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Systematic review

Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials

J Pundir,[a] D Psaroudakis,[a] P Savnur,[a] P Bhide,[b] L Sabatini,[a] H Teede,[c] A Coomarasamy,[d] S Thangaratinam[e]

[a] Centre for Reproductive Medicine, St. Bartholomew's Hospital, London, UK [b] Fertility and Assisted Reproduction, Homerton University Hospital, Queen Mary University of London, London, UK [c] Monash Centre for Health Research and Implementation, Monash University, Clayton, Vic., Australia [d] Tommy's National Centre for Miscarriage Research, University of Birmingham, Birmingham, UK [e] Women's Health Research Unit, The Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK

Correspondence: J Pundir, Consultant in Reproductive Medicine and Surgery, Centre for Reproductive Medicine, Floor 2, Kenton and Lucas Wing, St Bartholomew's Hospital, West Smithfield, London, UK. Email jyotsnapundir@yahoo.com

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Polycystic ovary syndrome is a common cause of anovulation and infertility, and a risk factor for development of metabolic syndrome and endometrial cancer. Systematic review and meta-analysis of randomised controlled trials (RCT) that evaluated the effects of inositol as an ovulation induction agent. We searched MEDLINE, EMBASE, Cochrane and ISI conference proceedings, Register and Meta-register for RCT and WHO trials' search portal. We included studies that compared inositol with placebo or other ovulation induction agents. Quality of studies was assessed for risk of bias. Results were pooled using random effects meta-analysis and findings were reported as relative risk or standardised mean differences. We included ten randomised trials. A total of 362 women were on inositol (257 on myo-inositol; 105 on di-chiro-inositol), 179 were on placebo and 60 were on metformin. Inositol was associated with significantly improved ovulation rate (RR 2.3; 95% CI 1.1–4.7; I^2 = 75%) and increased frequency of menstrual cycles (RR 6.8; 95% CI 2.8–16.6; I^2 = 0%) compared with placebo. One study reported on clinical pregnancy rate with inositol compared with placebo (RR 3.3; 95% CI 0.4–27.1), and one study compared with metformin (RR 1.5; 95% CI 0.7–3.1). No studies evaluated live birth and miscarriage rates. Inositol appears to regulate menstrual cycles, improve ovulation and induce metabolic changes in polycystic ovary syndrome; however, evidence is lacking for pregnancy, miscarriage or live birth. A further, well-designed multicentre trial to address this issue to provide robust evidence of benefit is warranted.

Keywords Inositol, meta analysis, ovulation induction, polycystic ovary syndrome.

Tweetable abstract Inositols improve menstrual cycles, ovulation and metabolic changes in polycystic ovary syndrome

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Introduction

Absence of ovulation is a key problem in women who are diagnosed with polycystic ovary syndrome (PCOS), a condition also characterised by hyperandrogenaemia, hyperinsulinaemia and a typical sonographic ovarian morphology.[1] It affects up to one in six women, and is a major contributor to infertility.[2,3] In the long term, it increases the risk of endometrial hyperplasia and endometrial cancer.[4] Furthermore, it predisposes women to type 2 diabetes mellitus, and associated cardiovascular complications.[5,6] The obesity epidemic may be a contributory factor to the increasing numbers diagnosed with PCOS.[7]

Regarding fertility, lifestyle interventions targeting weight loss remain the primary therapy in PCOS, since a reduction in weight of as little as 5% can restore regular menstruation and improve response to ovulation-inducing agents, but it is known to be associated with low adherence and sustainability.[8,9] Pharmacological ovulation induction options include clomiphene citrate or metformin or a combination of both.[10,11] If clomiphene citrate is given, ultrasound monitoring is necessary in secondary care, to guide dose

adjustment and monitor complications including multiple pregnancy, which is reported to be about 10%.[12] Moreover, it is not advisable to continue the treatment for longer than 6 months (may be considered up to 12 months) for women who are taking clomiphene citrate.[13,14]

Inositols (myo-inositol and di-chiro-inositol) are nutritional supplements, available over-the-counter. In women with PCOS, a defect in tissue availability or altered metabolism of inositol and/or inositolphosphoglycan mediators (a second messenger pathway in insulin signalling) has been suggested to contribute to insulin resistance.[15] Studies have also demonstrated a physiological role of inositol and its metabolites in human reproduction and supplementation has been proposed to improve endocrine and reproductive outcome in these women, including ovulation, in women with PCOS, at low cost and potentially with fewer adverse effects.[16]

The primary studies on inositol are too small,[17] and existing reviews are narrative, without quantifiable estimates of effect on ovulation and live births.[18–20] We aimed to undertake a systematic review to assess the effects of inositol on ovulation induction and reproductive outcomes, as well as on hormonal and glycaemic profile, when compared with placebo and/or metformin or clomiphene, in women with PCOS.

Methods

Literature search

We searched MEDLINE (1950 to August 2016), EMBASE (1980 to August 2016), the Cochrane Library and ISI conference proceedings for randomised controlled trials (RCTs) on the effects of myo-inositol on ovulation, clinical pregnancy rate, miscarriage rate, live birth rate and hormonal and glycaemic profile in women with PCOS. We also searched for ongoing and archived RCTs using the International Standard Randomised Controlled Trial Number (ISRCTN) Register and Meta-register for RCTs (www.controlled-trials.com), and WHO trials' search portal (ICTRP, http://www.who.int/ictrp/search/en/). We combined the Medical Subject Headings (MeSH) and text words for PCOS (PCOS; Polycystic ovary syndrome; polycystic ovar*; PCO)'and 'Inositol' (Inositol; myo-inositol; DCI; di-chiro-inositol). The reference lists of all known primary and review articles were examined for relevant citations not captured by the electronic searches. There were no language restrictions.

Study selection

Studies were selected in a two-step process by two independent researchers (JP, DP). In the first step, we reviewed the abstracts of identified studies for potential eligibility. The full texts of studies that were considered to be relevant were retrieved in the second stage for detailed evaluation. Any disagreements about inclusion were resolved by consensus or arbitration by a third reviewer (ST). We included studies if the target population was women with PCOS undergoing treatment for ovulation induction. The intervention was inositol (myo- or di-chiro isomers) compared with placebo, clomiphene and/or metformin. We also included studies that compared the effects of the two isomeric forms of inositol. The primary outcomes were rates of ovulation induction, and clinical pregnancy and live births. We considered menstrual regularisation as a surrogate marker of ovulation. Secondary outcomes were changes in hormonal (total androgens, total testosterone, free testosterone, dehydroepiandrosterone, and sex hormone-binding globulin levels) and glycaemic (fasting insulin, fasting glucose, glucose/insulin ratio, homeostatic model assessment [HOMA—a method used to quantify insulin resistance]) profiles. In cases of duplicate publication, the most recent or complete versions were selected. We excluded observational studies.

Assessment of study quality and data extraction

Two independent reviewers completed data extraction (DP and MA) and quality assessment (JP and DP). The qualities of included studies were assessed using the Cochrane risk-of-bias tool. We obtained information on adequacy of randomisation, allocation concealment, blinding, intention-to-treat analysis, incomplete outcome data, selective outcome reporting, follow-up rates and other potential sources of bias. Data were extracted in 2×2 tables for dichotomous outcomes, and as 1×2 tables for continuous outcomes.

Analysis

We estimated the relative risk (RR) for dichotomous outcomes, and standardised mean difference (SMD) with 95% CI for each study. The estimates were pooled using random effects meta-analysis. We considered $P < 0.05$ to be statistically significant. The results from individual studies were pooled using either a fixed effect[21] or random effects[22] model, as appropriate. We evaluated the statistical heterogeneity of the exposure effects graphically using forest plots[23] and statistically using the I^2 statistic.[24] All statistical analyses were performed using RevMan 5.2.7 software (Cochrane Collaboration, Oxford, UK). A funnel plot was produced to assess publication bias for the primary outcome measure.

Results

From 107 potential citations, we included ten studies (601 women) in the review. Figure 1 provides the details of study identification and selection. The list of included and excluded studies is provided in the Supplementary material

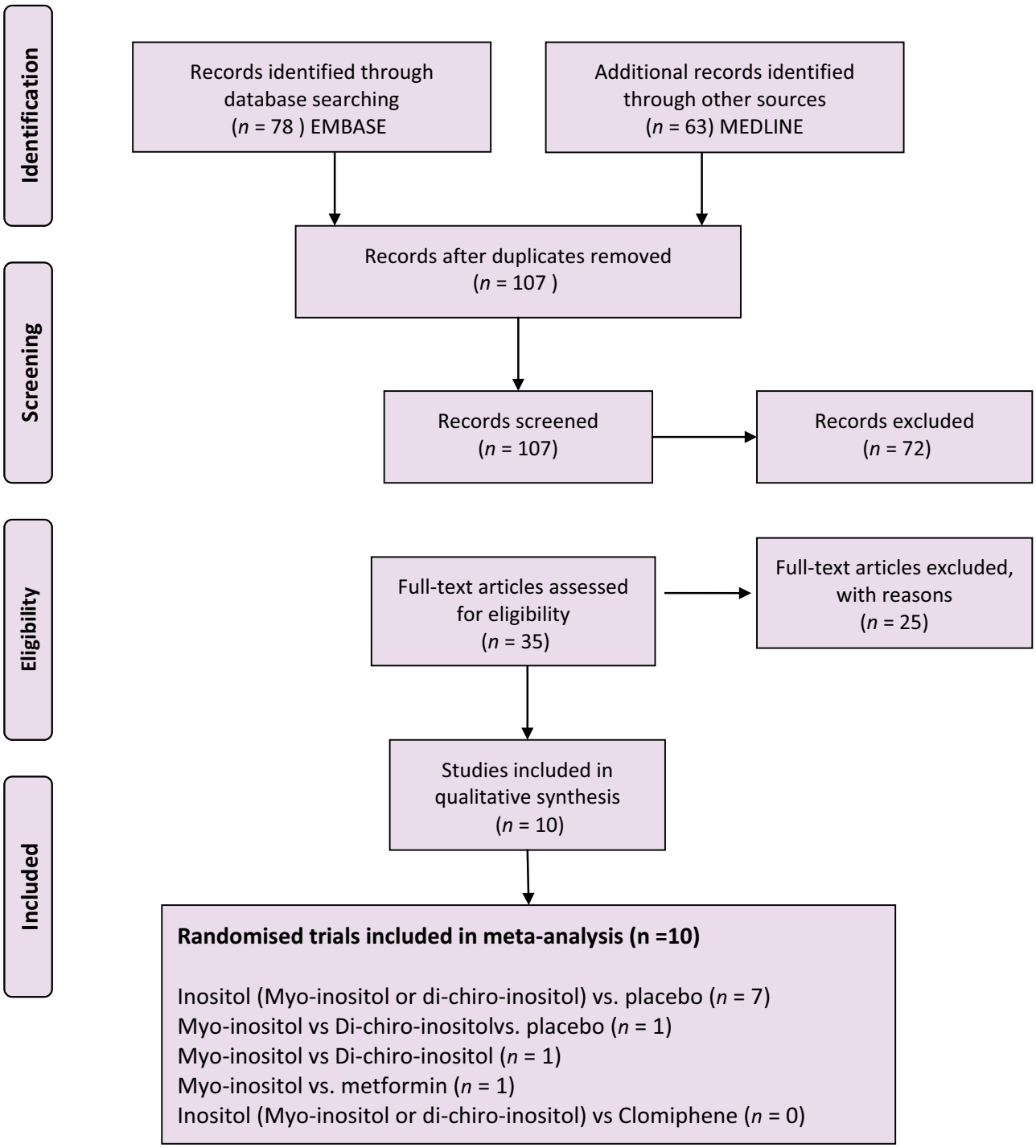

Figure 1. PRISMA 2009 Flow Diagram. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials.

(Table S3) and also the search strategy (see Appendix S1). Inositol (myo-inositol or di-chiro-inositol) was compared with placebo in seven trials,[25–31] myo-inositiol was compared with di-chiro-inositol and with placebo in a three-arm trial,[32] myo-inositiol was compared with di-chiro-inositol in one trial,[33] and one trial compared myo-inositol with metformin.[34] We found no RCTs that compared myo-inositol with clomiphene. In total, 362 women on inositol were included (257 on myo-inositol; 105 on di-chiro-inositol), 179 were on placebo and 60 were on metformin.

Characteristics and quality of the included studies

One study involved obese women with PCOS,[31] and others did not pre-specify or included women of any body mass index. All the studies used pre-defined criteria for PCOS, and the population was relatively homogeneous by meeting the Rotterdam diagnostic criteria for PCOS.[35] Eight trials studied myo-inositol in doses ranging from 1.2 to 4 g; two evaluated di-chiro-inositol with doses from 600 mg to 1.2 g. Seven trials evaluated the effects of inositol on reproductive, hormonal and glycaemic outcomes. Pregnancy rates with myo-inositol were reported in two trials,[29,34] five studies reported ovulation induction.[26,29–31,34] Three trials reported on the improved frequency of menstrual cycles,[28,32,33] and six trials reported the effects on hormonal profile, such as serum total androgens, total testosterone, free testosterone, dehydroepiandrosterone and sex-hormone-binding globulin levels, and on glycaemic outcomes such as serum fasting insulin, fasting glucose, glucose/insulin ratio, homeostatic model assessment to quantify insulin resistance, glucose area under the curve and insulin area under the curve.[25–28,30,31] The details of the study characteristics are provided in the Supplementary material (Table S1).

The risk of bias in selection for randomisation was low in half the trials (5/10), and 20% (2/10) had low risk of allocation concealment. The risk of bias in performance was low in 70% of studies (7/10), which blinded participants and healthcare providers and the outcome assessors. There was no attrition bias in any of the studies. The quality of the included studies is provided in the Supplementary material (Figure S1 and Table S2).

Effects of inositol on reproductive outcomes

Ovulation induction

In anovulatory women with PCOS, treatment with inositol significantly increased the ovulation rate (RR 2.3; 95% CI 1.1–4.7; $I^2 = 75\%$) compared with placebo (Figure 2A). One small study (120 women) that compared the effects of myo-inositol and metformin found no differences between the groups (RR 1.5; 95% CI 0.7–3.1).[34]

In women diagnosed with PCOS and known to have oligomenorrhoea or amenorrhoea, inositol increases the frequency of menstrual cycles six-fold (RR 6.8; 95% CI 2.8–16.6; $I^2 = 0\%$) compared with placebo. There was no difference in cycle regularisation between myo-inositol and di-chiro-inositol (RR 1.0; 95% CI 0.8–1.3) (Figure 2B). Sensitivity analysis, by including studies on menstrual regularisation as a surrogate for ovulation induction, showed a three-fold increase in the effect with inositol compared with placebo (RR 3.2; 95% CI 1.4–7.1) (see Figure S2).

Pregnancy outcomes

When compared with placebo, there were no differences in the rates of clinical pregnancy with myo-inositol (RR 3.30; 95% CI 0.40–27.13) in one study involving 92 women, but the study was underpowered for this outcome.[29] There was no difference in clinical pregnancy rate between myo-inositol and metformin in another small study of 120 women (RR 1.64; 95% CI 0.85–3.16).[34] No studies evaluated live birth and miscarriage rates as an outcome (Figure 2C).

Effects of inositol on hormonal profile

Treatment with inositol in anovulatory women with PCOS showed a significant decrease in levels of total androgen (standardised mean difference [SMD] −1.6; 95% CI −2.5 to −0.6; $P = 0.001$), total testosterone (SMD −3.3; 95% CI −5.1 to −1.5; $P = 0.0004$), free testosterone (SMD −4.4; 95% CI −9.0 to 0.2; $P = 0.06$) and serum dehydroepiandrosterone (SMD −3.2; 95% CI −5.7 to −0.6; $P = 0.02$) compared with placebo. The levels of sex-hormone-binding globulin were significantly increased (SMD 1.3; 95% CI 0.9–1.7; $P < 0.00001$) (Figure 3).

Effects of inositol on glycaemic parameters

Treatment with inositol in anovulatory women with PCOS significantly decreased levels of serum fasting insulin (SMD −2.1, 95% CI −3.2 to −0.9; $P = 0.0003$), fasting glucose (SMD −1.0 95% CI −1.7 to −0.2; $P = 0.01$), HOMA (SMD −1.8; 95% CI −2.6 to −1.0; $P < 0.00001$) and insulin area under the curve (SMD −1.6; 95% CI −2.8 to −0.4; $P = 0.01$). The decrease in glucose area under the curve was not significant (SMD −2.7; 95% CI −5.5 to 0.1; $P = 0.06$). The glucose/insulin ratio was significantly higher with inositol compared with the placebo group (SMD 2.9; 95% CI 2.2–3.6; $P < 0.00001$) (Figure 4).

The shape of the funnel plot for each indicator of the ovulation and metabolic factors did not reveal any asymmetry (see Figure S3).

Discussion

Main findings

In women with PCOS, inositol supplementation appears to increase the rates of ovulation and frequency of menstrual cycles. Two trials evaluated clinical pregnancy rate with inositol, and both showed no differences from placebo or metformin, respectively, although studies were underpowered and no studies reported live birth or miscarriage rates. There was a consistent improvement in glycaemic parameters such as fasting glucose, insulin levels and insulin resistance with inositol compared with placebo. The levels of total androgens, serum testosterone and dehydroepiandrosterone were lowered significantly, and levels of sex-

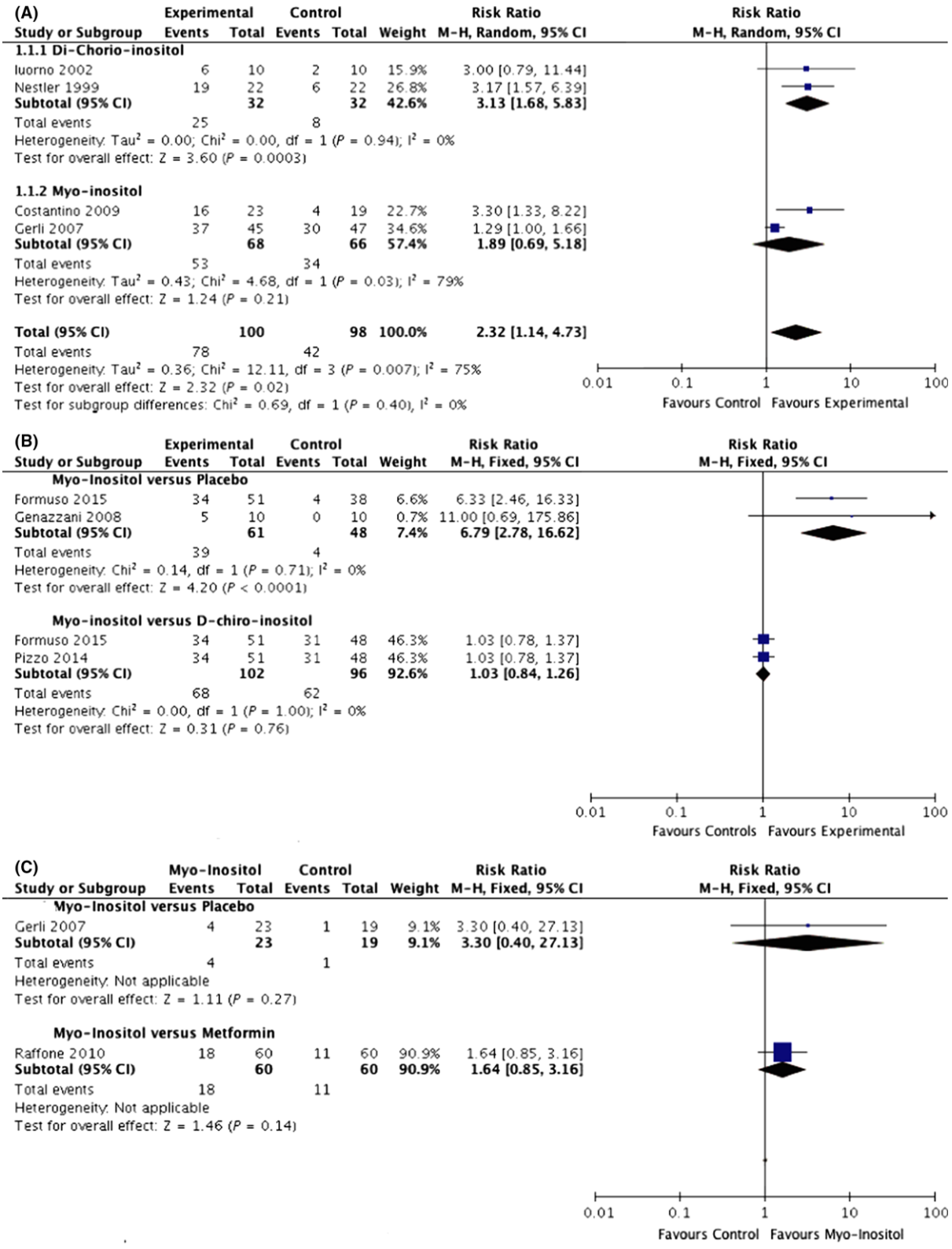

Figure 2. Forest plot of comparison. (A) Forest plot of comparison; inositol versus placebo, outcome: ovulation. (B) Forest plot of comparison; myo-inositol versus placebo; myo-inositol versus di-chloro-inositol, outcome: menstrual cycle regularisation. (C) Forest plot of comparison; myo-inositol versus placebo; myo-inositol versus metformin, outcome: clinical pregnancy rate.

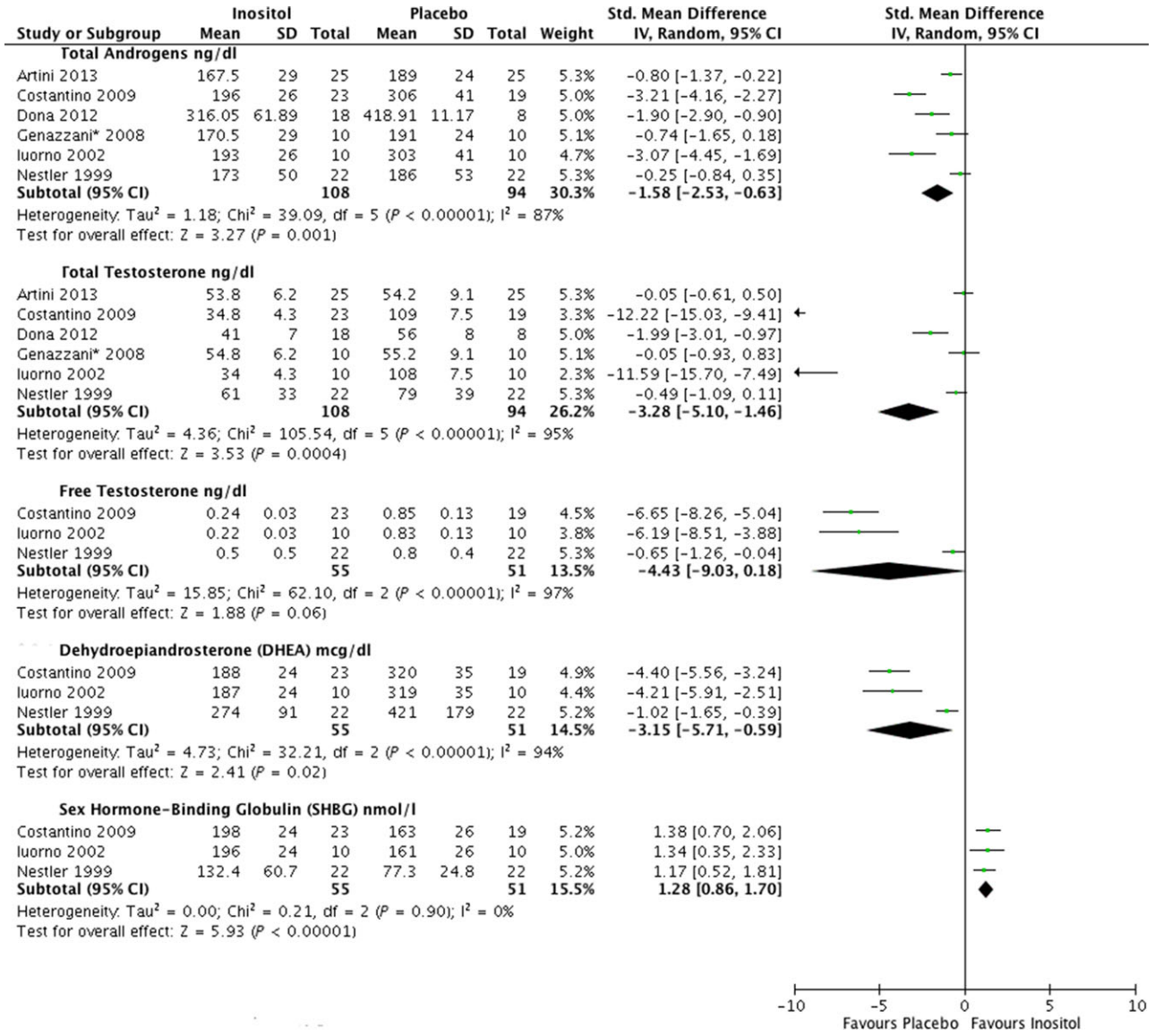

Figure 3. Forest plot of comparison; inositol versus placebo, outcome: hormonal factors.

hormone-binding globulin were improved with inositol. There were no differences in the performance of di-chiro-inositol or myo-inositol for any of the above outcomes.

Strengths and limitations

To our knowledge, this is the first systematic review to provide quantitative estimates of the effects of inositol polymers on ovulation and to explore them in pregnancy rates in women with PCOS. We adopted stringent inclusion criteria and included only RCTs to remove potential bias. We did not have any language restrictions. All studies used predefined Rotterdam diagnostic criteria for PCOS;[35] however, they were heterogeneous by body mass index status and ethnicity. We studied the effects of myo-inositol on both clinical and laboratory parameters. In addition to inositol versus placebo, we compared the performances of the inositol polymers against each other, and against metformin.

The meta-analysis included small numbers of studies with relatively small sample sizes. This contributed to the imprecision in estimates. Studies varied in the type of outcomes reported, and used inconsistent and proxy measures for insulin resistance to assess them. There was variation in the dose and type of inositol and the duration of follow up in these studies, leading to heterogeneity in the findings. Very few studies reported on clinical pregnancy rates, none were powered for this outcome and none reported on the clinically relevant outcome of live birth. We analysed outcomes of ovulation rate and menstrual regularisation

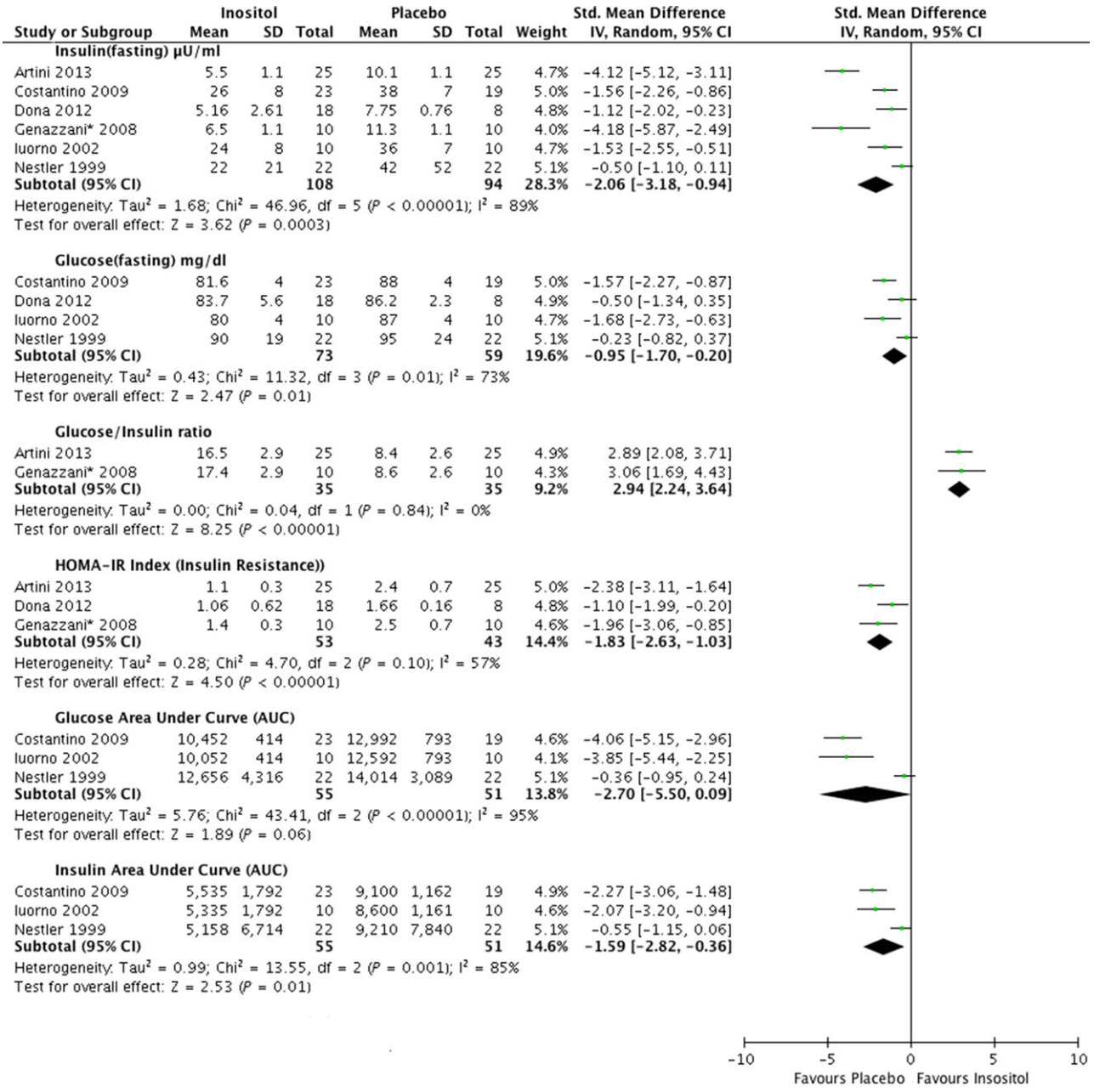

Figure 4. Forest plot of comparison; inositol versus placebo, outcome: glycaemic factors.

separately, and also performed sensitivity analysis by combining these, considering menstrual regularisation as a proxy for ovulation. Both these outcomes individually and in combination showed significant improvement with inositol.

Interpretation

The Cochrane review[36] included only two studies[31,37] on the effects of insulin-sensitising agents on ovulation induction, but suggested a potential benefit with di-chiro-inositol, which was not significant. Other systematic reviews on inositol in PCOS did not provide summary estimates of benefit.[17,18] In comparison, we have included additional studies,[25–30,32–34] with improved precision in estimates for ovulation induction. Only two studies reported on clinical pregnancy rate comparing with placebo and metformin, respectively.[29,34] None of the studies compared inositol with clomiphene and none reported on miscarriage or live birth rates. Randomised trials on myo-inositol in pregnancy have also shown preliminary

beneficial effects in reducing the risk of gestational diabetes,[38] which is likely to be mediated through an improvement in insulin sensitisation.

Insulin resistance and hyperinsulinaemia is an intrinsic feature of both obese and non-obese PCOS women. It is observed in up to 95% of obese women and 75% of lean PCOS women,[39] and is considered to play a key role in the pathogenesis of anovulation, increased ovarian testosterone production and development of various features of metabolic syndrome.[40] Moreover, women with PCOS have an increased risk and prevalence of obesity, which further exacerbates the intrinsic PCOS-related insulin resistance and worsens clinical features.[39,41,42] Insulin sensitisers and lifestyle have been used to treat PCOS; however, they fail to normalise insulin resistance and further interventions are needed.[36,39,43]

In anovulatory women diagnosed with PCOS, a defect in tissue availability, or altered metabolism of inositol and/or inositol phosphoglycan mediators (involved in the second messenger pathway of insulin signalling) have been suggested to contribute to insulin resistance.[15] Inositol, a vitamin B complex nutritional supplement, is available as an over-the-counter product. Epimerisation of the six hydroxyl groups of inositol leads to the formation of up to nine stereoisomers. Of these, myo-inositol and di-chiro-inositol, may have potential roles in improving endocrine and reproductive outcomes in women with PCOS, because of their involvement, as second messengers of insulin, resulting in insulin sensitisation.[16,31]

PCOS has clinical implications throughout a woman's lifespan and it is also relevant to family members, with an increased risk for metabolic conditions reported in first-degree relatives. From a public health point of view, it has a huge economic burden on the healthcare system because of both reproductive issues and long-term chronic morbidity affecting later life.[4,44] The cost of evaluating for PCOS and its associated morbidities, and treating the long-term morbidities, exceeds $4 billion annually (in 2004 dollars) in the USA alone.[4] Furthermore, these women also have obstetric complications, including a high risk of gestational diabetes.[45,46]

Until now, insulin-sensitising compounds, such as metformin, pioglitazone and troglitazone, have been considered to induce ovulation and improve features of metabolic syndrome in women with PCOS.[36] Of these, thiazolidinedione, category C drug, is associated with significant adverse effects such as myocardial infarction,[47] weight gain and adverse effects in animal studies in pregnancy. Therefore they are unlikely to have a major clinical role in treating women with PCOS. Although metformin has a role in reducing insulin resistance, it does not normalise insulin resistance in PCOS and has limited efficacy in infertility; its use is limited by mild gastrointestinal adverse effects possibly reducing compliance.

Our systematic review has shown a clear benefit with inositol in improving ovulation rate and on the hormonal and glycaemic profiles in women with PCOS. Whether this translates into clinical benefit with improved pregnancy and increased live birth rate and into reduced development of metabolic complications including gestational diabetes, type II diabetes or metabolic disease is yet to be shown. If found to be effective at improving primary clinical outcomes, inositol supplementation, alongside lifestyle advice, could become a first-line treatment to improve fertility in women with PCOS. By regularising menstrual cycles, it also has the potential to also reduce the burden of endometrial hyperplasia and malignancy in these women. With no significant adverse effects and easy accessibility, it is likely to result in high compliance. Unlike clomiphene citrate, the supplement could be provided in primary-care settings and does not require expensive specialist review and monitoring.

There is a clear need for a large randomised trial to compare the effects of inositol alongside lifestyle advice compared with placebo and lifestyle advice as a first line of treatment for reproductive outcomes across ovulation induction, pregnancy rates and live birth rates in women with PCOS. The possibility of addition of clomiphene and/or metformin in both arms after a set period of trial with the above needs to be further evaluated. Likewise, longer-term studies on the effect of inositol on metabolic outcomes and pregnancy outcomes is also warranted.

Conclusions

Inositol appears to significantly improve the ovulation rate, and metabolic and hormonal profiles in women with PCOS compared with placebo. There is a need to assess its effect on pregnancy and live birth rates and on longer term metabolic health outcomes. This review shows promising but preliminary favourable results with myo-inositol in women with PCOS. A well-designed and well-conducted multicentre trial to address this issue to provide robust evidence of benefit is warranted before the widespread use of inositol can be recommended.

Disclosure of interest

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

JP contributed to the conception, planning, carrying out, analysing and writing up. DP performed data extraction and literature search and PS performed data extraction. LS, PB, HT and AC revised the article critically for important intellectual content. ST contributed to the conception and planning, and revised the article critically for important intellectual content.

Details of ethics approval
Not needed.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Risk of bias for studies on inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials.

Figure S2. Forest plot of comparison; inositol versus placebo, outcome: ovulation induction and menstrual regularisation used as a surrogate.

Figure S3. Funnel plot of comparison: inositol versus placebo, outcome: ovulation.

Table S1. Characteristics of the studies included in the review of inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials.

Table S2. Quality of studies included in the review of inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials.

Table S3. Excluded and included studies.

Appendix S1. Search strategy. ■

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