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Inositol for subfertile women with polycystic ovary syndrome (Protocol)

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[Intervention Protocol]

Inositol for subfertile women with polycystic ovary syndrome

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the effectiveness and safety of oral supplementation with inositol on reproductive outcomes for subfertile women with polycystic ovary syndrome (PCOS).

BACKGROUND

Description of the condition

Polycystic ovary syndrome (PCOS) is a syndrome with no single clinical symptom, that 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). It is the most common endocrine abnormality in reproductive women (Abu Hashim 2012), and is thought to affect 6% to 10% of women in the reproductive age group, although this 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 effect on metabolic and reproductive features seems to be an important factor, while genetic and environmental causes also play a role (Facchinetti 2015; Franks 1995). A study of Indian women with PCOS showed 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, however 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).

The diagnostic criteria are based on the *Revised 2003 consensus* (Rotterdam 2004), jointly proposed by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine. In order to make a diagnosis of PCOS a woman must exhibit at least two of the following three criteria;

1. oligo-ovulation (infrequent ovulation) or anovulation (absence of ovulation), or both;
2. hyperandrogenism (high levels of male hormones), either clinically with excessive hair growth, or biochemically with raised blood serum androgen levels;
3. polycystic ovaries, 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)".

Diagnosis of PCOS using these criteria is made only after exclusion of other disorders such as congential adrenal hyperplasia, androgen-secreting tumours or Cushing syndrome (Vause 2010).

Anovulation is the reason that approximately one-third of couples seek fertility advice, and about 90% of these women have PCOS (Balen 2002). The 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) is unknown (Brown 2009). The hypersecretion of LH is found only in women with PCOS and this is thought to impact on fertility and miscarriage by disturbing the timing of the 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). The current leading treatments for ovulation induction are clomiphene citrate (an antioestrogen 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 the prevalence is thought to be between 10% to 25% (Rotterdam 2004). The Burghen 1980 study first demonstrated the positive correlation between hyperandrogenism and hyperinsulinism in women with PCOS. There is a negative effect on having both PCOS and obesity on insulin action and the resulting hyperinsulinaemia contributes to reproductive problems in women with PCOS (Fauser 2012). The combination of obesity, metabolic, inflammatory and endocrine disorders may lead to problems in ovulatory function, oocyte quality and endometrial receptivity. In pregnancies of women with PCOS there is an increased incidence of gestational diabetes (40% to 50%; and when this occurs it may result in fetal macrosomia (large babies)), gestation hypertensive disorders (such as pre-eclampsia and gestational hypertension; 5%), and babies that are small for their gestational age (10% to 15%) (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 the absorption of this free inositol can be inhibited by glucose (Beemster 2002). Inositol also acts 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 in the cells (Ruder 2008).

Inositol is proposed as a therapy for many disorders including, diabetic nerve pain, high cholesterol, insomnia, depression and PCOS. Inositol is critical for many biological pathways: the concentration of inositol is much higher in the reproductive organs than in the serum, perhaps indicating the importance of these substances in reproduction (Unfer 2014). The MI form is largely responsible for glucose uptake, while DCI is responsible for glycogen synthesis (Kamenov 2015). Inositol is available in tablet and powder form and has been given in a dose of 2 g/day to 4 g/day (Lisi 2016), however the literature does not provide clarity on the appropriate therapeutic dose or any adverse effects. Inositol can also be given as Inofolic, a supplement that contains 2 g MI and 200 µg folic acid (Papaleo 2011).

How the intervention might work

Studies show altered metabolic parameters and a lower 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 as they act as an insulin sensitising agent and free radical scavenger, helping to regulate metabolism and promote 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). An experimental study by Kamenov 2015 showed that MI is a well tolerated and may be effective for ovulation induction and metabolic balance in women with PCOS. Another study of MI in normal weight women with PCOS showed a modulating effect on hormones including androstenedione, plus a decrease in insulin response after 12 weeks of treatment (Genazzani 2014a). Another study by the same researchers, Genazzani 2014, assessed the effects of DCI in obese women with PCOS and this study also demonstrated a positive effect on insulin resistance and hormonal balance. A longitudinal study, Minozzi 2013, found that a combination of both MI and DCI led to improved glucose metabolism. A systematic review of randomised controlled trials showed that MI supplementation in women with PCOS may lead to an improvement in insulin sensitivity, restoration of ovulation, improvement in oocyte quality and a reduction in hyperandrogenism through the reduction of insulin plasma levels, which may, in turn, help to increase their fertility (Unfer 2012).

Why it is important to do this review

Subfertile women are highly motivated to try different adjunctive therapies in order to have a baby, and there is a widespread perception that dietary supplements such as MI and DCI are associated only with benefit and 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 that indicates that higher doses of DCI may lead to greater numbers of immature and lower quality oocytes compared to placebo (Rosalbino 2012). Although DCI is widely used to treat PCOS, it is not US Food and Drug Administration (FDA) approved. A review showed only limited evidence to support the use of inositol for improving fertility in women with PCOS, as the trials were small and very few used a placebo control (Vitek 2015). A Cochrane Review found that the important outcomes of live birth and clinical pregnancy were not reported in two trials that used DCI for women with PCOS, and there was no evidence of effect for improved ovulation rate (Tang 2012). It is important to conduct this review in order to provide evidence of any benefits or harms, or both, in the use of inositol for these women.

OBJECTIVES

To evaluate the effectiveness and safety of oral supplementation with inositol on reproductive outcomes for subfertile women with polycystic ovary syndrome (PCOS).

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished randomised controlled trials (RCTs) will be eligible for inclusion. Cross-over trials will be considered eligible but we will include only data from the first phase (Dias 2006).

Types of participants

Subfertile women who have PCOS (as defined by the criteria in the Rotterdam consensus workshop (Rotterdam 2004), who are trying to become pregnant will be eligible for inclusion. This will include subfertile women undergoing expectant management, timed intercourse, ovulation induction, intrauterine insemination (IUI) or in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI). We define subfertility, or infertility, as the failure to achieve a successful pregnancy after 12 months of timed, unprotected intercourse (ASRM 2013).

Types of interventions

Inclusion criteria

1. Oral inositol versus:
   i) placebo or no treatment;
   ii) any active intervention (e.g. another antioxidant, insulin sensitising agent, ovulation induction agent).
2. One type (stereoisomer) of oral inositol versus another type (e.g. MI, DCI). We will include any of the following inositol compounds; myo-inositol, D-*chiro*-inositol and L-*chiro* inositol. Any fertility agent (i.e. metformin, clomiphene citrate or another antioxidant) given in addition to inositol and appearing in both the intervention and comparator arms will be analysed as inositol versus no treatment, e.g. metformin + inositol versus metformin.

Types of outcome measures

Primary outcomes

1. Live birth or ongoing pregnancy: live birth will be reported by preference, but if data are unavailable we will report ongoing pregnancy (footnoted in the forest plot). Live birth is defined as delivery of a live fetus after 20 completed weeks of gestation, and ongoing pregnancy is defined as evidence of a gestational sac with fetal heart motion at 12 weeks, confirmed with ultrasound.
2. Any adverse event (including miscarriage, multiple birth, ectopic pregnancy, fetal abnormalities, drug side effects, ovarian hyperstimulation syndrome) as reported by the trials. These events will be subgrouped according to the type of adverse event reported.

Secondary outcomes

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

Search methods for identification of studies

We will search for all published and unpublished RCTs of inositol, without language restrictions and in consultation with the Gynaecology and Fertility Group (CGFG) Information Specialist.

Electronic searches

We will search the following electronic databases, trial registers and websites:

The Gynaecology and Fertility Group (CGF) Specialised Register of Controlled Trials (Appendix 1), the Cochrane Central Register of Controlled Trials Online (Appendix 2), MEDLINE (Appendix 3), Embase (Appendix 4), PsycINFO (Appendix 5), CINAHL (Appendix 6) and AMED (Appendix 7). The MEDLINE search will be combined with the Cochrane highly sensitive search strategy for identifying randomised trials which appears in chapter 6 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Lefebvre 2011). The Embase, PsycINFO and CINAHL searches will be combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (Scottish Intercollegiate Network).

Other electronic sources of trials will include:

1. Trial registers for ongoing and registered trials (note: it is now mandatory for Cochrane Reviews to include searches of trial registers):
   i) Clinicaltrials.gov (www.clinicaltrials.gov) (a service of the US National Institutes of Health);
   ii) the World Health Organization International Trials Registry Platform search portal (www.who.int/trialsearch/Default.aspx) (Appendix 8).
2. LILACS and other Spanish/Portuguese databases via the Virtual Health Library Regional Portal (VHL) (regional.bvsalud.org/php/index.php?lang=en) (Appendix 9);
3. PubMed and Google Scholar (for recent trials not yet indexed in the major databases) (Appendix 10);
4. OpenGrey (www.opengrey.eu/) for unpublished literature from Europe (Appendix 11);
5. The Web of Science (wokinfo.com/) (another source of trials and conference abstracts) (Appendix 12).

Searching other resources

We will handsearch reference lists of articles retrieved by the search, and contact experts in the field to obtain additional studies.

We will use ENDNOTE bibliographic management software to manage the search output.

Data collection and analysis

Selection of studies

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

Two review authors (MS and RMP) will conduct an initial screen of titles and abstracts retrieved by the search, then we will retrieve the full texts of all potentially eligible studies. Independently, two review authors (MS and RMP) will examine these full text articles for compliance with the inclusion criteria and select studies eligible for inclusion in the review. Any study that we exclude following a review of the full text will have the reason for exclusion recorded. We will correspond with study investigators as required, to clarify study eligibility. Disagreements regarding study eligibility will be resolved by discussion or by a third review author (VJ). We will document the selection process with a PRISMA flow chart.

Data extraction and management

Independently, two review authors (MS and RMP) will extract data from eligible studies using a data extraction form in COVIDENCE. Any disagreements will be resolved by discussion or by a third review author (VJ). Data extracted will include study characteristics and outcome data. Where studies have multiple publications, the authors will collate multiple reports of the same study, so that each study - rather than each report - is the unit of interest in the review, and these studies will have a single study ID with multiple references.

We will correspond with study investigators for further information about methods and results, as required.

Assessment of risk of bias in included studies

Independently, two review authors (MS and RMP) will use the Cochrane tool to assess the risk of bias of 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 will resolve disagreements by discussion or by a third review author (VJ). We will describe all judgements fully and present the conclusions in the 'Risk of bias table, which will be incorporated into the interpretation of review findings by means of sensitivity analyses (see below).

We will take care to search for within-trial selective reporting, such as trials failing to report obvious outcomes, or reporting them in insufficient detail. We will seek published protocols and compare the outcomes specified in the protocol and reported in the final published study.

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

Criteria for:

1. low risk of bias, e.g. coin toss, random number table; computer random number generator;
2. unclear risk of bias, e.g. studies that give insufficient information or do not describe the methods used for randomisation.

Any study deemed to be at high risk of bias i.e. quasi randomised, will be excluded from the review

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

Criteria for:

1. low risk of bias e.g. telephone, web based or central randomisation or sequentially numbered sealed opaque envelopes;
2. high risk of bias e.g. open allocation, unsealed or see-through envelopes, alternation or date of birth or medical record number;
3. unclear risk of bias e.g. no description of how allocation was concealed or insufficient information.

3. Blinding of participants and personnel (possible performance bias; due to knowledge of the 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 will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. Lack of blinding of the 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 irritations or digestive problems.

Criteria for participants and personnel:

1. low risk of bias, if no blinding of personnel or outcome assessment and the review authors judge that outcome was unlikely to be affected by lack of blinding; or the study was blinded and it was unlikely that the blinding could have been broken;
2. high risk of bias, no blinding and the outcome was likely to be influenced by lack of blinding, or if blinded then blinding was likely to be broken;
3. unclear risk of bias, insufficient information or the study did not address this outcome.

4. Incomplete outcome data (possible attrition bias due to the amount, nature and handling of incomplete outcome data)

Criteria for:

1. low risk of bias, e.g. no missing outcome data, or missing outcome data are balanced across groups, or missing data are imputed using appropriate methods;
2. high risk of bias, e.g. the reason for missing outcome data is likely to be related to the true outcome with either an imbalance in numbers, or reasons for missing data across intervention groups, or 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation;
3. 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, or no reasons for missing data given.

5. Selective reporting (possible reporting bias)

We will attempt to find protocols of the included studies and compare the outcomes between the protocol and the final published study in order to assess within-trial selective reporting. If no protocol is available we will assess the reporting of outcomes from the methods section of the paper and also assess whether an outcome was likely to be have been planned or measured, but not reported in the paper.

Criteria for:

1. low risk of bias, when it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported;
2. high risk of bias, where not all the study's prespecified outcomes have been reported, one or more reported primary outcomes were not prespecified, or outcomes of interest are reported incompletely and so cannot be entered into a meta-analysis, or the study fails to report results of a key outcome that would have been expected to have been reported;
3. unclear risk of bias, insufficient information available to permit a judgement of high or low risk.

6. Other bias (possible bias due to problems not covered in biases 1-5)

1. low risk of bias, the study appears to be free of any other source of bias;
2. high risk of bias, e.g. use of a specific study design or a fraudulent study;
3. unclear risk of bias due to insufficient information.

Measures of treatment effect

For dichotomous data (e.g. live birth rates), we will use the numbers of events in the control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (OR). We do not anticipate that there will be any continuous data. We will present 95% confidence intervals (CI) for all outcomes. Where data to calculate ORs are not available, we will utilise the most detailed numerical data available that may facilitate similar analyses of included studies (e.g. test statistics, P values).

Unit of analysis issues

The primary analysis will be per woman randomised; per pregnancy data may also be included for some outcomes (e.g. miscarriage). Data that do not allow valid analysis (e.g. 'per cycle' data) will be briefly summarised in an additional table and will not be pooled or used in quantitative synthesis. However 'per cycle' data will be analysed when the trial provides data for only one cycle per woman. Multiple live births (e.g. twins or triplets) will be counted as one live birth event. Only first-phase data from cross-over trials will be included (Dias 2006).

Dealing with missing data

We will analyse the data on an intention-to-treat basis as far as possible and attempts will be made to obtain missing data from the trial authors. Where these are unobtainable, we will undertake imputation of individual values for live birth and pregnancy. Live births and pregnancies will be assumed not to have occurred in participants without a reported outcome. For other outcomes, we will analyse only the available data. Any imputation undertaken will be subjected to sensitivity analysis.

Assessment of heterogeneity

We will consider whether the clinical and methodological characteristics of the included studies are sufficiently similar for meta-analysis to provide a clinically meaningful summary. We will assess 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, the authors will aim to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If there are ten or more studies in an analysis, we will use a funnel plot (Higgins 2011) to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

If the studies are sufficiently similar, we will combine the data using a fixed-effect model in the following comparisons.

1. Inositol versus placebo, no treatment or folic acid (we will assume that all women will be given folic acid as standard treatment, i.e. folic acid will be given to both the intervention and control arms)
2. Inositol versus another type of antioxidant
3. Inositol versus an insulin-sensitising agent
4. Inositol versus an ovulation-induction agent
5. Inositol versus another type of inositol (e.g. MI or DCI)

Any fertility agent (i.e. metformin, clomiphene citrate or another antioxidant) given in addition to inositol and appearing in both the intervention and comparator arms will be analysed as inositol versus no treatment e.g. metformin + inositol versus metformin. We plan to pool the data in these comparisons.

An increase in the odds of a particular outcome, which may be beneficial (e.g. live birth) or detrimental (e.g. adverse effects), will be displayed graphically in the meta-analyses to the right of the centre-line and a decrease in the odds of an outcome to the left of the centre-line.

Statistical analysis will be performed using Review Manager 5.3 (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

In order to answer questions of clinical interest we will conduct subgroup analyses to determine the separate evidence within the following subgroups, if data are available for the outcomes of live birth and clinical pregnancy.

1. type of inositol; MI or DI
2. type of comparator
3. women who have undergone IVF/ICSI

For the outcome of adverse events we will subgroup the data on the basis of the type of event.

In addition to visual inspection of the subgroup differences, we will use a significance test to determine the percentage of the variability in effect estimates from the different subgroups that is due to genuine subgroup differences rather than sampling error (chance) (Higgins 2011). We will take any statistical heterogeneity into account when interpreting the results, especially if there is any variation in the direction of effect.

Sensitivity analysis

We will conduct sensitivity analyses for live birth and clinical pregnancy to determine whether the conclusions are robust to different decisions made regarding the eligibility and analysis. These analyses will include consideration of whether the review conclusions would have differed if:

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

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

We will prepare a 'Summary of findings' table using GRADEpro GDT and Cochrane methods (GradePro). This table will evaluate the overall quality of the body of evidence for the main review outcomes (live birth, adverse events, clinical pregnancy and gestational diabetes mellitus) for the main review comparison (inositol versus placebo or no treatment). Additional 'Summary of findings' tables will be prepared for these outcomes for other important comparisons (inositol versus another type of inositol, inositol versus another type of antioxidant, inositol versus an insulin-sensitising agent, inositol versus an ovulation induction agent. We will assess the quality of the evidence using GRADE criteria: risk of bias, consistency of effect, imprecision, indirectness and publication bias). Judgements about evidence quality (high, moderate, low or very low) will be made by two review authors working independently, with disagreements resolved by discussion. Judgements will be justified, documented, and incorporated into the reporting of results for each outcome.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility specialised register search strategy

PROCITE Platform

From inception until present
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”

Appendix 2. CENTRAL CRSO search strategy

Web platform

From inception until present
MESH DESCRIPTOR Polycystic Ovary Syndrome EXPLODE ALL TREES
(PCOS or PCOD):TI,AB,KY
(stein leventhal syndrome):TI,AB,KY
(polycystic ovar*):TI,AB,KY
#1 OR #2 OR #3 OR #4
MESH DESCRIPTOR Inositol EXPLODE ALL TREES
Inositol:TI,AB,KY
myoinositol:TI,AB,KY
#6 OR #7 OR #8
#5 AND #9

Appendix 3. MEDLINE search strategy

OVID platform

From 1946 until present
1 exp Inositol/
2 Inositol.tw.
3 mesoinositol.tw.
4 myoinositol.tw.
5 or/1-4
6 exp Polycystic Ovary Syndrome/
7 PCOS.tw.
8 PCOD.tw.
9 (ovar$ adj2 sclerocystic).tw.
10 stein leventhal syndrome.tw.
11 polycystic ovar$.tw.
12 or/6-11
13 5 and 12
14 randomized controlled trial.pt.
15 controlled clinical trial.pt.
16 randomized.ab.
17 randomised.ab.
18 placebo.tw.
19 clinical trials as topic.sh.
20 randomly.ab.
21 trial.ti.
22 (crossover or cross-over or cross over).tw.
23 or/14-22
24 exp animals/ not humans.sh.
25 23 not 24
26 13 and 25

Appendix 4. Embase search strategy

OVID platform

From 1974 until present
1 exp inositol/
2 Inositol.tw.
3 mesoinositol.tw.
4 myoinositol.tw.
5 or/1-4
6 exp ovary polycystic disease/
7 PCOS.tw.
8 PCOD.tw.
9 (ovar$ adj2 sclerocystic).tw.
10 stein leventhal syndrome.tw.
11 polycystic ovar$.tw.
12 or/6-11
13 5 and 12
14 Clinical Trial/
15 Randomized Controlled Trial/
16 exp randomization/
17 Single Blind Procedure/
18 Double Blind Procedure/
19 Crossover Procedure/
20 Placebo/
21 Randomi?ed controlled trial$.tw.
22 Rct.tw.
23 random allocation.tw.
24 randomly.tw.
25 randomly allocated.tw.
26 allocated randomly.tw.
27 (allocated adj2 random).tw.
28 Single blind$.tw.
29 Double blind$.tw.
30 ((treble or triple) adj blind$).tw.
31 placebo$.tw.
32 prospective study/
33 or/14-32
34 case study/
35 case report.tw.
36 abstract report/ or letter/
37 or/34-36
38 33 not 37
39 13 and 38

Appendix 5. PsycINFO search strategy

OVID platform

From 1806 until present
1 Inositol.tw.
2 mesoinositol.tw.
3 myoinositol.tw.
4 1 or 2 or 3
5 exp Endocrine Sexual Disorders/
6 polycystic ovar$.tw.
7 PCOS.tw.
8 PCOD.tw.
9 (ovar$ adj2 sclerocystic).tw.
10 stein leventhal syndrome.tw.
11 5 or 6 or 7 or 8 or 9 or 10
12 4 and 11

Appendix 6. CINAHL search straegy

EBSCO platform

From 1982 until present

#	Query
S10	S5 AND S9
S9	S6 OR S7 OR S8
S8	TX myoinositol
S7	TX Inositol
S6	(MM "Inositol+")
S5	S1 OR S2 OR S3 OR S4
S4	TX polycystic ovar*
S3	TX stein leventhal syndrome
S2	TX PCOS or TX PCOD
S1	(MM "Polycystic Ovary Syndrome")

Appendix 7. AMED search strategy

OVID platform

From inception until present
1 exp Polycystic Ovary Syndrome/
2 (PCOS or PCOD).tw.
3 stein leventhal syndrome.tw.
4 polycystic ovar$.tw.
5 1 or 2 or 3 or 4
6 Inositol.tw.
7 myoinositol.tw.
8 6 or 7
9 5 and 8

Appendix 8. Clinical Trial Registries search strategies

From inception until present
Clinicaltrials.gov
https://clinicaltrials.gov/
inositol and polycystic
WHO International Clinical Trials Registry Platform (ICTRP)
http://apps.who.int/trialsearch/
inositol and polycystic

Appendix 9. Virtual Health Library Platform (including LILACS)

http://pesquisa.bvsalud.org/portal/
From inception until present
tw:(inositol AND polycystic ovar*) AND (instance:"regional")

Appendix 10. PubMed search strategy

https://www.ncbi.nlm.nih.gov/pubmed
From inception until present
(("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]

Appendix 11. OpenGrey search strategy

http://www.opengrey.eu/
From inception until present
inositol and polycystic

Appendix 12. Web of Science search strategy

https://apps.webofknowledge.com/WOS˙GeneralSearch˙input.do?product=WOS&search˙mode=GeneralSearch&SID=Q1kFRhCd56OoxAiiCa1&preferencesSaved=
From inception until present
inositol and polycystic ovar*

CONTRIBUTIONS OF AUTHORS

MS wrote the the protocol and designed the search strategies.

RMP commented on the draft protocol.

VJ gave methodological advice and commented on the draft protocol.

RH gave clinical advice and commented on the draft protocol.

JB commented on the draft protocol.

CF reviewed and commented on the draft protocol.

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.

JB has no conflicts of interest to declare.

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

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