			
Ovulation	Not reported in this comparison				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; IVF: in vitro fertilisation; OR: odds ratio; PCOS: polycystic ovary syndrome; RCT: randomised controlled trial

GRADE Working Group grades of evidence.
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Downgraded two levels due to risk of bias, as domains in allocation concealment and blinding were unclear.
[b] Downgraded one level due to imprecision, as the confidence intervals overlap the line of no effect, and this is a single trial.

Myo-inositol compared to D-*chiro*-inositol in women undergoing IVF for subfertile women with polycystic ovary syndrome

Patient or population: subfertile women with polycystic ovary syndrome
Setting: clinic
Intervention: myo-inositol
Comparison: D-*chiro*-inositol in women undergoing IVF

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with D-*chiro*-inositol in women undergoing IVF	Risk with myo-inositol			
Live birth	Not reported in this comparison				
Adverse event - miscarriage	Study population		OR 1.30 (0.27 to 6.20)	84 (1 RCT)	⊕◯◯◯ VERY LOW[a,b]
	73 per 1000	93 per 1000 (21 to 329)			
Adverse event - multiple pregnancy	Not reported in this comparison				
Clinical pregnancy	Study population		OR 3.86 (1.25 to 11.89)	84 (1 RCT)	⊕◯◯◯ VERY LOW[a,b]
	122 per 1000	349 per 1000 (148 to 623)			
Ovulation	Not reported in this comparison				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; IVF: in vitro fertilisation; OR: odds ratio; PCOS: polycystic ovary syndrome; RCT: randomised controlled trial

GRADE Working Group grades of evidence.
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Downgraded two levels due to risk of bias, as risk for allocation concealment was unclear and risk for blinding of participants was high, as only the outcome assessor was blinded.
[b] Downgraded one level due to imprecision, as a single study

Myo-inositol compared to an insulin-sensitising agent in women undergoing ovulation induction for subfertile women with polycystic ovary syndrome

Patient or population: subfertile women with polycystic ovary syndrome
Setting: clinic
Intervention: myo-inositol
Comparison: insulin-sensitising agent for women undergoing ovulation induction

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with an insulin-sensitising agent in women undergoing ovulation induction	Risk with myo-inositol			
Live birth	Not reported in this comparison				
Adverse events	Not reported in this comparison				
Clinical pregnancy	Study population		OR 1.91 (0.81 to 4.49)	120 (1 RCT)	⊕◯◯◯ VERY LOW[a,b]
	183 per 1000	300 per 1000 (154 to 502)			
Ovulation	Study population		OR 1.86 (0.89 to 3.87)	120 (1 RCT)	⊕◯◯◯ VERY LOW[a,b]
	500 per 1000	650 per 1000 (471 to 795)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; OR: odds ratio; PCOS: polycystic ovary syndrome; RCT: randomised controlled trial

GRADE Working Group grades of evidence.
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]Downgraded two levels due to unclear risk of bias in the domains of sequence generation, allocation concealment, and blinding.
[b]Downgraded one level due to imprecision, as it is only one study.

Myo-inositol compared to an ovulation induction agent in women undergoing ovulation induction for subfertile women with polycystic ovary syndrome

Patient or population: subfertile women with polycystic ovary syndrome
Setting: clinic
Intervention: myo-inositol
Comparison: an ovulation induction agent in women undergoing ovulation induction

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Risk with an ovulation induction agent in women undergoing ovulation induction	Risk with myo-inositol			
Live birth	Study population		OR 1.27 (0.48 to 3.40)	75 (1 RCT)	⊕◯◯◯ VERY LOW[a,b]
	282 per 1000	333 per 1000 (159 to 572)			
Adverse event - miscarriage	Not reported in this comparison				
Adverse event - multiple pregnancy	Study population		OR 0.21 (0.01 to 4.43)	75 (1 RCT)	⊕◯◯◯ VERY LOW[a,b]
	51 per 1000	11 per 1000 (1 to 193)			
Clinical pregnancy	Not reported in this comparison				
Ovulation rate	Study population		OR 0.59 (0.20 to 1.68)	75 (1 RCT)	⊕◯◯◯ VERY LOW[a,b]
	795 per 1000	696 per 1000 (437 to 867)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; OR: odds ratio; PCOS: polycystic ovary syndrome; RCT: randomised controlled trial

GRADE Working Group grades of evidence.
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a] Downgraded two levels due to unclear risk of bias in the domains of sequence generation, allocation concealment, and blinding.
[b] Downgraded one level due to imprecision, as it is only one study.

DISCUSSION

Summary of main results

Effectiveness of myo-inositol versus no treatment or standard treatment (folic acid) in women undergoing pre-treatment to in vitro fertilisation (IVF)

We are uncertain whether myo-inositol (MI) improves the live birth rate for women with polycystic ovary syndrome (PCOS) hoping to have a baby when compared to standard treatment. The quality of the evidence is very low. Only two trials with a total of 84 women reported on live birth and provided wide confidence intervals (Summary of findings for the main comparison). We could not perform subgroup analyses, in accord with our protocol, as all trials in this meta-analysis enrolled women taking MI versus standard treatment, so subgrouping on type of inositol or type of comparator was inappropriate. Sensitivity analysis for the live birth outcome was not possible, as we included only two trials in this meta-analysis.

We are uncertain whether MI may be associated with a decrease in miscarriage rates when compared to standard treatment; evidence was of very low quality (Summary of findings for the main comparison), as only four trials with a total of 535 women reported on this outcome; one trial reported an unusually high number of miscarriages in the control arm and carried 93% of the weight in the meta-analysis, so heterogeneity was very high (I^2 = 66% with a fixed-effect model). We performed a sensitivity analysis while excluding trials with unclear risk of bias for sequence generation and allocation concealment; this sensitivity analysis provided no conclusive evidence of a difference in miscarriage rates between MI and standard treatment and showed decreased heterogeneity (I^2 = 0% with a fixed-effect model).

Low-quality evidence suggests that MI may make little or no difference in multiple pregnancy rates when compared with standard treatment (Summary of findings for the main comparison). Only two trials with 425 women reported on multiple pregnancy for this comparison.

We are uncertain whether MI may be associated with an increase in clinical pregnancy rate when compared to standard treatment (very low-quality evidence) (Summary of findings for the main comparison). Only four trials including 535 women reported on this outcome. We performed a sensitivity analysis while excluding two trials with an unclear rating for allocation concealment, and there remained no association between use of MI and clinical pregnancy when compared to no treatment/standard treatment.

Effectiveness of myo-inositol versus an antioxidant (melatonin) as pre-treatment to IVF for women with PCOS

Only one trial reported on myo-inositol (MI) versus melatonin. Very low-quality evidence shows that we are uncertain of an association between MI and outcomes of miscarriage, multiple pregnancy, and clinical pregnancy when compared with melatonin (Summary of findings 2). This trial did not report the outcome of live birth.

Effectiveness of myo-inositol compared to another type of inositol (D-chiro-inositol) as pre-treatment to IVF for women with PCOS

Only one trial reported on myo-inositol (MI) versus D-*chiro*-inositol (DCI). Very low-quality evidence suggests that we are uncertain of an association between MI and outcomes of miscarriage and clinical pregnancy rates when compared to DCI (Summary of findings 3). This trial did not report the outcomes of live birth and multiple pregnancy.

Effectiveness of myo-inositol compared to an insulin-sensitising agent (metformin) for women with PCOS undergoing ovulation induction

Only one trial reported on myo-inositol (MI) versus metformin. Very low-quality evidence suggests that we are uncertain of an association between MI and outcomes of clinical pregnancy or ovulation rates when compared with melatonin (Summary of findings 4). This trial did not report the outcomes of live birth, adverse events such as miscarriage and multiple pregnancy, and ovulation rates.

Effectiveness of myo-inositol compared to an ovulation induction agent for women with PCOS undergoing ovulation induction

Only one trial reported on myo-inositol (MI) versus clomiphene citrate. Very low-quality evidence suggests that we are uncertain of an association between MI and outcomes of live birth, multiple pregnancy, and ovulation rates when compared to clomiphene citrate (Summary of findings 5). This trial did not report the outcomes of miscarriage and clinical pregnancy.

Overall completeness and applicability of evidence

Of the 13 trials included in this review, we could include only seven in the quantitative analysis, and of these, only three reported on live birth or ongoing pregnancy, and seven reported on clinical pregnancy - six of which we were able to include in the meta-analysis. Trials did not clearly report adverse events; only five trials provided data on miscarriage, and only two reported multiple pregnancy. Only two trials reported ovulation rate, and none of the included trials reported on the outcome of gestational diabetes mellitus. None of the trials in the IVF pre-treatment group nor in

the ovulation induction group reported on side effects related to myo-inositol.

We tried to assess whether inositol might have a beneficial effect on the outcomes of interest in this review compared to placebo, other antioxidants, other types of inositols, insulin-sensitising agents, and ovulation induction agents, but we found no trials comparing inositol versus placebo, and we could include only one trial for each of the other comparisons, so meta-analysis was not possible. We were able to include only two trials looking at myo-inositol and ovulation induction.

Quality of the evidence

The quality of evidence according to the 'Summary of findings tables' (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5) ranged from 'low' to 'very low'. The overall quality of evidence was limited by serious risks of bias associated with poor reporting of methods, indirectness, imprecision, and inconsistency, leading to downgrading of the evidence. Risk of bias within the evidence was moderately high (Figure 2; Figure 3 Characteristics of included studies). Not all trials described their sequence generation or allocation concealment methods, and most trials randomly assigned only small numbers of women.

Heterogeneity was low in most of the analyses when inositol was compared with standard treatment, with an I^2 value of 0% in the live birth analysis; however in the miscarriage analysis, heterogeneity was high, with an I^2 value of 66%. None of the included trials used a placebo control in the inositol versus placebo comparison nor in the no treatment/standard treatment comparison; all trials used a standard treatment control, thus possibly overestimating the effect of inositol.

Potential biases in the review process

We believe that we identified all relevant studies. The only known potential bias in this review may have been introduced by the addition of a sensitivity analysis for miscarriage, in addition to the proposed analysis on live birth and clinical pregnancy. We did not do this as a reaction to the included trials, but because the protocol had failed to report the option of sensitivity analysis for adverse events, and these events (such as miscarriage) were primary outcomes (Differences between protocol and review).

Agreements and disagreements with other studies or reviews

The results of our review are consistent with those of other published reviews. Mendoza 2017 (IVF pre-treatment) and Pundir 2018 (ovulation induction) also concluded that no firm evidence is available to support the use of inositol for subfertile women with PCOS in terms of clinical pregnancy. These systematic reviews did not report live births or adverse events. Pundir 2018 did find an association between myo-inositol (MI) and increased ovulation rates, but we did not include these trials in our review, as they did not meet the inclusion criteria for the review population in that these women were not intending to become pregnant. Another systematic review - Arentz 2017 - looked at various nutritional supplements for both populations given pre-treatment for IVF and ovulation induction and found that pregnancy rates were higher in the inositol group; it is unclear whether these were biochemical or clinical pregnancies, and the meta-analysis of only three trials included two that had been excluded from this systematic review for the reason that only a small percentage of the total population wanted to achieve pregnancy (Gerli 2003; Gerli 2007). Another Cochrane Review - Morley 2017 - looked at the insulin-sensitising agent, D-*chiro*-inositol (DCI) for ovulation induction in women with PCOS and concluded that DCI may improve ovulation rates; however this review also included women who were not necessarily wanting to become pregnant, and therefore we did not include these two studies in the present review. Neither of these systematic reviews included gestational diabetes mellitus as an outcome. Authors of these four systematic reviews - Arentz 2017, Mendoza 2017, Morley 2017, and Pundir 2018 - all agree on the need for further investigation via better-quality placebo-controlled randomised trials with larger populations to confirm the efficacy and safety of these supplements.

AUTHORS' CONCLUSIONS

Implications for practice

Based upon very low-quality evidence, we are uncertain whether MI improves live birth rate or clinical pregnancy rate for subfertile women with PCOS undergoing IVF pre-treatment by taking MI versus standard treatment. We are also uncertain whether MI decreases miscarriage rates or multiple pregnancy rates for these same women taking MI compared to standard treatment. No pooled evidence is available for the use of MI compared to placebo, another antioxidant, insulin-sensitising agents, ovulation induction agents, or another type of inositol for women with PCOS undergoing pre-treatment for IVF. Also, no pooled evidence is available on the use of MI among women undergoing ovulation induction.

Implications for research

We need trialists to further investigate this question using better-quality placebo-controlled blinded randomised trials with adequate power to assess the clinically relevant outcomes of live birth, adverse events, and clinical pregnancy and ovulation rates, to determine the efficacy and safety of inositol. We need this research to encompass both women with PCOS who are undergo-

ing pre-treatment for IVF and women with PCOS who are undergoing ovulation induction. We also need large, good quality randomised controlled trials to compare inositol versus another antioxidant, another type of inositol (D-*chiro*-inositol), insulin-sensitising agents, and ovulation induction agents.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Artini 2013

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	Women were undergoing IVF (N = 50) **Baseline characteristics:** Age (mean 35 to 36 years), duration of infertility, and BMI (mean < 26) were similar for both groups **Inclusion criteria:** overweight with PCOS; presence of micro-polycystic ovaries at ultrasound; mild to severe hirsutism and/or acne; oligomenorrhoea (menstrual cycle > 35 days) or amenorrhoea; absence of enzymatic adrenal deficiency and/or other endocrine disease; normal PRL (prolactin) levels (range 5 to 25 ng/mL); no hormonal treatment for at least 6 months before the study **Exclusion criteria:** women who did not meet the inclusion criteria **Pre-treatment:** baseline characteristics given in Table 1, page 377; no significant differences in terms of age, duration of infertility, or BMI **Outcomes reported in the paper:** plasma LH, FSH, PRL, E2, 17OHP, A, T, glucose, insulin, C-peptide concentrations, BMI, HOMA index, and glucose-to-insulin ratio, and restoration of menstrual cycle in all amenorrhoeic and oligomenorrhoeic participants
Interventions	**Intervention:** Inositol • *2* g myo-inositol + 200 mcg folic acid, dissolved in a glass of water + an additional 200 mcg folic acid (oral) (n = 25) **Control:** • 400 mcg folic acid (oral) (n = 25)
Outcomes	Clinical pregnancy • **Outcome type:** dichotomous outcome • **Reporting:** fully reported • **Direction:** higher is better • **Data value:** change from baseline • **Notes:** hCG at day 15, USS at 5 to 6 weeks Live birth • **Outcome type:** dichotomous outcome • **Direction:** higher is better
Identification	**Sponsorship source:** none reported in the paper **Country:** Italy **Setting:** Department of Reproductive Medicine and Child Development, Division of Obstetrics and Gynaecology, University of Pisa, Italy **Comments:** this study was performed for 12 months (April 2008 to April 2009); treatment was provided over 12 weeks before IVF **Author's name:** Paolo Giovanni Artini **Institution:** University of Pisa

Artini 2013 (*Continued*)

	Email: paolo.artini@med.unipi.it **Address:** University of Pisa, Via Roma 56, 56126 Pisa, Italy; tel: 39.050.554104; fax: 39.050.551293
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer generated randomisation list"
Allocation concealment (selection bias)	Low risk	Quote: "Computer generated randomisation list" "Sealed numbered envelopes were given to the ART centre nurse coordinator who assigned patients to study arms"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "No response from author, nothing described"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome; all loses accounted for and ITT used
Selective reporting (reporting bias)	Unclear risk	Live birth and clinical pregnancy reported; however no trial registration number or protocol found
Other bias	Low risk	No other bias noted

Brusco 2013

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	Women were undergoing ICSI with PCOS plus poor responders (N = 149) **Baseline characteristics:** "The two groups were homogeneous within the parameters of inclusion adopted for the study" However, large number differences were evident between intervention (n = 58) and control groups (n = 91) **Inclusion criteria:** "The recruitment criteria include being under 40 years old, at least one previous failed attempt with ICSI with low-quality oocyte recovery, diagnosis of

	PCOS (i.e., with oligomenorrhoea, hyperandrogenism and pelvic ultrasonographic appearance characterized by multiple anechoic areas), diagnosis of 'poor responders' (i.e. with poor ovarian response to hormonal stimulation, an age greater than 37 years and the need for high doses of FSH stimulation in previous cycles). Only ICSI treatments arrived to the transfer of embryos in the uterus (Embryo-Transfer) and carried out on Day +2/3 are included in the study" **Exclusion criteria:** "Patients with a partner with a diagnosis of severe male infertility such as crypto-zoospermia (i.e. retrieval of sperm in the semen after centrifugation) and azoospermia (i.e. eventual retrieval of sperm from the testicle or epididymis)" were excluded from the study **Other outcomes provided in the paper:** average number of oocytes retrieved, quality of oocytes retrieved, number of embryos transferred, quality of embryos transferred, biochemical pregnancy **Treatment duration:** women received treatment for 3 months before ICSI and for only 1 cycle
Interventions	**Intervention:** Inositol • 2000 mg/d of myo-inositol, D-*chiro*-inositol 400 mg/d, and folic acid 400 mg/d (n = 58) **Control:** • Folic acid 400 mg/d (n = 91)
Outcomes	Clinical pregnancy • **Outcome type:** dichotomous outcome • **Reporting:** fully reported • **Unit of measure:** per woman • **Direction:** higher is better • **Data value:** endpoint
Identification	**Sponsorship source:** unknown **Country:** Italy **Setting:** Perugia Hospital, Italy **Comments:** "A total of 149 patients undergoing ICSI cycles were included in the study in the 'Servizio di Diagnosi e Cura della Riproduzione Umana', Struttura Complessa di Ostetricia e Ginecologia, Azienda Ospedaliera di Perugia, in the period between June 2012 and May 2013" "Each patient was included only once; therefore, the results for each patient refer to a single treatment cycle" **Author's name:** Gian Francesco Brusco, MD **Institution:** Perugia Hospital, Italy **Email:** gianfrancesco.brusco@ospedale.perugia.it **Address:** unknown
Notes	**Study design:** Quote: "according to a randomised pattern" *Marian G* on 16/11/2017 10:29 **Included:**

	"I have completed the data extraction but there is no division of the PCOS women from the poor responders etc, so we cannot use the data. I emailed the author first to ask if he has separate data for the PCOS women, randomisation and allocation concealment methods. I emailed Dr. Brusco on 16.11.17 and sent another email 08.03.18"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "'randomised pattern' authors contacted and 'Dynamic Minimization Method': There is no randomisation list; the first patient is assigned randomly and the subsequent allocations related to the distribution of the main prognostic factors with the aim of minimizing the imbalance between the two groups. With the progress of enrolment, if the main prognostic factors are balanced, the next patient is randomly assigned (closed envelopes)" Assessment of bias remains high due to randomisation done in part by minimisation and in part by closed envelopes; the numbers of women randomised to each arm are very unequal: 58 to the treatment arm and 91 to the control arm
Allocation concealment (selection bias)	High risk	Quote: "Allocation concealment: prepare, by professionals not involved in patient enrolment, a numbered sequence of opaque and sealed envelopes containing the assignment code. In order to prevent subversion, the list must remain inaccessible and envelopes should be opened sequentially after enrolling the patient and obtaining consent" Remains at high risk as done in part by minimisation and in part by envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No explanation given regarding blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No explanation given
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition reported; used intention-to-treat

Brusco 2013 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No selective reporting, clinical pregnancy apparent; however no trial registration number or protocol found
Other bias	Low risk	No other sources of bias apparent

Ciotta 2011

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	IVF/ICSI (N = 34) **Baseline characteristics:** No baseline data provided **Inclusion criteria:** women with PCOS younger than 40 years attending a fertility clinic - Gynaecological Endocrinology Clinics and Human Reproduction Pathophysiology Centre **Exclusion criteria:** concomitant endocrine and metabolic pathologies, such as hypothyroidism, hyperthyroidism, diabetes mellitus, androgen-secreting cancers, adrenal hyperplasia, Cushing's syndrome **Other outcomes reported in the paper:** numbers of follicles and oocytes, number and quality of embryos, and number of biochemical pregnancies **Treatment period:** treatment given for 3 months before IVF
Interventions	**Intervention:** Inositol • Myo-inisitol 2 g + folic acid 200 mcg: 1 tablet of each twice a day (n = 16) **Control:** • 200 mcg folic acid: 1 tablet twice a day (n = 18)
Outcomes	Live birth • **Outcome type:** dichotomous outcome • **Reporting:** fully reported • **Unit of measure:** per woman • **Direction:** higher is better • **Data value:** endpoint • **Notes:** live birth, clinical pregnancy, miscarriage, and multiple pregnancy data received via email from study author
Identification	**Sponsorship source:** not reported **Country:** Italy **Setting:** Gynaecological Endocrinology Clinics and Human Reproduction Pathophysiology Centre **Comments:** this trial is included in the female antioxidant review, and study authors were contacted 21 November 2011 via letter and email regarding pregnancy data, allocation concealment, and who was blinded. Study author responded 28 November 2011. Emailed study author on 5 February 2012 to request data on clinical pregnancies and to learn whether the sealed envelopes were numbered. No reply was received

	Author's name: L. Ciotta **Institution:** Gynaecological Endocrinology Clinics and Human Reproduction Pathophysiology Centre **Email:** mariagrazia.stracquadanio@gmail.com **Address:** Santo Bambino Hospital (Catania)
Notes	**Outcomes:** Outcomes reported in the paper: number of follicles, number of oocytes retrieved, number of embryos transferred, embryo quality, biochemical pregnancy Live birth data received from study author via email. Clinical pregnancy data gained by email from Dr. Stracquadanio on 28.03.18. Email from study author on 28.03.18 saying allocation concealment was achieved by "opaque sequentially numbered envelopes"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "According to a randomisation table, patients were divided into two groups"
Allocation concealment (selection bias)	Low risk	Quote: "opaque sequentially numbered envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the investigation was performed in a double-blind design" Study author states, "clinicians and patients were blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The investigation was performed in a double-blind design" Email from study author: "outcome assessors" were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No women lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Live birth reported; however no trial registration number or protocol found
Other bias	Low risk	No other bias found

Colazingari 2013

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	IVF (N = 100) **Baseline characteristics:** Not reported in the paper **Inclusion criteria:** "All patients treated in our IVF department over a period greater than 12 months were asked to participate in the study. This included a total of 100 women having a BMI of less than 28 and FSH10 IU/L with a diagnosis of PCOS according to Rotterdam 2003 and a normal uterine cavity" Women were grouped by age into 2 groups (i.e. < 35 years and ≥ 35 years) **Exclusion criteria:** "The study excluded patients diagnosed with advanced stage (III or IV) endometriosis and those classified as poor responders or as suffering from premature ovarian failure"
Interventions	**Intervention:** Myo-inositol • 550 mg myo-inositol + 13.8 mg D-*chiro*-inositol plus Inofolic® twice a day (n = 47) **Control:** D-*chiro*-inositol • 500 mg D-*chiro*-inositol twice a day (n = 53) Treatments given for 12 weeks before recFSH administration and throughout pregnancy
Outcomes	Hormone levels Number and quality of oocytes Number and quality of embryos
Identification	**Sponsorship source:** none reported **Country:** Italy **Setting:** IVF Department **Comments:** no pregnancy or adverse effect data - emailed study author on 12/8/17 - no response **Author's name:** Sandra Colazingari **Institution:** Department of Psychology, Section of Neuroscience, University of Rome **Email:** arturo.bevilacqua@uniroma1.it **Address:** Department of Psychology, Section of Neuroscience, University of Rome "Sapienza", Via dei Marsi 78, 00185 Rome, Italy **Trial registration number:** NCT1338844 **Other outcomes:** number and quality of embryos
Notes	*Marian G* on 21/12/2017 08:00 **Identification:** Study author replied to email on 27.09.17 saying that she does not have any clinical pregnancy or live birth data "since our plan was to carry on a cross-sectional study without further observations" The study was closed early for ethical reasons - due to a paper publishing evidence of harm for women taking D-*chiro*-inositol (DCI) (i.e. reduced number of mature oocytes and reduced embryo quality) (Rosalbino 2012)

Colazingari 2013 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to a block of ten by a computer-generated program"
Allocation concealment (selection bias)	Low risk	Quote: "The key to the coding of the treatments was kept by the LoLi Pharma. Both the participants and the research team were blinded" Emailed 8 December
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The key to the coding of the treatments was kept by the LoLi Pharma. Both the participants and the research team were blinded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Both the participants and the research team were blinded", so the assumption is made that outcome assessors were part of the research team
Incomplete outcome data (attrition bias) All outcomes	Low risk	One dropout from the treatment group; reasons given. Intention-to-treat not used
Selective reporting (reporting bias)	Low risk	Quote: "All outcomes reported in the methods were reported in the results" Email from study author saying that she did not have any live birth or clinical pregnancy data "since our plan was to carry on a cross-sectional study without further observations" Trial registration number provided
Other bias	Low risk	No other bias found

Hoxha 2016

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	ICSI (N = 80) **Baseline characteristics:** Not reported **Inclusion criteria:** women with PCOS undergoing ICSI **Exclusion criteria:** none reported **Pre-treatment:** not reported

Hoxha 2016 (*Continued*)

	Outcomes reported in the paper: total recFSH units, number of days of stimulation, oestradiol levels at hCG administration, total number of oocytes retrieved, number of MII oocytes
Interventions	**Intervention:** Inositol • D-*chiro*-inositol 4 arms - doses of 300 mg, 600 mg, 1200 mg, 2400 mg daily (n = 16 for each dose) **Control:** • Placebo (n = 16) Treatment given for 8 weeks before FSH stimulation
Outcomes	Total recFSH units used Number of days of stimulation Total number of oocytes
Identification	**Sponsorship source:** no funding source reported **Country:** Albania **Setting:** gynaecological clinic **Comments:** conference abstract - 17th World Congress of Gynaecological Endocrinology, ISGE 2016, Italy **Author's name:** E. Hoxha **Institution:** Mbreteresha Geraldine Hospital **Email:** none given **Address:** University of Medicine, United Kingdom
Notes	Conference abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants randomly divided into 5 groups
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of allocation concealment provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, as the paper is a conference abstract providing no numbers - only description

Hoxha 2016 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration number available; outcomes of live birth and clinical pregnancy not reported
Other bias	Low risk	None noted

Lesoine 2016

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	IVF (N = 29) **Baseline characteristics:** Not provided in the paper **Inclusion criteria:** women with PCOS indicated by oligomenorrhoea and/or hyperandrogenism and/or hyperandrogaenemia and/or typical features of ovaries on ultrasound scan were enrolled in this study. At least 2 of the above-mentioned criteria were present in all participants. Women were undergoing IVF and were < 40 years of age (n = 29) **Exclusion criteria:** any other medical conditions causing ovulatory disorders such as hyperprolactinaemia or thyroidal disorders or Cushing syndrome **Other outcomes reported in the paper:** number of retrieved oocytes, ratio of follicles to retrieved oocytes, fertilisation rate, oocyte quality, quantity of FSH units used, days of stimulation
Interventions	**Intervention:** Inositol • Myo-inositol 4000 mg plus folic acid 400 μg: 1 tablet per day (n = 14) **Control:** • Placebo (n = 15)
Outcomes	Number and quality of oocytes retrieved Number and quality of embryos Amount of rFSH used Number of days of stimulation.
Identification	**Sponsorship source:** not reported **Country:** Germany **Setting:** Centre for Reproductive Medicine Bogenhausen, Munich, Germany **Author's name:** B. Lesonie **Institution:** Centre for Reproductive Medicine, Prinzregentenstraße 69, Bogenhausen, 81675 Munich, Germany **Email:** pedro-antonio.regidor@exeltis.com **Address:** emailed the study author regarding outcomes of clinical pregnancy and live birth on 16.11.17; study author replied, saying that he was looking for the data **Treatment and trial length:** treatment was given for 2 months before the IVF cycle; the trial ran for 4 months

Lesoine 2016 (*Continued*)

Notes	Email sent on 21.01.18, regarding clinical pregnancy/live births. This trial is also included in the "Antioxidants for female subfertility" review, and the study author replied in October 2016, regarding questions about clinical outcomes and risk of bias. Email sent 08.08.18, when the substudy was found in the 2018 search, saying there were now clinical data (no useful data in the abstract). Study author replied to an email, saying that he may be able to access the clinical data. I have emailed the study author twice regarding clinical data and received no reply. Last email sent 04.10.18 Dr. Regidor is an employee of a pharmaceutical company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The method of randomisation was a manual one. After fulfilling the including criteria the patients were allocated to the previously defined randomisation list"
Allocation concealment (selection bias)	Unclear risk	Quote: "Unknown methods of allocation concealment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: single-blinded "The biologist which carried out the fertilization was the blinded person. He did not know if the women were treated with myo-Inositol or not" (placebo used)
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded Quote: "The biologist which carried out the fertilization was the blinded person. He did not know if the women were treated with myo-inositol or not"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women analysed
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration number available; outcomes of live birth and clinical pregnancy not reported
Other bias	Low risk	No other bias found

Pacchiarotti 2015

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	IVF/ICSI (N = 569) **Baseline characteristics:** "The differences among the three groups were not statistically significant" **Inclusion criteria:** women with PCOS undergoing ICSI between 27 and 38 years of age (n = 569); absence of tubal, uterine, genetic, and male causes of infertility; serum levels of FSH on day 3 of the ovarian cycle 512 IU/L; Rotterdam criteria for PCOS; normal uterine cavity; BMI 20 to 26 kg/m²; first IVF treatment. Only women undergoing first-time ICSI procedure and fulfilling inclusion criteria were enrolled in the study to limit heterogeneity **Exclusion criteria:** none reported **Notes:** outcomes as reported in the paper: primary endpoints were oocyte and embryo quality, clinical pregnancy (identified by the presence of a gestational sac on ultrasonography 5 weeks after oocyte retrieval), and implantation rates. Secondary outcomes were gonadotropin IU administered, days of stimulation, serum oestradiol (E2) levels, and endometrial thickness on the day of human chorionic gonadotropin (hCG) administration. Trial ran from July 2009 to December 2011. 43 women dropped out - 16 from the control group, 13 from intervention group A, and 14 from intervention group B; reasons provided. Clinical trial registration number: NCT01540747 (ClinicalTrials.gov registry). Includes a study author who was an employee of a pharmaceutical company. Funding source not reported. This trial is included in the "Antioxidants for female subfertility" review, and in the process of writing that review, we emailed Dr. Pacchiarotti on 18 October 2016, to ask about allocation concealment and live birth data. Dr. Pacchiarotti replied on 20 March 2017, saying that the clinical pregnancy was per woman and that study authors have 80% of the live birth data. We replied asking whether we could include these data. We have received no reply yet. Email sent to study author 08.12.17. Power calculation performed
Interventions	**Intervention:** Inositiol • Group A: myo-inositol 4 g + folic acid 400 mcg (inofolic®) + melatonin 3 g twice a day (n = 178) • Group B: myo-inositol 4 g + folic acid 400 mcg (inofolic®) twice a day (n = 180) **Control:** • Folic acid 400 mcg twice a day (n = 211) Treatment given from the first day of the cycle until 14 days after embryo transfer
Outcomes	Clinical pregnancy • **Outcome type:** dichotomous outcome Multiple pregnancy • **Outcome type:** adverse event • **Direction:** lower is better Miscarriage
Identification	**Sponsorship source:** none reported in the paper **Country:** Italy **Setting:** patients were assessed for eligibility from July 2009 to December 2011, at Praxi

	Pro Vita IVF Center (Rome, Italy) **Comments:** patients were undergoing IVF/ICSI **Author's name:** Alessandro Pacchiarotti **Trial registration number:** NCT01540747 **Institution:** Praxi Pro Vita Centro di Fertilita **Email:** arypac@gmail.com **Address:** Via Magna Grecia,117 Rome, Italy; tel/fax: +39 06 70450860 Emailed on 5 December 2017, re allocation concealment, blinding, and live birth data. Emailed again on 4.10.18
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using a computer-based random assignment schedule for each patient"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment unknown
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Double blinded"; does not describe who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Among the 569 recruited patients, 43 subjects dropped out: 16 in controls, of which 9 with low ovarian response (estradiol level 51000 pg/mL and less than two follicles developed), and 7 owing to an excessive ovarian response; 13 in group A (MI + M + folic acid) of which 7 low responders, and 6 owing to excessive ovarian response; 14 in group B (MI + folic acid) of which 8 low responders and 6 with excessive ovarian response" Intention-to-treat used Judgement comment: 43 dropouts
Selective reporting (reporting bias)	Low risk	Nil known. Clinical pregnancy, multiple pregnancy, and miscarriage reported; trial registration number provided
Other bias	Low risk	No other sources of bias noted

Papaleo 2008

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	Natural intercourse (N = 75) **Baseline characteristics:** None reported in the conference abstract **Inclusion criteria:** women with polycystic ovarian syndrome (n = 75) **Exclusion criteria:** none given **Pre-treatment:** not reported in the paper **Outcomes reported in the paper:** ovulatory activity, hormone profile, ongoing pregnancy, miscarriage
Interventions	**Intervention:** Inositol • Myo-inositol 4 g plus 400 mg folic acid (n = 36) (unknown length of treatment time) **Control:** • Clomiphene citrate 50 mg daily for 5 days (increased to 100 mg if resistance occurred) (n = 39)
Outcomes	Live birth (reported as ongoing pregnancy) • **Outcome type:** dichotomous outcome • **Reporting:** fully reported • **Unit of measure:** per woman • **Direction:** higher is better • **Data value:** endpoint Multiple pregnancy Ovulation rate
Identification	**Sponsorship source:** none reported **Country:** Italy **Setting:** IVF clinic **Comments:** conference abstract only **Author's name:** Dr. E. Papeleo **Institution:** St. Raffaele Hospital IVF, Milan, Italy **Email:** not given **Address:** S. Raffaele Hospital, Milan, Italy The trial had a 6-month follow-up period; treatment was given for 5 days
Notes	**Outcomes:** Need to contact study author re clinical pregnancy rates and miscarriage numbers discussed; the numbers are not reported. Also risk of bias domains; however no email address found Conference abstract

Risk of bias

Bias	Authors' judgement	Support for judgement

Papaleo 2008 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "We randomly assigned"; no explanation given
Allocation concealment (selection bias)	Unclear risk	No explanation provided regarding allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No explanation given regarding blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No explanation given
Incomplete outcome data (attrition bias) All outcomes	Low risk	No women lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Live birth reported; however no trial registration number or protocol found
Other bias	Low risk	No other bias found

Papaleo 2009

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	IVF/ICSI (N = 60) **Baseline characteristics:** No significant differences between groups in terms of age (< 40 years), numbers, duration of infertility, BMI (> 26 kg/m²), and hormone levels **Inclusion criteria:** all patients treated in our IVF department for a period longer than 12 months were asked to participate in the study. A total of 60 women aged < 40 years with polycystic ovary syndrome, indicated by oligomenorrhoea (≤ 6 menstrual cycles during a period of 1 year), hyperandrogenism (hirsutism, acne, or alopecia) or hyperandrogaenemia (elevated levels of total or free T), and typical features of ovaries on ultrasound scan, were enrolled in the study **Exclusion criteria:** other medical conditions causing ovulatory disorders, such as hyperinsulinaemia, hyperprolactinaemia, or hypothyroidism, or androgen excess, such as adrenal hyperplasia or Cushing syndrome
Interventions	**Intervention:** Inositiol • Myo-inositol 2 g + folic acid 400 mcg (Inofolic®) (n = 30) **Control;** • Folic acid 400 mcg (n = 30) Treatment started on the day of GnRHa administration

Outcomes	Clinical pregnancy • **Outcome type:** dichotomous outcome Miscarriage • **Outcome type:** dichotomous outcome • **Reporting:** fully reported • **Direction:** lower is better • **Data value:** endpoint
Identification	**Sponsorship source:** Study author relied to an email 27.11.17, saying that he did not receive any funding. LoLi Pharma provided the product to participants for free **Country:** Italy **Setting:** IVF unit, Gynecologic-Obstetric Department, Istituto di Ricovera e Cura a Carattere Scientifico, San Raffaele Hospital **Comments:** **Author's name:** Enrico Papaleo **Institution:** Gynecology Association Unfer Costabile (A.G.UN.CO.) **Email:** vittorio.unfer@lycos.com **Address:** Gynecology Association Unfer Costabile (A.G.UN.CO.), Obstetrics and Gynecology Center, Via G. Cassiani, 15, 00155 Rome, Italy
Notes	*Marian G* on 21/12/2017 06:42 **Outcomes:** No live birth data available in the paper. Emailed study author on 27.11.17; study author replied that no live birth data were available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A prospective, controlled, randomised trial" Study author replied to an email on 27.11.17, saying that randomisation was performed using EXCEL
Allocation concealment (selection bias)	Low risk	Not reported in the paper, but the study author replied to an email on 27.11.17, saying that researchers used a sequentially numbered method
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Papaleo 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised women analysed in their original treatment or control group
Selective reporting (reporting bias)	High risk	Live birth stated as a secondary outcome in the abstract, but study authors provided no data in the paper and replied to an email saying that no live birth data were available. No trial registration number or protocol found
Other bias	Low risk	No other source of bias noted

Piomboni 2014

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	IVF/ICSI (N = 68) **Baseline characteristics:** No differences noted in mean age (mean approximately 32 to 34 years), body mass index (mean approximately 25 kg/m²), insulin levels, HOMA index, and smoking status among study groups **Inclusion criteria:** women with PCOS undergoing IVF/ICSI treatment for female factor of infertility **Exclusion criteria:** congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumours **Outcomes reported in the paper:** Number of oocytes retrieved, quality of oocytes, fertilised oocytes, evolutive embryos
Interventions	Inositol • D-*chiro*-inositol 500 mg twice a day (n = 26) vs • Metformin 850 mg twice a day (n = 20) vs • No treatment (n = 22) Started 3 months before IVF ovarian stimulation protocol
Outcomes	Number of oocytes retrieved Quality of oocytes Fertilised oocytes Evolutive embryos
Identification	Center for Couple Sterility of Obstetrics and Gynecology Unit, University Hospital of Siena and Modena, V. De Leo, Institute of Obstetrics and Gynecology, University of Siena, Policlinico Le Scotte, Viale Bracci, 53100 Siena, SI, Italy Email: vincenzo.deleo@unisi.it

Piomboni 2014 (*Continued*)

Notes	No data for pregnancy outcomes provided Email sent on 08.03.18 regarding clinical pregnancy and live birth data and risk of bias details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was computer generated"
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women analysed in groups as randomised
Selective reporting (reporting bias)	Unclear risk	Protocol and trial registration number not available; outcomes of live birth and clinical pregnancy not reported
Other bias	Low risk	None known

Raffone 2010

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	Natural intercourse (N = 120) **Baseline characteristics:** Myo-inositiol 4 g/d + folic acid 400 µg (n = 60) • **Age, years:** 29.1 + 5.6 • **BMI, kg/m²:** 25 + 2.1 • **WHR:** 0.88 + 0.3 • **Duration of infertility, months:** 22.2 + 2.5 Metformin 1500 mg/d (n = 60) • **Age, years:** 29.7 + 6 • **BMI, kg/m²:** 24.9 + 2.7 • **WHR:** 0.90 + 0.4 • **Duration of infertility, months:** 20.1 + 3.5 **Inclusion criteria:** "A total of 120 women, aged less than 35 years, with PCOS, defined

	by Rotterdam Criteria, were enrolled in the study from June 2006 and June 2008. All patients attended our infertility department for infertility that lasted for a period of more than 14-16 months" **Exclusion criteria:** other medical condition causing ovulatory dysfunction: hyperprolactinaemia or hypothyroidism, or androgen excess, adrenal hyperplasia, or Cushing's syndrome; tubal defects: in fact, all women underwent assessment of tubal patency; semen parameter defects: all male partners were evaluated with 2 different sperm semen samples with no defects found **Pre-treatment:** baseline characteristics similar between groups; BMI mean approximately 25 kg/m² **Outcomes reported in the paper:** spontaneous ovarian activity, myo-inositol or metformin resistance, pregnancy (biochemical and clinical), and abortion (miscarriage rate)
Interventions	**Intervention:** Inositol • Myo-inositiol 4 g/d + folic acid 400 µg (n = 60) **Control:** • Metformin 1500 mg/d (n = 60) Treatment given for 6 months
Outcomes	Clinical pregnancy • **Outcome type:** dichotomous outcome Ovulation • **Outcome type:** dichotomous outcome • **Reporting:** fully reported • **Unit of measure:** per woman • **Direction:** higher is better • **Data value:** endpoint • **Notes:** primary endpoint was to evaluate the restoration of spontaneous ovarian activity by weekly serum progesterone dosage, as well as by transvaginal ultrasound scan documenting the presence of follicular growth or luteal cyst. Progesterone levels higher than 8.0 ng/mL were considered significant for spontaneous ovulation
Identification	**Sponsorship source:** none reported **Country:** Italy **Setting:** Obstetrics and Gynaecology Department G **Comments:** study ran from June 2006 to June 2008, with follow-up period of 6 months **Author's name:** Emanuela Raffone **Institution:** Martino Hospital, Messina, Italy **Email:** emaraff@gmail.com
Notes	*Marian G* on 12/12/2017 08:13 **Interventions:** Intervention was given for 1 cycle, then if no pregnancy occurred, all were given recFSH in addition to insulin-sensitising drugs for a maximum of 3 attempts. For the purposes of this review, we are using only the first cycle with insulin-sensitising drugs *Marian G* on 12/12/2017 09:49 **Outcomes:**

Raffone 2010 (*Continued*)

	Email sent to study author on 12.12.17 to ask for information on sequence generation and miscarriage rates in the group of women who did not go on to receive recFSH

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods of sequence generation unknown
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not explained
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding explained
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding explained
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat used and reasons for 11 dropouts given, along with numbers from each group (7 from the metformin group and 4 from the MYO group)
Selective reporting (reporting bias)	Unclear risk	Clinical pregnancy and ovulation reported, but no trial registration number or protocol found
Other bias	Low risk	No other risk of bias noted

Rosalbino 2012

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	IVF (N = 54) **Baseline characteristics:** D-*chiro*-inositiol 300 mg: 1 tablet a day (n = 10) • **Age, years:** 36.8 ± 1.6 • **BMI, kg/m²:** 25.2 ± 3.5 • **Duration of infertility, months:** 49.4 ± 7.6 D-*chiro*-inositol 600 mg: 1 tablet a day (n = 11) • **Age, years:** 36.9 ± 1.52 • **BMI, kg/m²:** 24.7 ± 3.5 • **Duration of infertility, months:** 50.0 ± 7.2 D-*chiro*-inositol 1200 mg: 1 tablet a day (n = 10)

	• **Age, years:** 36.7 ± 1.57 • **BMI, kg/m²:** 25.1 ± 3.1 • **Duration of infertility, months:** 49.9 ± 6.1 D-*chiro*-inositol 2400 mg: 1 tablet a day (n = 12) • **Age, years:** 37.0 ± 1.25 • **BMI, kg/m²:** 25.6 ± 2.9 • **Duration of infertility, months:** 48.9 ± 8.8 Placebo (n = 11) • **Age, years:** 36.9 ± 1.5 • **BMI, kg/m²:** 24.4 ± 2.8 • **Duration of infertility, months:** 48.2 ± 9.4 **Inclusion criteria:** women < 40 years of age with PCOS undergoing ICSI. Mean age Group 1: 36.8; Group 2: 36.9; Group 3: 36.7; Group 4: 37.0; placebo: 36.9 **Exclusion criteria:** women with insulin resistance and/or hyperglycaemia **Pre-treatment:** baseline characteristics of age, BMI, and duration of infertility were very similar in all 5 groups **Other outcomes reported in the paper:** number of oocytes, total recFSH, 17B-E2 levels on hCG administration, stimulation days, number of cycles cancelled
Interventions	**Intervention:** • D-*chiro*-inositiol 300 mg: 1 tablet a day (n = 10) vs • D-*chiro*-inositol 600 mg: 1 tablet a day (n = 11) vs • D-*chiro*-inositol 1200 mg: 1 tablet a day (n = 10) vs • D-*chiro*-inositol 2400 mg: 1 tablet a day (n = 12) vs • Placebo (n = 11) Teatment given for 8 weeks before ICSI stimulation
Outcomes	Number of oocytes Total FSH used Oestrogen levels on hCG administration Stimulation days Number of cycles cancelled
Identification	**Sponsorship source:** funding source not reported **Country:** conducted in Italy; study dates not reported **Setting:** fertility clinic providing ICSI **Comments:** trial dates not reported in the paper. Email sent to Dr. Rosalbino on 04.12.17; however email undeliverable **Author's name:** Rosalbino Isabella **Institution:** C.I.S. Reproductive Medicine, Lameda Terme, Italy **Email:** rosalbinoisabella@gmail.com **Address:** C.I.S. Reproductive Medicine, Lamezia Terme, Italy
Notes	Emailed study author regarding risk of bias and outcomes, but email returned undeliverable twice. Tried to reach co-author by email at emaraff@gmail.com on 01.03.18

Rosalbino 2012 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation procedure was performed using a computer-based program"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment unknown
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition; no dropouts noted
Selective reporting (reporting bias)	Unclear risk	Protocol and registration number not available; outcomes of live birth and clinical pregnancy not reported
Other bias	Low risk	No other bias found

Unfer 2011

Methods	**Study design:** randomised controlled trial **Study grouping:** parallel group
Participants	ICSI (N = 84) **Baseline characteristics:** Baseline differences not significant for numbers of women in each group, age, duration of fertility, BMI, or hormone levels. Mean BMI approximately 25 kg/m² **Inclusion criteria:** women attending IVF clinic longer than 12 months and PCOS according to Rotterdam criteria. Women younger than 40 years **Exclusion criteria:** women who showed insulin resistance and/or hyperglycaemia
Interventions	**Intervention:** Inositol • Myo-inositol 2 g twice daily (n = 43) **Control:** • D-*chiro*-inositol 600 mg twice daily (n = 41)

Unfer 2011 (*Continued*)

Outcomes	Miscarriage • **Outcome type:** dichotomous outcome Clinical pregnancy • **Outcome type:** dichotomous outcome
Identification	**Sponsorship source:** no sponsorship source provided in the paper; study author replied on 27.11.17, saying that funding was not received **Country:** Italy **Setting:** IVF Department of Infertility **Author's name:** Vittorio Unfer **Institution:** AGUNCO Obstetrics and Gynecology Centre **Email:** vunfer@gmail.com **Address:** AGUNCO Obstetrics and Gynecology Centre, Rome, Italy
Notes	Treatments performed for 8 weeks before recFSH was administered *Marian G* on 21/12/2017 10:12 **Outcomes:** No live birth data evident in the paper; email from Gianfranco 27.11.17 says no live birth data available Trial length unknown

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "All patients were randomly assigned" by EXCEL according to email from Gianfranco on 27.11.17
Allocation concealment (selection bias)	Unclear risk	No explanation given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Email on 27.11.17 stating that only outcome assessor was blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Email on 27.11.17 saying that outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts reported
Selective reporting (reporting bias)	Unclear risk	Outcomes of clinical pregnancy and miscarriage reported in the paper, but no trial registration number or protocol found
Other bias	Low risk	No other bias noted

17OHP: 17-hydroxyprogesterone.
A: androstenedione.
ART: assisted reproduction technology.
BMI: body mass index.
E2: oestradiol.
FSH: follicle-stimulating hormone.
hCG: human chorionic gonadotrophin.
HOMA: homeostatic model assessment.
ICSI: intracytoplasmic sperm injection.
ITT: intention-to-treat.
IVF: in vitro fertilisation.
LH: luteinising hormone.
MI: myo-inositol.
MII: metaphase II.
PCOS: polycystic ovary syndrome.
PRL: prolactin.
recFSH: recombinant human FSH.
rFSH: recombinant FSH.
T: testosterone.
USS: ultrasound scan.
WHR: waist-to-hip ratio.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agarwal 2015	Inappropriate patient population; women not intending pregnancy
Benelli 2016	Inappropriate patient population; women not intending pregnancy
Cappelli 2013	Inappropriate patient population; women not intending pregnancy
Cheang 2008	Inappropriate patient population; women not intending pregnancy
Cianci 2015	Inappropriate patient population; women not intending pregnancy
Ciotta 2012	Inappropriate patient population; women not intending pregnancy
Ciotta 2012a	Inappropriate patient population; women not intending pregnancy
Costantino 2009	Inappropriate patient population; women not intending pregnancy
DeLeo 2012	Inappropriate study design
DeLeo 2014	Inappropriate study design
Don 2012	Inappropriate patient population; women not intending pregnancy

(*Continued*)

Emekci Ozay 2017	Inappropriate study design; women divided according to patient protocol numbers (i.e. odd and even)
Formuso 2015	Inappropriate patient population; women not intending pregnancy
Fruzzetti 2017	Inappropriate patient population; women not intending pregnancy
Genazzani 2008	Inappropriate patient population; women not intending pregnancy
Gerli 2003	Inappropriate patient population; only 15% of total randomised population intended pregnancy
Gerli 2007	Inappropriate patient population; only 15% of total randomised population intended pregnancy
Immediata 2014	Inappropriate patient population; women not intending pregnancy
Iuorno 2002	Inappropriate patient population; women not intending pregnancy
Jamilian 2017	Inappropriate patient population; women not intending pregnancy
LeDonne 2012	Inappropriate patient population; women not intending pregnancy
Lisi 2012	Inappropriate patient population; women not intending pregnancy
Moretti 2016	Inappropriate patient population; women not intending pregnancy
Morgante 2015	Inappropriate patient population; women not intending pregnancy
Nazzaro 2011	Not randomised; emailed study author on 01.03.18 to ask how groups were divided
Nehra 2017	Inappropriate patient population; women not intending pregnancy
Nestler 1999	Inappropriate patient population; women not intending pregnancy
Nestler 2001	Inappropriate patient population; women not intending pregnancy
Nordio 2012	Inappropriate patient population; women not intending pregnancy
Orbetzova 2016	Inappropriate patient population; women not intending pregnancy
Ozay 2016	Inappropriate patient population; women not intending pregnancy
Papaleo 2007	Inappropriate study design
Pizzo 2014	Inappropriate patient population; women not intending pregnancy
Tagliaferri 2017	Inappropriate patient population; women not intending pregnancy

(*Continued*)

Wdowiak 2016	Inappropriate study design

Characteristics of studies awaiting assessment *[ordered by study ID]*

Llaneza 2018

Methods	A multi-centre controlled randomised double-blind parallel study
Participants	Women meeting Rotterdam criteria for PCOS with BMI < 30 and undergoing ICSI (N = 60)
Interventions	Myo-inositol 550 mg + D-*chiro*-inositol 150 mg 2×/d (n = 30) vs Myo-inositol 550 mg + D-*chiro*-inositol 13.8 mg 2×/d (n = 30)
Outcomes	Number of MII oocytes Embryo quality Pregnancy Live birth Hormone levels
Notes	NCT03201601 Therapy given for 12 weeks ESHRE 2018 conference abstract **Contact:** P Llaneza, HUCA, Obstetrics and Gynaecology, Oviedo, Spain

Mahey 2018

Methods	Randomised controlled trial
Participants	Infertile women with PCOS (N = 120)
Interventions	Metformin 500 mg + myo-inositol 600 mg TDS (n = 60) vs Metformin 500 mg TDS (n = 60)
Outcomes	Clinical pregnancy rate Ovulation rate Ongoing pregnancy rate OHSS Miscarriage Multiple pregnancy rate Metabolic profile
Notes	Trial ran from January 2016 to May 2017. Therapy was given for 6 months. Couples were advised to attempt natural conception and after 3 months were given ovulation induction and IUI CTRI/2017/07/009021

Mahey 2018 (*Continued*)

	ESHRE 2018 conference abstract **Contact:** R. Mahey, All India Institute of Medical Sciences, Obstericsa and Gynaecology, Delhi, India

BMI: body mass index.
ICSI: intracytoplasmic sperm injection.
IUI: intrauterine insemination.
MII: metaphase II.
PCOS: polycystic ovary syndrome.
TDS: three times a day.

Characteristics of ongoing studies *[ordered by study ID]*

IRCT2017021432525N2

Trial name or title	Study the Effects of Pretreatment With Myoinositol on Oocyte Quality in Patients With Polycyctic Ovary Syndrome
Methods	Randomised blinding double-blinded placebo-controlled
Participants	**Inclusion criteria:** infertile women with PCOS over 35 years old; candidate for IVF procedure; normal sperm test and hysterosalpingography; agreement of patients to participate in the study
Interventions	**Intervention 1:** myo-inositol 2000 mg + 400 mg folic acid daily for 3 months. **Intervention 2:** 400 mg folic acid daily for 3 months
Outcomes	Chemical and clinical pregnancy (time point: 3 months after intervention. Method of measurement: pregnancy proved by positive beta-hCG test, 14 days after ovum transportation; sonography approved) OHSS
Starting date	2017-04-30
Contact information	Dr. Maryam Nemati, Alzahra Infertility Clinic, Shahrekord, Shahrekord Iran (Islamic Republic of); tel: +98 38 3222 0478; email: nemati.m@skums.ac.ir
Notes	Recruitment complete

IRCT2017070234845N1

Trial name or title	Comparison of Effectiveness of Inositol and Metformin in Infertile Women With Polycystic Ovary Syndrome (PCOS)
Methods	Randomised single-blinded
Participants	Infertile women with polycystic ovary syndrome

IRCT2017070234845N1 (*Continued*)

Interventions	**Group 1:** inositol 2 g plus 200 micrograms of folic acid twice daily; **Group 2:** 1500 mg metformin daily plus 200 micrograms folic acid; **Group 3:** 200 micrograms folic acid (as placebo) for 3 months
Outcomes	Ovary function (time point: monthly. Method of measurement: follicle size > 16 mm)
Starting date	2016-03-19
Contact information	Dr. Sajadeh Pourghasem, No. 7916839319, Vice Chancellor for Research, Shahid Mohammadi Hospital, Bandarabbas Bandarabbas Bandarabbas, Iran (Islamic Republic of); res@hums.ac.ir; Hormozgan University of Medical Science
Notes	

NCT01514942

Trial name or title	Myo-inositol Versus D-chiro-inositol in the Treatment of Polycystic Ovary Syndrome and Insulin Resistance: Evaluation of Clinical, Metabolic, Endocrine and Ultrasound Parameters
Methods	Clinical trial randomised
Participants	PCOS
Interventions	**Dietary supplement:** myo-inositol + folic acid **Dietary supplement:** D-*chiro*-inositol, manganese, folic acid, vitamin B12 **Drug:** folic acid, vitamin B12
Outcomes	Body mass index (BMI) | Menstrual cycle | Score acne (acne grading system by Cremoncini et al) | Score hirsutism (Ferriman-Gallwey score) | Alopecia | Oral glucose tolerance test (OGTT) | Glucagon levels | C-peptide test | Myo-inositol serum concentration | D-*chiro*-inositol serum concentration | Luteinising hormone (LH), follicle-stimulating hormone (FSH), and oestradiol (E2) levels test | Prolactin (PRL) levels test | Thyroid-stimulating hormone (TSH), free thyroid hormone (fT3 and fT4), and alpha-1 antitrypsin (AAT) test | Total and free testosterone levels | Sex hormone-binding globulin (SHBG) test | 17-Hydroxyprogesterone (17-OHP) levels | Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS) levels | Delta 4-androstenedione levels | Progesterone levels | Adrenocorticotrophic hormone (ACTH) stimulation test | Ovarian size and morphology | Antral follicle counts | Stromal/Cortical ratio in the ovary | Endometrial thickness
Starting date	Null
Contact information	AGUNCO Obstetrics and Gynecology Centre, Istituto di Patologia Ostetrica e Ginecologica, Catania, Italy
Notes	?randomised, ?pregnancy outcomes

NCT01540747

Trial name or title	Role of Melatonin Supplementation in Follicular Fluid of In Vitro Fertilization (IVF) Patients With Polycystic Ovarian Syndrome
Methods	Interventional
Participants	PCOS, body mass index 20 to 26 kg/m², first IVF
Interventions	**Dietary supplement:** myo-inositol + folic acid + melatonin
Outcomes	Pregnancy rate
Starting date	17/02/2012
Contact information	AGUNCO Obstetrics and Gynecology Centre, Italy
Notes	?Randomised

NCT01555190

Trial name or title	Combination Therapy With Myo-inositol and Folic Acid Versus Myo-inositol Alone
Methods	Clinical trial randomised
Participants	Women with PCOS, BMI > 25, age 18 to 35 years
Interventions	**Drug:** myo-inositol 1500 g vs myo-inositol 2000 g + folic acid 200 mcg
Outcomes	Number of cycles in 6 months of therapy on oral glucose tolerance test, Thornton assay, lipid profile
Starting date	January 2012
Contact information	**Principal investigator:** Maurizio Guido; maurizioguido@libero.it
Notes	?fertility as an outcome. Likely wrong population

NCT02221154

Trial name or title	Use of Myo-inositol as Adjuvant Therapy in Patients With Polycystic Ovary Syndrome (PCOS) In Vitro Fertilization (IVF)
Methods	Randomised
Participants	Polycystic ovary syndrome
Interventions	**Dietary supplement:** Inofolic® | Other: gonadotropins; folic acid
Outcomes	Incidence of OHSS in each group, graded mild, moderate, or severe based on recommendations

NCT02221154 (*Continued*)

Starting date	November 2014
Contact information	CHI de Créteil, Créteil, France; CHD Vendée, La Roche sur Yon, France; CHU de Nantes, Nantes, France; CH de Saint Nazaire, Saint Nazaire, France Fabienne Delay
Notes	**Terminated** due to difficulty recruiting

NCT02385396

Trial name or title	Myo-inositol Therapy on the Dynamics of Embryo Development in Patients Suffering From PCOS Undergoing ICSI Treatment
Methods	Intervention model: parallel assignment | Masking: none
Participants	Polycystic ovary syndrome, infertility
Interventions	**Dietary supplement:** Inofolic®: myo-inositol and folic acid
Outcomes	Oestradiol (E2) level in blood serum (pg/mL) | Progesterone (ng/mL) level in blood serum | Superoxide dismutase (SOD) activity level in follicular fluid (mIU/mg) | Catalase activity level in follicular fluid (mIU/mg) | Period of blastocyst and embryo development | Pregnancy rate
Starting date	Null
Contact information	Medical University of Lublin, Poland
Notes	?not randomised. Recruitment completed

NCT02630485

Trial name or title	Graceful Lifestyle Changes Study for PCOS and Infertility GLC
Methods	Randomised
Participants	All women with PCOS trying to conceive who are between 18 and 37 years of age (PCOS defined by Rotterdam criteria)
Interventions	**Behavioural:** graceful lifestyle changes, myo-inositol, letrozole
Outcomes	Ovulation occurrence Conception
Starting date	December 2015
Contact information	Anthony P. Cheung, MBBS, MPH, MBA; tel: 604-558-4886; email: ACheung@fertilitywithgrace.com; University of British Columbia, Canada

NCT02630485 (*Continued*)

Notes	

NCT03059173

Trial name or title	Interest of Myo-inositol Supplementation in Women With Polycystic Ovarian Syndrome
Methods	Randomised
Participants	Polycystic ovary syndrome
Interventions	**Dietary supplement:** Inofolic® | **Drug:** clomiphene citrate | **Dietary supplement:** placebo
Outcomes	Total resistance rate under CC for ovulation induction in patients with PCOS. Rate of responders (i.e. 100% cycles with ovulation and/or occurrence of a pregnancy) at doses of 50 and 100 mg of CC | Rate of dropout | Cumulative incidence of clinical pregnancy (cardiac activity on ultrasound at 6 weeks of amenorrhoea) | Rate of participants switched to second-line treatment with exogenous gonadotrophins over the whole period of the study
Starting date	February 2018
Contact information	**Contact:** Didier Dewailly, MD, PhD; tel: 320446252 ext: +33; didier.dewailly@chru-lille.fr; University Hospital, Lille, France
Notes	Not yet recruiting

NCT03177122

Trial name or title	Myo-Inositol-Based Co-treatment in Women With PCOS Undergoing Assisted Reproductive Technology
Methods	Randomised
Participants	Women diagnosed with PCOS according to Rotterdam criteria indicated by oligomenorrhoea (≤ 6 menstrual cycles during a period of 1 year), hyperandrogenism (hirsutism, acne, or alopecia) or hyperandrogaenemia (elevated levels of total or free T), and typical features of ovaries on ultrasound scan
Interventions	Myo-inositol
Outcomes	Live birth rate Ongoing pregnancy Miscarriage Adverse events Neonatal outcomes
Starting date	25/05/2017
Contact information	Johnny Awwad, MD; tel: 009611350000; email: jawwad@aub.edu.lb; American University of Beirut Medical Center

NCT03177122 (*Continued*)

Notes	

NCT03201601

Trial name or title	Evaluation of the Mixture Myoinositol:D-chiro-inositol 3.6:1 in Women With Polycystic Ovary Syndrome
Methods	Randomised
Participants	Polycystic ovarian syndrome infertility
Interventions	D-*chiro*-inositol, myo-inositol
Outcomes	Pregnancy rate Mature MII oocytes Grade I, II, III embryos Days of stimulation Gestational sacs Transferred embryos Total testosterone Glucose Insulin
Starting date	February 2016
Contact information	Nicolás Mendoza, MD, PhD, Faculty of Medicine Granada, Spain Sponsored by Biosearch S.A.
Notes	Active, not recruiting (05.10.18)

17-OHP: 17-hydroxyprogesterone.
AAT: alpha-1-antitrypsin.
ACTH: adrenocorticotrophic hormone.
BMI: body mass index.
CC: clomiphene citrate.
DHEA: dehydroepiandrosterone.
DHEAS: dehydroepiandrosterone sulfate.
E2: oestradiol.
FSH: follicle-stimulating hormone.
fT3: free thyroid hormone.
fT4: free thyroid hormone.
hCG: human chorionic gonadotrophin.
IVF: in vitro fertilisation.
LH: luteinising hormone.
OGTT: oral glucose tolerance test.
OHSS: ovarian hyperstimulation syndrome.
PCOS: polycystic ovary syndrome.
PRL: prolactin.

SHBG: sex hormone-blinding globulin.
SOD: superoxide dismutase.
TSH: thyroid-stimulating hormone.

DATA AND ANALYSES

Comparison 1. Myo-inositol versus placebo, no/standard treatment as pre-treatment to IVF in women with PCOS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 No treatment/standard treatment	2	84	Odds Ratio (M-H, Fixed, 95% CI)	2.42 [0.75, 7.83]
2 Adverse event	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Miscarriage	4	535	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.19, 0.86]
2.2 Multiple pregnancy	2	425	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.63, 1.71]
3 Clinical pregnancy	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 No treatment/standard treatment	4	535	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.87, 1.85]
4 Sensitivity analysis on clinical pregnancy	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Studies reporting clinical pregnancy and also live birth	2	84	Odds Ratio (M-H, Fixed, 95% CI)	2.54 [0.84, 7.65]
4.2 Studies reporting clinical pregnancy but not live birth	2	451	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.77, 1.72]

Comparison 2. Myo-inositol versus antioxidant as pre-treatment to IVF in women with PCOS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse event	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Miscarriage	1	358	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.22, 2.24]
1.2 Multiple pregnancy	1	358	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.57, 1.59]
2 Clinical pregnancy	1	358	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.53, 1.28]

Comparison 3. Myo-inositol versus D-*chiro*-inositol as pre-treatment to IVF in women with PCOS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse event	1	84	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.27, 6.20]
1.1 Miscarriage	1	84	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.27, 6.20]
2 Clinical pregnancy	1	84	Odds Ratio (M-H, Fixed, 95% CI)	3.86 [1.25, 11.89]

Comparison 4. Myo-inositol versus an insulin-sensitising agent (metformin) in women with PCOS undergoing ovulation induction

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical pregnancy	1	120	Odds Ratio (M-H, Fixed, 95% CI)	1.91 [0.81, 4.49]
2 Ovulation	1	120	Odds Ratio (M-H, Fixed, 95% CI)	1.86 [0.89, 3.87]

Comparison 5. Myo-inositol versus an ovulation induction agent in women with PCOS undergoing ovulation induction

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	1	75	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.48, 3.40]
2 Adverse event	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Multiple pregnancy	1	75	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.43]
3 Ovulation rate	1	75	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.20, 1.68]

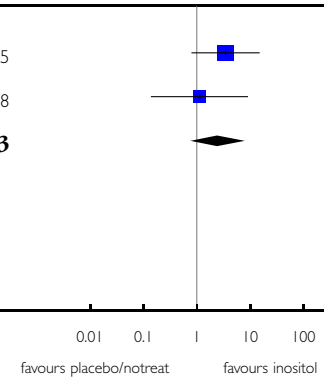
Analysis 1.1. Comparison 1 Myo-inositol versus placebo, no/standard treatment as pre-treatment to IVF in women with PCOS, Outcome 1 Live birth.

Review: Inositol for subfertile women with polycystic ovary syndrome

Comparison: 1 Myo-inositol versus placebo, no/standard treatment as pre-treatment to IVF in women with PCOS

Outcome: 1 Live birth

Study or subgroup	Inositol n/N	placebo or no treatment n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 No treatment/standard treatment					
Artini 2013 (1)	8/25	3/25		55.3 %	3.45 [0.79, 15.01]
Ciotta 2011 (2)	2/16	2/18		44.7 %	1.14 [0.14, 9.21]
Subtotal (95% CI)	**41**	**43**		**100.0 %**	**2.42 [0.75, 7.83]**
Total events: 10 (Inositol), 5 (placebo or no treatment)					
Heterogeneity: Chi^2 = 0.72, df = 1 (P = 0.40); I^2 =0.0%					
Test for overall effect: Z = 1.48 (P = 0.14)					
Test for subgroup differences: Not applicable					



(1) Myoinositol 2g + folic acid 200mcg, dissolved in a glass of water + an additional folic acid 200mcg (oral) vs folic acid 200mcg. Administered 12 weeks pre IVF

(2) Myoinositol 2g + folic acid 200mcg twice a day vs 200mcg folic acid.Treatment administered 12 weeks prior to IVF. Nine month follow up. IVF/ICSI

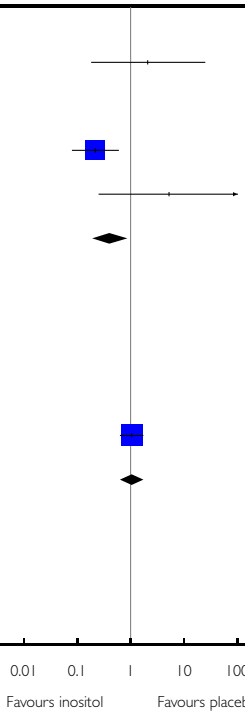
Analysis 1.2. Comparison 1 Myo-inositol versus placebo, no/standard treatment as pre-treatment to IVF in women with PCOS, Outcome 2 Adverse event.

Review: Inositol for subfertile women with polycystic ovary syndrome

Comparison: 1 Myo-inositol versus placebo, no/standard treatment as pre-treatment to IVF in women with PCOS

Outcome: 2 Adverse event

Study or subgroup	Inositol n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Miscarriage					
Artini 2013 (1)	2/25	1/25		4.0 %	2.09 [0.18, 24.61]
Ciotta 2011 (2)	0/16	0/18			Not estimable
Pacchiarotti 2015 (3)	5/180	24/211		94.0 %	0.22 [0.08, 0.60]
Papaleo 2009 (4)	2/30	0/30		2.0 %	5.35 [0.25, 116.31]
Subtotal (95% CI)	**251**	**284**		**100.0 %**	**0.40 [0.19, 0.86]**
Total events: 9 (Inositol), 25 (Control)					
Heterogeneity: Chi^2 = 5.81, df = 2 (P = 0.05); I^2 =66%					
Test for overall effect: Z = 2.34 (P = 0.019)					
2 Multiple pregnancy					
Ciotta 2011 (5)	0/16	0/18			Not estimable
Pacchiarotti 2015 (6)	36/180	41/211		100.0 %	1.04 [0.63, 1.71]
Subtotal (95% CI)	**196**	**229**		**100.0 %**	**1.04 [0.63, 1.71]**
Total events: 36 (Inositol), 41 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.14 (P = 0.89)					
Test for subgroup differences: Chi^2 = 4.14, df = 1 (P = 0.04), I^2 =76%					



(1) Miscarriage rate calculated as the difference between clinical pregnancy rate and live birth. Administered 12 weeks pre IVF

(2) Treatment administered 12 weeks prior to IVF

(3) Treatment was given from the first day of cycle until 14 days after embryo transfer

(4) Treatment given on the first day of GnRHa administration. ICSI

(5) IVF

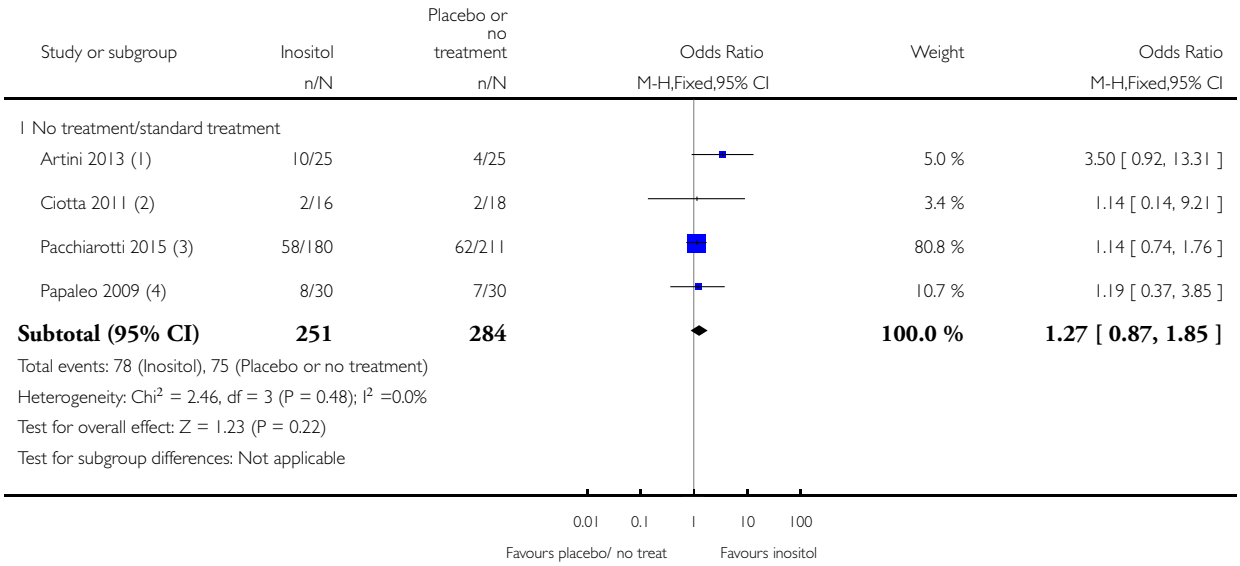
(6) Twin pregnancy rate (IVF)

Analysis 1.3. Comparison 1 Myo-inositol versus placebo, no/standard treatment as pre-treatment to IVF in women with PCOS, Outcome 3 Clinical pregnancy.

Review: Inositol for subfertile women with polycystic ovary syndrome

Comparison: 1 Myo-inositol versus placebo, no/standard treatment as pre-treatment to IVF in women with PCOS

Outcome: 3 Clinical pregnancy



(1) Myoinositol 2g + folic acid 200mcg, dissolved in a glass of water + an additional folic acid 200mcg (oral) vs folic acid 200mcg. Administered 12 weeks pre IVF.

(2) Treatment administered 12 weeks prior to IVF

(3) Myo-inositol 4g + folic acid 400 mcg versus folic acid. IVF. Treatment was given from the first day of cycle until 14 days after embryo transfer

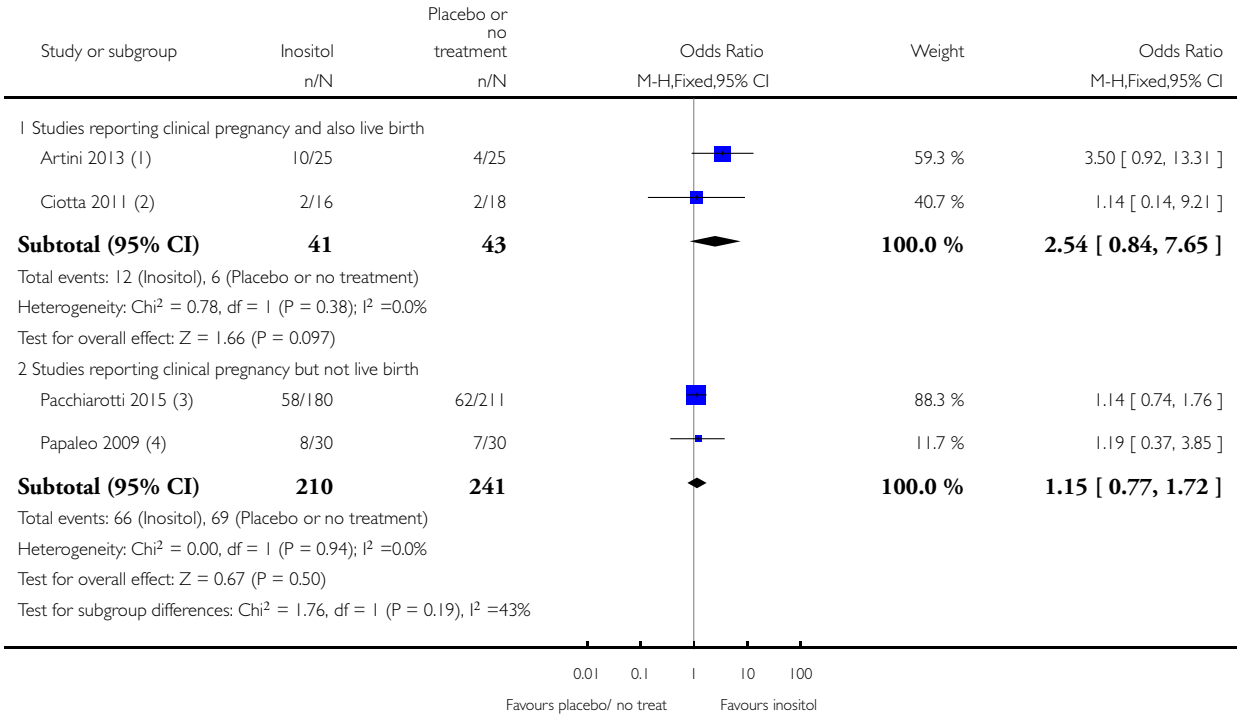
(4) Myo-inositol 2g + folic acid 400 mcg versus folic acid 400 mcg given on the first day of GnRHa administration. ICSI

Analysis 1.4. Comparison 1 Myo-inositol versus placebo, no/standard treatment as pre-treatment to IVF in women with PCOS, Outcome 4 Sensitivity analysis on clinical pregnancy.

Review: Inositol for subfertile women with polycystic ovary syndrome

Comparison: 1 Myo-inositol versus placebo, no/standard treatment as pre-treatment to IVF in women with PCOS

Outcome: 4 Sensitivity analysis on clinical pregnancy



(1) Myoinositol 2g + folic acid 200mcg, dissolved in a glass of water + an additional folic acid 200mcg (oral) vs folic acid 200mcg. Administered 12 weeks pre IVF.

(2) Treatment administered 12 weeks prior to IVF

(3) Myo-inositol 4g + folic acid 400 mcg versus folic acid. IVF. Treatment was given from the first day of cycle until 14 days after embryo transfer

(4) Myo-inositol 2g + folic acid 400 mcg versus folic acid 400 mcg given on the first day of GnRHa administration. ICSI

Analysis 2.1. Comparison 2 Myo-inositol versus antioxidant as pre-treatment to IVF in women with PCOS, Outcome 1 Adverse event.

Review: Inositol for subfertile women with polycystic ovary syndrome

Comparison: 2 Myo-inositol versus antioxidant as pre-treatment to IVF in women with PCOS

Outcome: 1 Adverse event

Study or subgroup	Inositol n/N	Antioxidant n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Miscarriage					
Pacchiarotti 2015 (1)	5/180	7/178		100.0 %	0.70 [0.22, 2.24]
Subtotal (95% CI)	**180**	**178**		**100.0 %**	**0.70 [0.22, 2.24]**
Total events: 5 (Inositol), 7 (Antioxidant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.60 (P = 0.55)					
2 Multiple pregnancy					
Pacchiarotti 2015	36/180	37/178		100.0 %	0.95 [0.57, 1.59]
Subtotal (95% CI)	**180**	**178**		**100.0 %**	**0.95 [0.57, 1.59]**
Total events: 36 (Inositol), 37 (Antioxidant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.18 (P = 0.85)					
Test for subgroup differences: Chi^2 = 0.23, df = 1 (P = 0.63), I^2 =0.0%					

(1) Myo-inositol + folic acid versus melatonin (antioxidant) IVF

Analysis 2.2. Comparison 2 Myo-inositol versus antioxidant as pre-treatment to IVF in women with PCOS, Outcome 2 Clinical pregnancy.

Review: Inositol for subfertile women with polycystic ovary syndrome

Comparison: 2 Myo-inositol versus antioxidant as pre-treatment to IVF in women with PCOS

Outcome: 2 Clinical pregnancy

Study or subgroup	Inositol n/N	Antioxidant n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Pacchiarotti 2015 (1)	58/180	65/178		100.0 %	0.83 [0.53, 1.28]
Total (95% CI)	**180**	**178**		**100.0 %**	**0.83 [0.53, 1.28]**
Total events: 58 (Inositol), 65 (Antioxidant)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.86 (P = 0.39)					
Test for subgroup differences: Not applicable					

(1) treatment is myo-inositol control (antioxidant) is melatonin

Analysis 3.1. Comparison 3 Myo-inositol versus D-*chiro*-inositol as pre-treatment to IVF in women with PCOS, Outcome 1 Adverse event.

Review: Inositol for subfertile women with polycystic ovary syndrome

Comparison: 3 Myo-inositol versus D-*chiro*-inositol as pre-treatment to IVF in women with PCOS

Outcome: 1 Adverse event

Study or subgroup	Inositol n/N	Another type of inositol n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Miscarriage					
Unfer 2011 (1)	4/43	3/41		100.0 %	1.30 [0.27, 6.20]
Total (95% CI)	**43**	**41**		**100.0 %**	**1.30 [0.27, 6.20]**
Total events: 4 (Inositol), 3 (Another type of inositol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					
Test for subgroup differences: Not applicable					

(1) other inositol is D-chiro-inositol, data per pregnancy

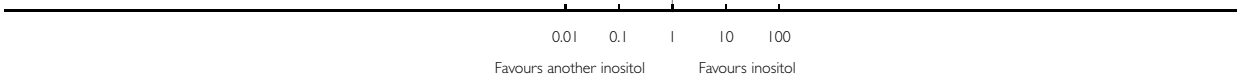
Analysis 3.2. Comparison 3 Myo-inositol versus D-*chiro*-inositol as pre-treatment to IVF in women with PCOS, Outcome 2 Clinical pregnancy.

Review: Inositol for subfertile women with polycystic ovary syndrome

Comparison: 3 Myo-inositol versus D-*chiro*-inositol as pre-treatment to IVF in women with PCOS

Outcome: 2 Clinical pregnancy

Study or subgroup	Inositol n/N	Another type of inositol n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Unfer 2011 (1)	15/43	5/41		100.0 %	3.86 [1.25, 11.89]
Total (95% CI)	**43**	**41**		**100.0 %**	**3.86 [1.25, 11.89]**
Total events: 15 (Inositol), 5 (Another type of inositol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.35 (P = 0.019)					
Test for subgroup differences: Not applicable					



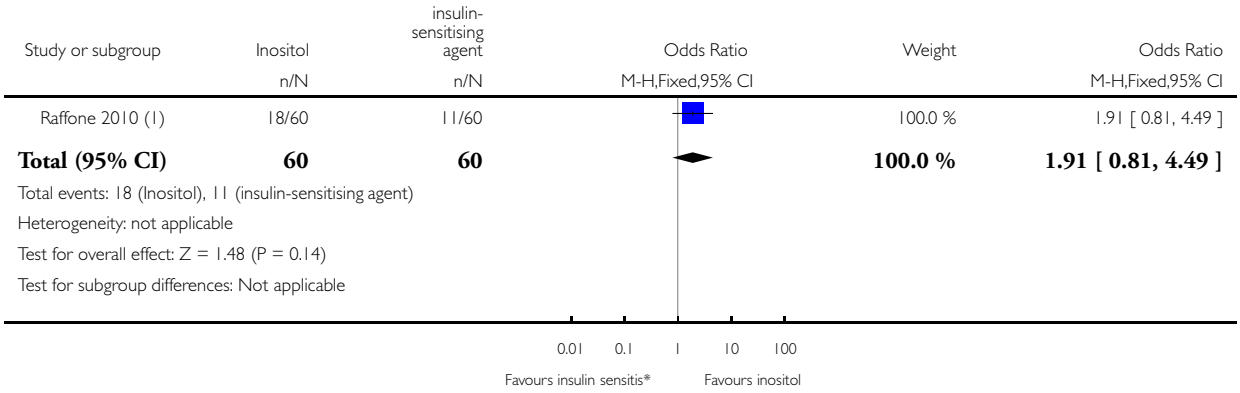
(1) Myo-inositol (treatment) versus D-chiro-inositol (control)

Analysis 4.1. Comparison 4 Myo-inositol versus an insulin-sensitising agent (metformin) in women with PCOS undergoing ovulation induction, Outcome 1 Clinical pregnancy.

Review: Inositol for subfertile women with polycystic ovary syndrome

Comparison: 4 Myo-inositol versus an insulin-sensitising agent (metformin) in women with PCOS undergoing ovulation induction

Outcome: 1 Clinical pregnancy



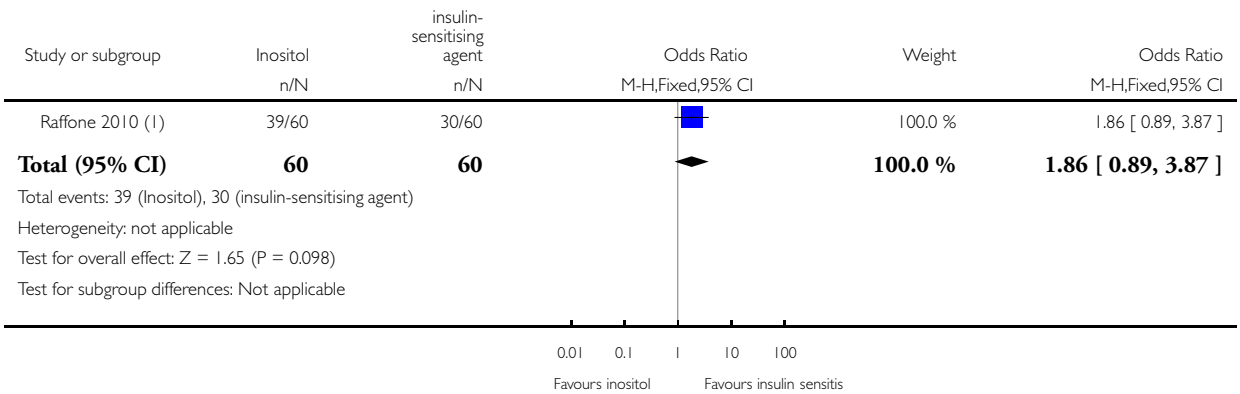
(1) Myoinositol 4g + folic acid 400mcg/day vs Metformin 1500mg/day. Ovulation Induction

Analysis 4.2. Comparison 4 Myo-inositol versus an insulin-sensitising agent (metformin) in women with PCOS undergoing ovulation induction, Outcome 2 Ovulation.

Review: Inositol for subfertile women with polycystic ovary syndrome

Comparison: 4 Myo-inositol versus an insulin-sensitising agent (metformin) in women with PCOS undergoing ovulation induction

Outcome: 2 Ovulation



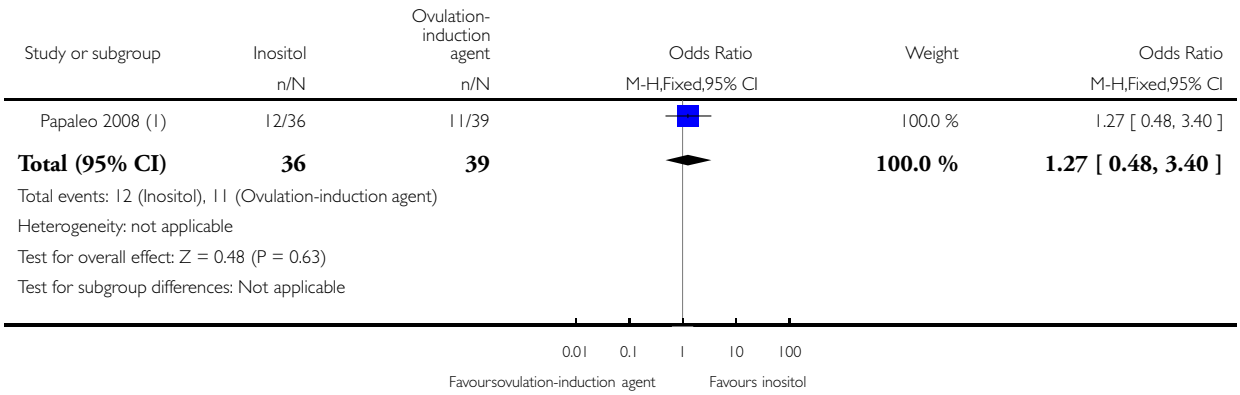
(1) Myoinositol 4g + folic acid 400mcg/day vs Metformin 1500mg/day over a six month period

Analysis 5.1. Comparison 5 Myo-inositol versus an ovulation induction agent in women with PCOS undergoing ovulation induction, Outcome 1 Live birth.

Review: Inositol for subfertile women with polycystic ovary syndrome

Comparison: 5 Myo-inositol versus an ovulation induction agent in women with PCOS undergoing ovulation induction

Outcome: 1 Live birth



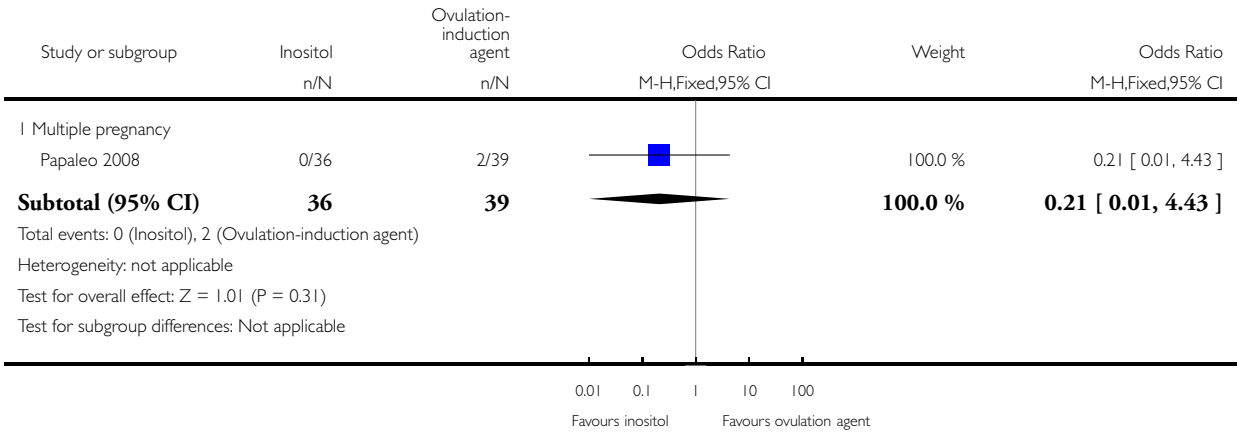
(1) Myoinositol 4 gm + folic acid 400mg vs clomiphene citrate 50mg (increasing to 100mg if resistant). Reported as ongoing pregnancy. Follow up at 6 months. Ovulation induction

Analysis 5.2. Comparison 5 Myo-inositol versus an ovulation induction agent in women with PCOS undergoing ovulation induction, Outcome 2 Adverse event.

Review: Inositol for subfertile women with polycystic ovary syndrome

Comparison: 5 Myo-inositol versus an ovulation induction agent in women with PCOS undergoing ovulation induction

Outcome: 2 Adverse event

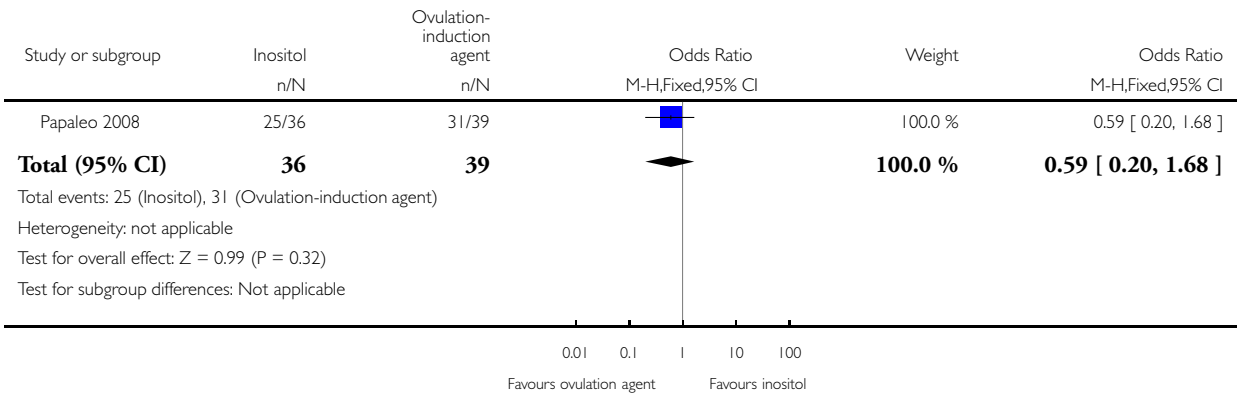


Analysis 5.3. Comparison 5 Myo-inositol versus an ovulation induction agent in women with PCOS undergoing ovulation induction, Outcome 3 Ovulation rate.

Review: Inositol for subfertile women with polycystic ovary syndrome

Comparison: 5 Myo-inositol versus an ovulation induction agent in women with PCOS undergoing ovulation induction

Outcome: 3 Ovulation rate



APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Specialised Register search strategy

PROCITE platform

Searched 30 July 2018
Keywords CONTAINS “polycystic ovary morphology” or “Polycystic ovary syndrome” or “PCOS” or Title CONTAINS “polycystic ovary morphology” or “Polycystic ovary syndrome” or “PCOS” or “hirsutism” or “hirsutism-outcome” or “hirsutism scores”
AND
Keywords CONTAINS “inositol” or “Myo-inositol” or “d-chiro-inositol”or “d-chiro-inositol-containing inositolphosphoglycan mediator” or Title CONTAINS “inositol” or “Myo-inositol” or “d-chiro-inositol”or “d-chiro-inositol-containing inositolphosphoglycan mediator” (46 hits)

Appendix 2. CENTRAL CRSO search strategy

Web platform

Searched 30 July 2018
#1 MESH DESCRIPTOR Polycystic Ovary Syndrome EXPLODE ALL TREES 1242
#2 (PCOS or PCOD):TI,AB,KY 2005
#3 (stein leventhal syndrome):TI,AB,KY 3
#4 (polycystic ovar*):TI,AB,KY 2459
#5 #1 OR #2 OR #3 OR #4 2677
#6 MESH DESCRIPTOR Inositol EXPLODE ALL TREES 382
#7 Inositol:TI,AB,KY 608
#8 myoinositol:TI,AB,KY 62
#9 #6 OR #7 OR #8 706
#10 #5 AND #9 99

Appendix 3. MEDLINE search strategy

OVID platform

From 1946 until 30 July 2018
1 exp Inositol/ (22426)
2 Inositol*.tw. (35223)
3 (mesoinositol or d-chiro-inositol).tw. (238)
4 (myoinositol or myo-inositol).tw. (7019)
5 or/1-4 (43017)
6 exp Polycystic Ovary Syndrome/ (12845)

7 PCOS.tw. (9337)
8 PCOD.tw. (281)
9 (ovar$ adj2 sclerocystic).tw. (99)
10 stein leventhal syndrome.tw. (560)
11 polycystic ovar$.tw. (14413)
12 or/6-11 (17239)
13 5 and 12 (182)
14 randomized controlled trial.pt. (465108)
15 controlled clinical trial.pt. (92522)
16 randomized.ab. (417153)
17 randomised.ab. (83282)
18 placebo.tw. (195646)
19 clinical trials as topic.sh. (184251)
20 randomly.ab. (294326)
21 trial.ti. (185125)
22 (crossover or cross-over or cross over).tw. (77100)
23 or/14-22 (1220301)
24 exp animals/ not humans.sh. (4478492)
25 23 not 24 (1123563)
26 13 and 25 (58)

Appendix 4. Embase search strategy

OVID platform

From 1980 until 30 July 2018
1 exp inositol/ (11326)
2 Inositol.tw. (37751)
3 mesoinositol.tw. (10)
4 myoinositol.tw. (1555)
5 or/1-4 (42166)
6 exp ovary polycystic disease/ (23786)
7 PCOS.tw. (14303)
8 PCOD.tw. (379)
9 (ovar$ adj2 sclerocystic).tw. (98)
10 stein leventhal syndrome.tw. (370)
11 polycystic ovar$.tw. (20042)
12 or/6-11 (27495)
13 5 and 12 (302)
14 Clinical Trial/ (963653)
15 Randomized Controlled Trial/ (508870)
16 exp randomization/ (79089)
17 Single Blind Procedure/ (31974)
18 Double Blind Procedure/ (149457)
19 Crossover Procedure/ (56117)
20 Placebo/ (314548)
21 Randomi?ed controlled trial$.tw. (185218)
22 Rct.tw. (29231)
23 random allocation.tw. (1806)
24 randomly.tw. (381271)
25 randomly allocated.tw. (30095)

26 allocated randomly.tw. (2334)
27 (allocated adj2 random).tw. (800)
28 Single blind$.tw. (21144)
29 Double blind$.tw. (184114)
30 ((treble or triple) adj blind$).tw. (803)
31 placebo$.tw. (271343)
32 prospective study/ (463567)
33 or/14-32 (2144151)
34 case study/ (55745)
35 case report.tw. (359237)
36 abstract report/ or letter/ (1045533)
37 or/34-36 (1451682)
38 33 not 37 (2095002)
39 13 and 38 (119)

Appendix 5. PsycINFO search strategy

OVID platform

From 1806 until 30 July 2018
1 Inositol.tw. (1437)
2 mesoinositol.tw. (0)
3 myoinositol.tw. (134)
4 1 or 2 or 3 (1552)
5 exp Endocrine Sexual Disorders/ (1141)
6 polycystic ovar$.tw. (376)
7 PCOS.tw. (244)
8 PCOD.tw. (6)
9 (ovar$ adj2 sclerocystic).tw. (1)
10 stein leventhal syndrome.tw. (2)
11 5 or 6 or 7 or 8 or 9 or 10 (1393)
12 4 and 11 (0)

Appendix 6. CINAHL search straegy

EBSCO platform

From 1961 until 30 July 2018

#	Query	Results
S10	S5 AND S9	41
S9	S6 OR S7 OR S8	967
S8	TX myoinositol	87

(*Continued*)

S7	TX Inositol	833
S6	(MM "Inositol+")	261
S5	S1 OR S2 OR S3 OR S4	3,318
S4	TX polycystic ovar*	2,812
S3	TX stein leventhal syndrome	8
S2	TX PCOS or TX PCOD	1,734
S1	(MM "Polycystic Ovary Syndrome")	1,747

Appendix 7. AMED search strategy

OVID platform

From 1985 until 30 July 2018
1 exp Polycystic Ovary Syndrome/ (24)
2 (PCOS or PCOD).tw. (49)
3 stein leventhal syndrome.tw. (1)
4 polycystic ovar$.tw. (72)
5 1 or 2 or 3 or 4 (82)
6 Inositol.tw. (53)
7 myoinositol.tw. (1)
8 6 or 7 (54)
9 5 and 8 (2)

Appendix 8. Clinical Trial Registries search strategies

Searched 1 March 2018

Clinicaltrials.gov

https://clinicaltrials.gov/

- inositol and polycystic (18 hits)
- myoinositol and polycystic (18 hits)

WHO International Clinical Trials Registry Platform (ICTRP)

http://apps.who.int/trialsearch/

- inositol and polycystic (26 hits)
- myoinositol and polycystic (30 hits)

Appendix 9. Virtual Health Library platform (including LILACS)

Searched 1 March 2018
http://pesquisa.bvsalud.org/portal/
tw:(inositol AND polycystic ovar*) AND (instance:"regional") (4 hits)

Appendix 10. PubMed search strategy

Searched 1 March 2018
https://www.ncbi.nlm.nih.gov/pubmed
(("inositol"[MeSH Terms] OR "inositol"[All Fields]) AND (polycystic ovaria[All Fields] OR polycystic ovarian[All Fields] OR polycystic ovaries[All Fields] OR polycystic ovary[All Fields])) AND Clinical Trial[ptyp] (33 hits)

Appendix 11. OpenGrey search strategy

Searched 1 March 2018
http://www.opengrey.eu/
inositol and polycystic (0)

Appendix 12. Web of Science search strategy

Searched 1 March 2018
https://apps.webofknowledge.com/WOS_GeneralSearch_input.do?product=WOS&search_mode=GeneralSearch&SID=Q1kFRhCd56OoxAiiCa1&preferencesSaved=
inositol and polycystic ovar* (256 hits)

CONTRIBUTIONS OF AUTHORS

MS wrote the the protocol, designed the search strategies, ran the searches, screened studies, extracted data, analysed data, and wrote the review.

RMP commented on the draft protocol, screened studies, extracted data, and commented on the review.

VJ gave methodological advice and commented on the draft protocol, gave extensive methodological advice, edited the review, and wrote the plain language summary.

RH gave clinical advice and commented on the draft protocol and review.

CF reviewed and commented on the draft protocol and review.

DECLARATIONS OF INTEREST

MS has no conflicts of interest to declare.

RMP has no conflicts of interest to declare.

VJ has no conflicts of interest to declare.

RH has no conflicts of interest to declare.

CF is a director/shareholder of a fertility/gynaecology clinic and undertakes private practice within those premises.

SOURCES OF SUPPORT

Internal sources

- The Cochrane Gynaecology and Fertlity Editorial Team, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added a sensitivity analysis for miscarriage in addition to the proposed analysis on live birth and clinical pregnancy, as this adverse event was a primary outcome.

We changed the unit of analysis for the miscarriage data from per pregnancy to per woman on statistical advice at peer review.

We added the requirement that a trial should be registered to gain low risk of bias for selective outcome reporting.

On clinical advice at peer review, we were asked to separate the populations of women undergoing ovulation induction and those undergoing IVF. We also removed the subgroup for IVF, as it was no longer needed.

We added ovulation rates to summary of findings tables on clinical advice at peer review.

We removed gestational diabetes from the summary of findings table on clinical advice at peer review.