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Pharmacological and non-pharmacological strategies for obese women with subfertility (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Pharmacological and non-pharmacological strategies for obese women with subfertility

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effectiveness and safety of pharmacological and non-pharmacological strategies compared with each other, placebo or no treatment, for obese women with subfertility.

BACKGROUND

Description of the condition

Obesity rates have been rising worldwide creating a global health problem. The World Health Organisation has defined obesity as a body mass index (BMI) $\geq$ 30 kg/m^2. According to estimates, in 2015 about 2.3 billion men and women were overweight (BMI 25 to 30 kg/m ^{2}) and 700 million were obese (BMI > 30 kg/m^2). The prevalence of obesity is estimated to range from 5% in some developing countries to more than 30% in developed countries (Hossain 2007; Ogden 2006).

The obesity epidemic has also contributed to fertility problems. Obese women have a lower chance of conceiving naturally than non-obese women (Chong 1986; Crosignani 1994; Hamilton-Fairley 1992) and a higher risk of miscarriage (Boots 2011) . Obesity can result in anovulation and a reduced chance of conceiving in ovulatory subfertile women (Metwally 2007; van der Steeg 2008). Obesity also has a negative impact on the outcomes of in vitro fertilisation (IVF) (Fedorcsák 2004; Koloszar 2002). Pregnancy and live birth rates following IVF are lower in obese women (Wang 2002). Moreover, literature suggests that obesity is related to maternal and neonatal complications including congenital anomalies, hypertensive disorder, gestational diabetes, prolonged labour, macrosomia, and shoulder dystocia (Edwards 1996; Garbaciak 1985; Waller 1994; Weiss 2004).

To prevent the adverse effects of obesity, weight loss is recommended as the first line of treatment in obese women seeking pregnancy (Thessaloniki 2008).

Description of the intervention

The treatment of obesity can involve both pharmacological and non-pharmacological strategies.

Non-pharmacological

Diet

Generally, weight loss occurs when energy intake is lower than energy expenditure. In two small studies in polycystic ovarian syndrome (PCOS) subjects, replacing protein for carbohydrate within the context of an energy-restricted diet using 12 week and 1 month dietary intervention provided the same improved reproductive outcomes (Moran 2005; Stamets 2004) although postprandial glucose response was 3.5 times lower on the higher-protein dietary pattern. Lifestyle modification through diet and exercise programmes in obese subjects with PCOS improves reproductive outcomes (Clark 1998; Huber-Buchholz 1999). An important point is that a minimal amount of weight loss (5% to 10%) over as little as 4 weeks is sufficient to improve the presentation of PCOS despite subjects remaining clinically overweight or obese (Clark 1998; Hamilton-Fairley 1993; Wahrenberg 1999).
In a Cochrane review aiming to assess the effectiveness of lifestyle treatment (diet, exercise, behavioral or combined treatments) in women with PCOS, lifestyle intervention improved body composition, hyperandrogenism and insulin resistance but there was a lack of evidence for an effect of diet on reproductive outcomes (Moran 2011).

Exercise

Exercise is an important component of any lifestyle modification and weight management program. The results of two studies that examined the effects of exercise on insulin resistance in women with PCOS who were followed for 16 to 24 weeks and 6 months were different. Neither of these studies reported changes in hormone or reproductive parameters (Brown 2009; Randeva 2002). On the other hand, the combination of diet with physical exercise has been implemented in other studies. The negative aspect is that exercise was not evaluated separately from diet and that the result may suffer from reporting bias (Thomson 2010).

Behavioral counselling

Behavioral counselling might contribute to greater weight loss when combined with medical therapy and diet. In one study (Wadden 2005) subjects were followed for 52 weeks during which time counselling was given including regular supportive and motivating personal or group sessions. Behaviour therapy improved weight loss as well as weight maintenance and control.

Complementary and traditional healthcare approaches

The terms 'complementary' and 'alternative' describe practices and products that people choose as adjuncts to or as alternatives to Western medical approaches (Kaptchuk 2001; Straus 2004). The National Institutes of Health has grouped such interventions into five somewhat overlapping domains (nccam.nih.gov/health/whatiscam) as follows.

1. Biologically-based practices. These include use of a vast array of vitamins and mineral supplements, natural products such as chondroitin sulfate, which is derived from bovine or shark cartilage; and herbals, such as ginkgo biloba and echinacea.
2. Manipulative and body-based approaches. These kinds of approaches, which include massage, have been used throughout history. In the 19th century, additional formal manipulative disciplines emerged in the United States: chiropractic medicine and osteopathic medicine.
3. Mind-body medicine. Many ancient cultures assumed that the mind exerts powerful influences on bodily functions and vice versa. Attempts to reassert proper harmony between these bodily systems led to the development of mind-body medicine, an array of approaches that incorporate spiritual, meditative, and relaxation techniques.
4. Alternative medical systems. Whereas the ancient Greeks postulated that health requires a balance of vital humors, Asian cultures considered that health depends on the balance and flow of vital energies through the body. This latter theory underlies the practice of acupuncture, for example, which asserts that vital energy flow can be restored by placing needles at critical body points.
5. Energy medicine. This approach uses therapies that involve the use of energy-either biofield- or bioelectromagnetic-based interventions. An example of the former is Reiki therapy, which aims to realign and strengthen healthful energies through the intervention of energies radiating from the hands of a master healer.

A systematic review and meta-analysis suggested that acupuncture for obesity might be beneficial compared to placebo or lifestyle control, but results were limited by the clinical heterogeneity and poor methodological quality of the included trials (Cho 2009).

Pharmacological

Numerous anti-obesity medications are prescribed for weight loss. These drugs may be classified as follows.

- Drugs acting on the gastrointestinal tract (GIT): lipase inhibitors (orlistat).
- Centrally-acting anti-obesity agents: catecholaminergic agents (phentermine).
- Serotonin and noradrenaline reuptake inhibitors such as sibutramine; and selective serotonin reuptake inhibitors (SSRIs) (sertraline).
- Dopamine reuptake antagonists (bupropion), and antidepressants (fluoxetine).
- Exercise mimetics ephedrine, caffeine, synephrine, beta 3 adrenergic agonists, uncoupling proteins 2 and 3 (thermogenin).

- Leptin-related agents: therapeutic leptin; leptin analogues, leptin receptor agonists.

A systematic review suggested that sibutramine, orlistat, phentermine, probably diethyl-propion, probably fluoxetine, bupropion, and topiramate might promote modest weight loss for at least six months when given along with recommendations for diet (and possibly other behavioral and exercise interventions) (Li 2005).
All of these drugs have side effects, and side effect profiles vary per drug. Sibutramine is associated with modest increases in heart rate and blood pressure; gastrointestinal symptoms predominate in the use of orlistat; phentermine can induce cardiovascular and gastrointestinal side effects; fluoxetine is associated with agitation and nervousness in addition to gastrointestinal side effects; bupropion with paraesthesia, insomnia, and central nervous system effects; and topiramate with paresthesia and changes in taste (Li 2005).

How the intervention might work

An adverse effect of obesity on female fertility could be mediated by several mechanisms. Firstly, obesity potentially contributes to excess oestrogen as a result of extraglandular aromatisation of androgen precursors. Moreover, sex hormone-binding globulin levels are diminished, resulting in more bioavailable oestrogen and androgen for aromatisation. Secondly, obesity increases leptin levels. The actions of leptin on the hypothalamus-pituitary-ovary (HPO) axis are believed to have differential effects on the central and peripheral components of the reproductive system In the central nervous system. Leptin has been shown to modulate GnRH pulse frequency in vitro (Scott 2009). On the gonadal level, leptin has been found in ovarian follicular fluid and leptin receptor has been localised to human granulosa and theca cells. In humans, leptin may interrupt normal oocyte maturation (Smith 2002).
Weight loss improves the metabolic, endocrine and reproductive profile of obese women (Falsetti 1992; Hollmann 1996; Kumar 1993). There is evidence that a 5% weight loss is improves both natural and induced conception, as well as the chance of a healthy live birth (Khaskheli 2013).
The etiology of obesity is believed to be multifactorial, with both genetic and environmental contributions. A key determinant of obesity is the balance between ingested calories and the body's basal energy expenditure. Obesity therefore results when small positive energy balances accumulate over a long period of time (Swinburn 2009, Flegal 2010). Weight loss can be achieved by lifestyle intervention programs incorporating the combination of a healthy diet, increase of physical activity, behavioral modification, and use of complementary and traditional healthcare approaches and medications.
Lifestyle modification, which generally consists of a combination of nutrition, physical activity, and behavioral modification, is an oft-used strategy to help patients achieve weight loss and maintenance (Berkel 2005; Lang 2006). It has been suggested that complementary and alternative medicine including acupuncture might improve weight loss by: a) regulating obesity-related neuropeptides (Cabioglu 2006; Gucel 2012); b) regulating hypothalamus-pituitary-adrenal cortex and sympathetic adrenal cortex (Yin 2005); and c) lipid-lowering effects (Abdallah 2011). Medications act on the mechanisms regulating appetite and satiety, and help combat the pathophysiological adaptations that drive weight regain (Garvey 2013).

Why it is important to do this review

The effectiveness of pharmacological and non-pharmacological interventions for obese women with subfertility is unclear. Moreover, despite the fact that non-pharmacological interventions are commonly recommended in the management of obese subfertile women, their effectiveness in comparison with pharmacological strategies has not been previously examined in a systematic review. The results of this review are likely to be important for informing clinical practice and determining whether further research is required to establish the value of non-pharmacological interventions and pharmacological strategies for obese women with subfertility.

OBJECTIVES

To assess the effectiveness and safety of pharmacological and non-pharmacological strategies compared with each other, placebo or no treatment, for obese women with subfertility.

METHODS

Criteria for considering studies for this review

Types of studies

We will include published and unpublished randomised controlled trials (RCTs), cross-over and cluster-randomised trials.
For cross-over trials only data from the first phase will be included in meta-analyses, as the cross-over is not a valid design in this context.

Types of participants

Studies of obese women (BMI $\geq$ 30 kg/m^2 or as appropriate for ethnicity of participants in primary study) of childbearing age (post-menarche and pre-menopause) of any ethnic origin, who have been unable to conceive for at least 12 months (including primary and secondary subfertility), with or without explained

reasons (anovulatory, unexplained, tubal disease, endometriosis, uterine abnormalities, male factor).

Types of interventions

We will include all studies where weight loss is the main treatment intervention or weight loss interventions are a part of a subfertility management program .
Eligible comparisons are pharmacological, non-pharmacological and no intervention or placebo
We will consider the following comparisons.

1. Non-pharmacological versus pharmacological intervention (e.g. acupuncture versus SSRI etc.).
2. Non-pharmacological versus non-pharmacological intervention (e.g. acupuncture versus physical therapy etc, or one type of physical therapy versus another).
3. Pharmacological versus pharmacological intervention (e.g. one SSRI versus one type of pharmacological intervention, etc, or one SSRI versus another).
4. Pharmacological versus no intervention or placebo.
5. Non-pharmacological versus no intervention or placebo.

The following interventions will be considered.

Non-pharmacological

1. Behavioural: behaviour modification, behaviour change, brief intervention, brief advice, nurse counselling, physician counselling, psychological counselling, waiting list for treatment with the promise of treatment upon achieving a weight target; behavioural advice, behaviour therapy, internet-based support, self-directed support, social support; group therapy, family therapy, psychotherapy, support group, relaxation; health education, health promotion; motivation, meditation, religious intervention.
2. Diet: diet modification, dietician-led dietary advice, self-directed dietary instruction, low-carbohydrate diet, low-fat diet, hypo-caloric diet.
3. Exercise: walking, jogging, running, swimming; aerobics, structured exercise referral/interventions; weight-lifting/training; gymnastics; resistance training; fitness training; endurance training; cycling; boxing, kick-boxing; pedometry; exercise therapy; sports therapy; written materials.
4. Complementary and traditional healthcare approaches: acupuncture, electro-therapy; physical therapy; aromatherapy; auricular stimulation; body therapy; acupuncture-moxibustion; tai-chi; phyto-oestrogens; soy products; phyto-vitamins; dietary supplements and herbal products including: conjugated linoleic, pyruvate, ephedra sinica (Ma Huang), chromium, hydroxy citric acid (Garcinia cambogia) and chitosan.

Pharmacological

1. Drugs acting on the GIT: lipase inhibitors orlistat (Xenical) or tetrahydrolipstatin; bulking agents - methylcellulose or celevac, ispaghula husk, sterculia, bran; guar gum; insulin sensitisers; gastro-intestinal peptides, glucagon-like peptide 1, enterostatin.
2. Centrally-acting anti-obesity agents: catecholaminergic agents phentermine, mazindol, diethylpropion, phenylpropanolamine; serotoninergic agents fenfluramine, dexfenfluramine, fluoxetine; combined catecholaminergic plus serotoninergic agents phentermine plus fenfluramine.
3. Serotonin and noradrenaline reuptake inhibitors sibutramine; selective serotonin reuptake inhibitors (SSRIs) sertraline.
4. Dopamine reuptake antagonists bupropion ; anti-depressants fluoxetine.
5. Exercise mimetics ephedrine, caffeine, synephrine, beta 3 adrenergic agonists, uncoupling proteins 2 and 3 (thermogenin).
6. Leptin-related agents: therapeutic leptin; leptin analogues, leptin receptor agonists.

We will exclude surgical interventions.

Types of outcome measures

Primary outcomes

1. Live birth or ongoing pregnancy (when live birth is not available)
   - Live birth is defined as delivery of a live fetus after 20 completed weeks of gestation
   - Ongoing pregnancy is defined as evidence of a gestational sac with fetal heart motion at 12 weeks, confirmed with ultrasound

2. Adverse events as reported by the included studies

Secondary outcomes

1. Clinical pregnancy, defined as evidence of a gestational sac, confirmed by ultrasound
2. Miscarriage (loss of pregnancy during the first 20 weeks of gestation)
3. Weight change (e.g. body mass index (BMI), waist to hip ratio (WHR), percentage of body fat)
4. Change in endocrine parameters: total and free testosterone (ng/dL or nmol/L), sex hormone-binding globulin (SHBG) (nmol/L), testosterone/SHBG ratio and diabetic tests such as glucose tolerance test (GTT) (mmol/L), glycated haemoglobin (HbA1c) (mmol/mol)
5. Quality of life or mental health outcome. If studies report more than one scale, preference will be given to the SF-36, then other validated generic scales, and finally condition-specific scales

Search methods for identification of studies

We will search for all published and unpublished studies of pharmacological and non-pharmacological strategies for obese women with subfertility, without language or date restrictions and in consultation with the Gynaecology and Fertility Information Specialist.

Electronic searches

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

- The Cochrane Gynaecology and Fertility Group (CGF) Specialised Register of Controlled Trials (Procite platform)(Appendix 1).
- Cochrane Central Register of Studies Online (CRSO) (Web platform) (Appendix 2).
- Ovid MEDLINE (from 1946) (Appendix 3).
- Ovid Embase (from 1980) (Appendix 4).
- Ovid PsycINFO (from 1806) (Appendix 5).
- Ovid AMED (from 1985) (Appendix 6).
- Ebsco CINAHL (from 1961) (Appendix 7).
- Trial registers for ongoing and registered trials: www.clinicaltrials.gov (a service of the US National Institutes of Health), the World Health Organization International Trials Registry Platform search portal at www.who.int/trialsearch/Default.aspx.
- Database of Abstracts of Reviews of Effects (DARE), part of the Cochrane Library at onlinelibrary.wiley.com/o/cochrane/cochrane_cldare_articles_fs.html (for reference lists from relevant non-Cochrane reviews).
- Relevant non-Cochrane reviews.
- the Web of Science wokinfo.com/ (another source of trials and conference abstracts) (from 1983).
- OpenGrey at www.opengrey.eu/ (for unpublished literature from Europe).
- PubMed (for recent trials not yet indexed in MEDLINE).
- ProQuest.

The MEDLINE search will be combined with the Cochrane highly sensitive search strategy for identifying randomised trials, which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011, chapter 6, 6.4.11). The Embase and CINAHL searches will be combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) www.sign.ac.uk/methodology/filters.html#random.

Searching other resources

We will handsearch reference lists of appropriate systematic reviews and trials retrieved by the search and contact experts in the field to obtain additional data.

Output of the searches will be managed with Endnote which lists all studies and removes duplicates.

Data collection and analysis

Selection of studies

After an initial screen of titles and abstracts retrieved by the search, conducted by FB and ST, we will retrieve the full texts of all potentially eligible studies. Two review authors (FB and MW) will independently examine these full text articles for compliance with the inclusion criteria and select eligible studies. We will correspond with study investigators, as required, to clarify study eligibility. Any disagreement about whether to include or exclude a study will be discussed with a third review author (SJ) until consensus is achieved. The selection process will be documented with a PRISMA flow chart.

Data extraction and management

Two review authors (FB and ST) will independently extract data from eligible studies using a data extraction form designed and pilot-tested by the authors. Any disagreements will be resolved by discussion. Data extracted will include study characteristics and outcome data. Where studies have multiple publications the authors will collate multiple reports of the same under a single study ID with multiple references. We will correspond with study investigators for further data on methods and/or results, as required. Data extracted will include population characteristics (like female age, BMI, waist-hip ratio, ethnicity) study characteristics and outcome data.

Assessment of risk of bias in included studies

The included studies will be assessed for risk of bias using the Cochrane 'Risk of bias' assessment tool (Higgins 2011) to assess: selection bias (random sequence generation, allocation concealment); performance bias (blinding of participants and personnel); detection bias (blinding of outcome assessors); attrition bias (incomplete outcome data); reporting bias (selective reporting); and other biases. Two authors (FB and MW) will assess risk of bias with any disagreements resolved by consensus or by discussion with a third author (SJ).

Random sequence generation will be scored low risk of bias when an appropriate method of sequence generation was described according to Cochrane methods (Higgins 2011). Allocation concealment will be low risk of bias if opaque and numbered envelopes or a centralised internet-based randomisation procedure was used. Lack of blinding is unlikely to affect live birth (will be scored low risk of bias) but might affect adverse events (will be scored high risk of bias). Attrition bias will be scored low when all or most (more than 95%) of the women randomised are analysed. Reporting bias will be scored low when all relevant outcomes are reported as planned in the protocol, as described in published protocols either in journals or in trial registers.To score other forms of bias

we will look at differences in baseline values and treatment details. If these issues are unclear the risk of bias will be scored unclear.
We will correspond with the trialists to identify any within-trial selective reporting. We will seek published protocols and compare the outcomes between the protocol and the final published study. The 'Risk of bias' table will be presented with the table 'Characteristics of included studies'. All judgements will be fully described. The conclusions will be presented in the 'Risk of bias' table and will be incorporated into the interpretation of review findings by means of sensitivity analyses.
With respect to within-trial selective reporting, where identified studies fail to report the primary outcome of live birth, but do report interim outcomes such as pregnancy, we will assess whether the interim values are similar to those reported in studies that also report live birth.

Measures of treatment effect

We will perform a statistical analysis in accordance with the statistical guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A fixed-effect model will be used for all analyses.
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 relative risks (RRs). For reporting purposes, primary outcomes will be translated to absolute risks.
For continuous data (e.g. weight loss), if all studies report exactly the same outcomes we will calculate mean difference (MDs) between treatment groups. If similar outcomes are reported on different scales (e.g. change in weight or quality of life) we will calculate the standardised mean difference (SMD). We will reverse the direction of effect of individual studies, if required, to ensure consistency across trials. We will treat ordinal data (e.g. quality of life scores) as continuous data. We will present 95% confidence intervals for all outcomes.
Where data to calculate RRs or MDs 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). We will assess whether the estimates calculated in the review for individual studies are compatible in each case with the estimates reported in the study publications.
Since cluster-RCTs are included in the review, we will first make an assessment as to whether the trial has been analysed in such a way as to account for clustering, and if not, we will make an adjustment to the trial results using one of several available approaches including generic inverse-variance method using the effect estimates and their standard errors extracted from cluster-RCTs.

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 meta-analysed. Multiple births will be counted as one live birth event. Only first-phase data from cross-over trials will be included. In order for the data of cluster-randomised trials to be included in the meta-analysis the following information must be available.

1. The number of clusters (or groups) randomised to each intervention group; or the average (mean) size of each cluster.
2. The outcome data ignoring the cluster design for the total number of individuals (for example, number or proportion of individuals with events, or means and standard deviations).
3. An estimate of the intracluster (or intraclass) correlation coefficient (ICC).

The ICC is an estimate of the relative variability within and between clusters (Donner 1980). It describes the 'similarity' of individuals within the same cluster. If the ICC is not provided, external estimates will be obtained from similar studies. The ICC is used to reduce the size of each trial to its 'effective sample size' (Rao 1992). The effective sample size of a single intervention group in a cluster-randomised trial is its original sample size divided by a quantity called the 'design effect'. The design effect is 1 + (M - 1) ICC, where M is the average cluster size and ICC is the intracluster correlation coefficient. A common design effect is usually assumed across intervention groups. For dichotomous data both the number of participants and the number experiencing the event are to be divided by the same design effect. For continuous data only the sample size need be reduced; means and standard deviations (SDs) should remain unchanged.

Dealing with missing data

We will analyse the data on an intention-to-treat basis as far as possible (i.e. including all randomised participants in the analysis, in the groups to which they were randomised). We will attempt to obtain missing data from the original trialists. Where these are unobtainable, we will undertake imputation of individual values for live birth only: live birth 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.
If studies report sufficient detail to calculate mean differences but no information on associated SD, we will assume the outcome to have an SD equal to the highest SD from other studies within the same 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 by the measure of the I^2. An I^2 measurement greater than 50% will be taken to indicate substantial heterogeneity (Higgins 2011).

Assessment of reporting biases

In view of the difficulty of detecting publication bias and other 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 10 or more studies in an analysis, we will use a funnel plot to assess the potential for publication bias.

Data synthesis

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

1. Non-pharmacological versus pharmacological intervention.
2. Non-pharmacological versus non-pharmacological intervention.
3. Pharmacological versus pharmacological intervention.
4. Pharmacological versus no intervention/placebo.
5. Non-pharmacological versus no intervention/placebo.

See Types of interventions for the exact study interventions we will investigate.

An increase in the risk of all outcomes will be displayed graphically in the meta-analyses to the right of the centre-line and a decrease in the risk of an outcome to the left of the centre-line.

Subgroup analysis and investigation of heterogeneity

Where sufficient data are available (at least five RCTs), we plan to perform the following subgroup analysis for the primary outcomes only.

1. Duration of intervention (short: 2 to 4 weeks, medium: 4 weeks to 6 months, long: greater than 6 months) (Moran 2011).
2. Cause of infertility: anovulatory versus unexplained versus other causes.
3. Maternal age: $\leq$ 35 or 36 years and older
4. Severity of obesity (BMI): 30.0 < BMI < 34.9 (class I obesity) versus 35.0 < BMI < 39.9 (class II obesity) versus BMI $\geq$ 40.0 (class III obesity).

Sensitivity analysis

We will conduct the following sensitivity analyses for the primary outcomes, to examine stability regarding the pooled outcomes.

- Restriction to studies without high risk of bias.
- Use of a random-effects model.
- Use of odds ratio rather than relative risk.

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

We will prepare a 'Summary of findings' table using GRADEpro (GRADEpro GDT 2014) and Cochrane methods (Higgins 2011). This table will evaluate the overall quality of the body of evidence for the primary review outcomes (live birth or ongoing pregnancy, adverse events, clinical pregnancy, miscarriage) for the main review comparison (pharmacological versus non-pharmacological strategies). Additional 'Summary of findings' tables will be also prepared for the main review outcomes for other important comparisons.

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 reporting of results for each outcome.

We plan to extract study data, format our comparisons in data tables and prepare a 'Summary of findings' table using the GRADEpro Guideline Development Tool (GDT) (GRADEpro GDT 2014) before writing the results and conclusions of our review.

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REFERENCES

Additional references

Abdallah 2011

Abdallah Ismail N, Ragab SH, Abd Elbaky A, Shoeib AR, Alhosary Y, Fekry D. Frequency of firmicutes and bacteroidetes in gut microbiota in obese and normal weight Egyptian children and adults. *Archives of Medical Science* 2011;**7**(3):501–7.

Berkel 2005

Berkel LA, Poston WS, Reeves RS, Foreyt JP. Behavioral interventions for obesity. *Journal of the American Dietetic Association* 2005;**105**(5 Suppl 1):S35–43.

Boots 2011

Boots C, Stephenson MD. Does obesity increase the risk of miscarriage in spontaneous conception: a systematic review. *Seminars in Reproductive Medicine* 2011;**29**(6):507–13.

Brown 2009

Brown AJ, Setji TL, Sanders LL, Lowry KP, Otvos JD, Kraus WE, et al. Effects of exercise on lipoprotein particles in women with polycystic ovary syndrome. *Medicine and Science in Sports and Exercise* 2009;**41**:497.

Cabioglu 2006

Cabioglu MT, Ergene N. Changes in serum leptin and beta endorphin levels with weight loss by electroacupuncture

and diet restriction in obesity treatment. *American Journal of Chinese medicine* 2006;**34**(1):1–11.

Cho 2009
Cho SH, Lee JS, Thabane L, Lee J. Acupuncture for obesity: a systematic review and meta-analysis. *International Journal of Obesity* 2009;**33**(2):183–96.

Chong 1986
Chong AP, Rafael RW, Forte CC. Influence of weight in the induction of ovulation with human menopausal gonadotropin and human chorionic gonadotropin. *Fertility and Sterility* 1986;**46**:599–603.

Clark 1998
Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Human Reproduction* 1998;**13**(6): 1502–5.

Crosignani 1994
Crosignani PG, Ragni G, Parazzini F, Wyssling H, Lombroso G, Perotti L. Anthropometric indicators and response to gonadotrophin for ovulation induction. *Human Reproduction* 1994;**9**:420–3.

Donner 1980
Donner A, Koval JJ. The estimation of intraclass correlation in the analysis of family data. *Biometrics* 1980;**36**(1):19–25.

Edwards 1996
Edwards LE, Hellerstedt WL, Alton IR, Story M, Himes JH. Pregnancy complications and birth outcomes in obese and normal-weight women: effects of gestational weight change. *Obstetrics & Gynecology* 1996;**87**:389–94.

Falsetti 1992
Falsetti L, Pasinetti E, Mazzani MD, Gastaldi A. Weight loss and menstrual cycle: clinical and endocrinological evaluation. *Gynecological Endocrinology* 1992;**6**(1):49–56.

Fedorcsák 2004
Fedorcsák P, Dale PO, Storeng R, Ertzeid G, Bjercke S, Oldereid N, et al. Impact of overweight and underweight on assisted reproduction treatment. *Human Reproduction* 2004;**19**:2523–8.

Flegal 2010
Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA* 2010;**303**(3):235–41.

Garbaciak 1985
Garbaciak JA, Richter M, Miller S, Barton JJ. Maternal weight and pregnancy complications. *American Journal of Obstetrics and Gynecology* 1985;**152**:238–45.

Garvey 2013
Garvey WT. New tools for weight-loss therapy enable a more robust medical model for obesity treatment: rationale for a complications-centric approach. *Endocrine Practice* 2013;**19**(5):864–74.

GRADEpro GDT 2014 [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed 10 August 2015. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Gucel 2012
Gucel F, Bahar B, Demirtas C, Mit S, Cevik C. Influence of acupuncture on leptin, ghrelin, insulin and cholecystokinin in obese women: a randomised, sham-controlled preliminary trial. *Acupuncture in Medicine* 2012;**30**(3): 203–7.

Hamilton-Fairley 1992
Hamilton-Fairley D, Kiddy D, Watson H, Paterson C, Franks S. Association of moderate obesity with a poor pregnancy outcome in women with polycystic ovary syndrome treated with low dose gonadotrophin. *BJOG* 1992;**99**:128–31.

Hamilton-Fairley 1993
Hamilton-Fairley D, Kiddy D, Anyaoku V, Koistinen R, Seppala M, Franks S. Response of sex hormone binding globulin and insulin-like growth factor binding protein-1 to an oral glucose tolerance test in obese women with polycystic ovary syndrome before and after calorie restriction. *Clinical Endocrinology* 1993;**39**(3):363–7.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org. The Cochrane Collaboration, 2011. Available from www.cochrane–handbook.org.

Hollmann 1996
Hollmann M, Runnebaum B, Gerhard I. Effects of weight loss on the hormonal profile in obese, infertile women. *Human Reproduction* 1996;**11**(9):1884–91.

Hossain 2007
Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world-a growing challenge. *New England Journal of Medicine* 2007;**356**(3):213–5.

Huber-Buchholz 1999
Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. *Journal of Clinical Endocrinology and Metabolism* 1999;**84**(4):1470–4.

Kaptchuk 2001
Kaptchuk TJ, Eisenberg DM. Varieties of healing. 2: a taxonomy of unconventional healing practices. *Annals of Internal Medicine* 2001;**135**(3):196–204.

Khaskheli 2013
Khaskheli MN, Baloch S, Baloch AS. Infertility and weight reduction: influence and outcome. *Journal of the College of Physicians and Surgeons Pakistan* 2013;**23**(10):798–801.

Koloszar 2002
Koloszar S, Daru J, Kereszturi A, Zavaczki Z, Szöllosi J, Pal A. Effect of female body weight on efficiency of donor AI. *Systems Biology in Reproductive Medicine* 2002;**48**:323–7.

Kumar 1993
Kumar A, Mittal S, Buckshee K, Farooq A. Reproductive functions in obese women. *Progress in Food & Nutrition Science* 1993;**17**(2):89–98.

Lang 2006
Lang A, Froelicher ES. Management of overweight and obesity in adults: behavioral intervention for long-term weight loss and maintenance. *European Journal of Cardiovascular Nursing* 2006;**5**(2):102–14.

Li 2005
Li Z, Maglione M, Tu W, Mojica W, Arterburn D, Shugarman LR, et al. Meta-analysis: pharmacologic treatment of obesity. *Annals of Internal Medicine* 2005;**142**(7):532–46.

Metwally 2007
Metwally M, Li T, Ledger W. The impact of obesity on female reproductive function. *Obesity Reviews* 2007;**8**(6):515–23.

Moran 2005
Moran LJ, Luscombe-Marsh ND, Noakes M, Wittert GA, Keogh JB, Clifton PM. The satiating effect of dietary protein is unrelated to postprandial ghrelin secretion. *Journal of Clinical Endocrinology and Metabolism* 2005;**90**(9):5205–11.

Moran 2011
Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: 10.1002/14651858.CD007506.pub3]

Ogden 2006
Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States,1999-2004. *JAMA* 2006;**295**(13):1549–55.

Randeva 2002
Randeva Harpal S, Lewandowski Krzysztof C, Drzewoski Józef, Brooke-Wavell Katherine, O'Callaghan Chris, Czupryniak Leszek, et al. Exercise decreases plasma total homocysteine in overweight young women with polycystic ovary syndrome. *The Journal of Clinical Endocrinology & Metabolism* 2002;**87**:4496–501.

Rao 1992
Rao JN, Scott AJ. A simple method for the analysis of clustered binary data. *Biometrics* 1992;**48**(2):577–85.

Scott 2009
Scott MM, Lachey JL, Sternson SM, Lee CE, Elias CF, Friedman JM, et al. Leptin targets in the mouse brain. *Journal of Comparative Neurology* 2009;**514**(5):518–32.

Smith 2002
Smith GD, Jackson LM, Foster DL. Leptin regulation of reproductive function and fertility. *Theriogenology* 2002;**57**(1):73–86.

Stamets 2004
Stamets K, Taylor DS, Kunselman A, Demers LM, Pelkman CL, Legro RS. A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. *Fertility and Sterility* 2004;**81**(3):630–7.

Straus 2004
Straus SE. Complementary and Alternative Medicine. In: Goldman L, Ausiello D editor(s). *Cecil Textbook of Medicine*. 22nd Edition. Philadelphia (PA): Saunders, 2004.

Swinburn 2009
Swinburn BA, Sacks G, Lo SK, Westerterp KR, Rush EC, Rosenbaum M, et al. Estimating the changes in energy flux that characterize the rise in obesity prevalence. *American Journal of Clinical Nutrition* 2009;**89**(6):1723–8.

Thessaloniki 2008
Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. *Human Reproduction* 2008;**23**(3):462–77.

Thomson 2010
Thomson RL, Buckley JD, Lim SS, Noakes M, Clifton PM, Norman RJ, et al. Lifestyle management improves quality of life and depression in overweight and obese women with polycystic ovary syndrome. *Fertility and Sterility* 2010;**94**:1812–6.

van der Steeg 2008
van der Steeg JW, Steures P, Eijkemans MJ, Habbema JDF, Hompes PG, Burggraaff JM, et al. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. *Human Reproduction* 2008;**23**(2):324–8.

Wadden 2005
Wadden TA, Berkowitz RI, Womble LG, Sarwer DB, Phelan S, Cato RK, et al. Randomized trial of lifestyle modification and pharmacotherapy for obesity. *New England Journal of Medicine* 2005;**353**(20):2111–20.

Wahrenberg 1999
Wahrenberg H, Ek I, Reynisdottir S, Carlstrom K, Bergqvist A, Arner P. Divergent effects of weight reduction and oral anticonception treatment on adrenergic lipolysis regulation in obese women with the polycystic ovary syndrome. *Journal of Clinical Endocrinology and Metabolism* 1999;**84**(6):2182–7.

Waller 1994
Waller DK, Mills JL, Simpson JL, Cunningham GC, Conley MR, Lassman MR, et al. Are obese women at higher risk for producing malformed offspring?. *American Journal of Obstetrics and Gynecology* 1994;**170**:541–8.

Wang 2002
Wang JX, Davies MJ, Norman RJ. Obesity increases the risk of spontaneous abortion during infertility treatment. *Obesity Research* 2002;**10**:551–4.

Weiss 2004
Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, et al. Obesity, obstetric complications and cesarean delivery rate-a population-based screening study. *American Journal of Obstetrics and Gynecology* 2004;**190**:1091–7.

Yin 2005
Yin S, Lin-shan Z. Therapeutic idea and approaches to obesity with acupuncture. *Journal of Acupuncture and Tuina Science* 2005;**3**(4):54–7.
* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility specialised register search strategy

PROCITE Platform
From inception to present
Keywords CONTAINS "IVF" or "ICSI" or "in-vitro fertilisation " or "in-vitro fertilisation procedure" or "in vitro fertilization" or "intracytoplasmic sperm injection" or "intracytoplasmic morphologically selected sperm injection" or "superovulation" or "superovulation induction" or "IUI" or "insemination, intrauterine " or "Intrauterine Insemination" or "ART" or "artificial insemination" or "assisted reproduction techniques" or "subfertility-Female" or "pregnancy" or "live birth" or"unexplained and endometriosis related infertility" or"unexplained infertility" or"unexplained subfertility" or "anovulation" or "infertile"or "infertility" or "ovulation" or "subfertility" or "ovarian hyperstimulation"or "ovarian stimulation"or"controlled ovarian "or "timed intercourse" or "in vivo maturation" or"in vitro maturation"or "IMSI"or "implantation"or "oocyte"or"oocytes"or"embryo" or "polycystic ovary syndrome" or"PCOS"or "assisted reproduction"or"assisted reproductive technology"or Title CONTAINS "infertile"
AND
Keywords CONTAINS "*Obesity" or "obese women" or "obese" or"overweight"or "overweight-to-obese"or "fat body mass"or "fat distribution"or "BMI"or "body mass index" or"body composition"or "body fat distribution" or"body fat mass" or"Body Mass"or "Body Mass Index" or"Body weight"or "Weight Loss"or "Diet" or"diet therapy"or "dietary intervention"or"Weight "or"Weight Gain" or Title CONTAINS "*Obesity" or "obese women" or "obese" or"overweight"or "overweight-to-obese"or "fat body mass"or "fat distribution"or "BMI"or "body mass index" or"body composition"or "body fat distribution" or"body fat mass" or"Body Mass"or "Body Mass Index" or"Body weight"or "Weight Loss"or "Diet" or"diet therapy"or "dietary intervention"or"Weight "or"Weight Gain"

Appendix 2. CENTRAL search strategy

CRSO web platform
From inception to present
#1 MESH DESCRIPTOR Obesity EXPLODE ALL TREES
#2 MESH DESCRIPTOR Overweight EXPLODE ALL TREES
#3 (Obesity or obese or overweight):TI,AB,KY)
#4 MESH DESCRIPTOR Obesity, Morbid EXPLODE ALL TREES
#5 MESH DESCRIPTOR Body Mass Index EXPLODE ALL TREES
#6 (High BMI or BMI above or BMI greater):TI,AB,KY
#7 (High body mass index or body mass index above or body mass index greater):TI,AB,KY
#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9 MESH DESCRIPTOR Infertility, Female EXPLODE ALL TREES
#10 MESH DESCRIPTOR Polycystic Ovary Syndrome EXPLODE ALL TREES
#11 MESH DESCRIPTOR Fertilization in Vitro EXPLODE ALL TREES
#12 (infertil* or subfertil*):TI,AB,KY
#13 (Polycystic Ovar*):TI,AB,KY
#14 PCOS:TI,AB,KY
#15 (ivf or icsi):TI,AB,KY
#16 (intrauterine insemination*):TI,AB,KY

#17 iui:TI,AB,KY
#18 MESH DESCRIPTOR Ovulation Induction EXPLODE ALL TREES
#19 (Ovulation Induction):TI,AB,KY
#20 (ovar* hyperstimulation):TI,AB,KY
#21 (ovar* adj2 stimulation):TI,AB,KY
#22 MESH DESCRIPTOR Reproductive Techniques, Assisted EXPLODE ALL TREES
#23 (assisted reproduct*):TI,AB,KY
#24 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25 #8 AND #24

Appendix 3. MEDLINE search strategy

OVID platform
From 1946 to present
1 (Obesity or obese or overweight).tw.
2 exp Obesity/ or exp Overweight/ or exp Body Weight/
3 exp Body Composition/ or exp Body Fat Distribution/
4 exp Body Mass Index/
5 exp Obesity, Morbid/ or exp Waist-Hip Ratio/
6 (High BMI or BMI above).tw.
7 (BMI adj3 over).tw.
8 Body Mass Index.tw.
9 or/1-8
10 exp Infertility, Female/
11 exp Polycystic Ovary Syndrome/
12 exp Fertilization in Vitro/
13 (infertil$ adj5 female$).tw.
14 (infertil$ adj5 wom?n).tw.
15 (subfertil$ adj5 wom?n).tw.
16 (subfertil$ adj5 female$).tw.
17 Polycystic Ovar$.tw.
18 PCOS.tw.
19 exp Amenorrhea/
20 amenorrh?ea.tw.
21 oligomenorrh$.tw.
22 exp Oligomenorrhea/
23 exp Hyperandrogenism/
24 hyperandrogenism.tw.
25 (ivf or icsi).tw.
26 intrauterine insemination$.tw.
27 iui.tw.
28 exp Ovarian Hyperstimulation Syndrome/
29 exp Ovulation Induction/
30 ovar$ hyperstimulation.tw.
31 ovar$ stimulation.tw.
32 exp Reproductive Techniques, Assisted/
33 assisted reproduct$.tw.
34 or/10-33
35 randomized controlled trial.pt.
36 controlled clinical trial.pt.
37 randomized.ab.
38 randomised.ab.

39 placebo.tw.
40 clinical trials as topic.sh.
41 randomly.ab.
42 trial.ti.
43 (crossover or cross-over or cross over).tw.
44 or/35-43
45 exp animals/ not humans.sh.
46 44 not 45
47 9 and 34 and 46

Appendix 4. Embase search strategy

OVID platform
From 1980 to present
1 exp obesity/
2 (obesity or obese or overweight).tw.
3 exp body weight/ or exp body mass/
4 waist hip ratio/
5 body mass index.tw.
6 (High BMI or BMI above).tw.
7 (BMI adj3 over).tw.
8 (weight adj3 above).tw.
9 (weight adj3 over).tw.
10 or/1-9
11 exp female infertility/ or exp ovary polycystic disease/ or exp fertilization in vitro/
12 (infertil$ adj5 female$).tw.
13 (infertil$ adj5 wom?n).tw.
14 (subfertil$ adj5 wom?n).tw.
15 (subfertil$ adj5 female$).tw.
16 Polycystic Ovar$.tw.
17 PCOS.tw.
18 exp amenorrhea/
19 amenorrh?ea.tw.
20 oligomenorrh$.tw.
21 exp oligomenorrhea/ or exp “amenorrhea and oligomenorrhea”/
22 exp hyperandrogenism/
23 hyperandrogenism.tw.
24 (ivf or icsi).tw.
25 intrauterine insemination$.tw.
26 iui.tw.
27 exp ovary hyperstimulation/ or exp ovulation induction/
28 ovar$ hyperstimulation.tw.
29 ovar$ stimulation.tw.
30 or/11-29
31 exp Diet Therapy/
32 diet$.tw.
33 (weight adj3 reduc$).tw.
34 (body mass index adj2 loss).tw.
35 (body mass index adj2 reduc$).tw.
36 (body mass index adj2 decreas$).tw.
37 (BMI adj2 loss).tw.
38 (BMI adj2 redu$).tw.

39 (BMI adj2 decreas$).tw.
40 exercise$.tw.
41 exp sport/
42 (run$ or jog$).tw.
43 (sport$ or walk$).tw.
44 (swim$ or cycl$).tw.
45 (train or training).tw.
46 exp cognitive therapy/ or exp psychotherapy/
47 (cognitive adj2 therap$).tw.
48 Psychotherapy.tw.
49 exp behavior therapy/
50 exp lifestyle/
51 (lifestyle adj2 change$).tw.
52 (lifestyle adj2 intervention$).tw.
53 exp social support/
54 (social adj2 support).tw.
55 weight loss.tw.
56 (weight adj2 control).tw.
57 dynamic exercise/ or isotonic exercise/ or exercise/ or aquatic exercise/ or leg exercise/ or anaerobic exercise/ or stretching exercise/ or aerobic exercise/ or isometric exercise/
58 behavio?r modif$.tw.
59 exp weight control/ or exp weight reduction/
60 behavio?r therap$.tw.
61 low calorie$.tw.
62 fitness.tw.
63 exp health behavior/
64 (decrease adj2 weight).tw.
65 hypnosis.tw.
66 group therap$.tw.
67 or/31-66
68 exp antiobesity agent/
69 antiobesity.tw.
70 lipase inhibitor$.tw.
71 (xenical or tetrahydrolipstatin or orlistat).tw.
72 exp tetrahydrolipstatin/
73 exp metformin/ or exp pioglitazone/ or exp insulin sensitizing agent/
74 insulin sensitizer$.tw.
75 exp antidiabetic agent/
76 exp 2,4 thiazolidinedione derivative/
77 exp thiazole derivative/
78 metformin.tw.
79 (Appetite adj3 (suppress$ or depress$)).tw.
80 exp serotonin uptake inhibitor/
81 exp serotonin antagonist/
82 exp antidepressant agent/
83 exp noradrenalin uptake inhibitor/
84 (Reductil or sibutramine or fenfluramine).tw.
85 fenfluramine/
86 exp dexfenfluramine/
87 exp phentermine/
88 exp phenylpropanolamine/
89 exp fluoxetine/
90 antidepressant$.tw.

91 anti depressant$.tw.
92 exp mazindol/
93 exp amfepramone/
94 antiandrogen/
95 androgen$ antagonist$.tw.
96 bulking agent$.tw.
97 fluoxetine.tw.
98 (methylcellulose or celevac).tw.
99 guar gum.tw.
100 anti obesity.tw.
101 exp Ephedra/
102 ephedra.tw.
103 bupropion.tw.
104 exp amfebutamone/
105 (Wellbutrin or Zyban or Amfebutamone).tw.
106 zonisamide.tw.
107 (Excegran or Zonegran).tw.
108 sertraline.tw.
109 exp sertraline/
110 (Serad or Serlain or Tresleen or Zoloft).tw
111 leptin/ae, dt [Adverse Drug Reaction, Drug Therapy]
112 topiramate.tw.
113 or/68-112
114 (lap band$ or lapband$).tw.
115 roux-en-y.tw.
116 bariatric surger$.tw.
117 exp gastroplasty/ or exp bariatric surgery/
118 exp gastrectomy/
119 (GASTROPLASTY or Gastrectomy or gastric surgery or Gastric Bypass or gastric band$).tw.
120 (Biliopancreatic Diversion$ or biliopancreatic bypass$ or gastro$gastrostomy or restrictive surgery).tw.
121 (obesity adj3 surg$).tw.
122 (obese adj3 surg$).tw.
123 (jejunoileal bypass$ or jejuno ileal bypass$).tw.
124 exp gastric banding/
125 or/114-124
126 67 or 113 or 125
127 Clinical Trial/
128 Randomized Controlled Trial/
129 exp randomization/
130 Single Blind Procedure/
131 Double Blind Procedure/
132 Crossover Procedure/
133 Placebo/
134 Randomi?ed controlled trial$.tw.
135 Rct.tw.
136 random allocation.tw.
137 randomly allocated.tw.
138 allocated randomly.tw.
139 (allocated adj2 random).tw.
140 Single blind$.tw.
141 Double blind$.tw.
142 ((treble or triple) adj blind$).tw.
143 placebo$.tw.

144 prospective study/
145 or/127-144
146 case study/
147 case report.tw.
148 abstract report/ or letter/
149 or/146-148
150 145 not 149
151 10 and 30 and 126 and 150

Appendix 5. PsycINFO search strategy

OVID platform
From 1806 to present
1 exp Obesity/
2 (obesity or obese or overweight).tw.
3 exp Body Weight/ or exp Body Mass Index/
4 Body Mass Index.tw.
5 Body Weight.tw.
6 BMI.tw.
7 or/1-6
8 exp Infertility/
9 (infertil$ adj5 female$).tw.
10 (infertil$ adj5 wom?n).tw.
11 (subfertil$ adj5 wom?n).tw.
12 (subfertil$ adj5 female$).tw.
13 Polycystic Ovar$.tw.
14 PCOS.tw.
15 exp Amenorrhea/
16 amenorrh?ea.tw.
17 oligomenorrh$.tw.
18 exp Menstrual Disorders/
19 hyperandrogenism.tw.
20 (ivf or icsi).tw.
21 intrauterine insemination$.tw.
22 iui.tw.
23 exp Reproductive Technology/
24 ovar$ hyperstimulation.tw.
25 ovar$ stimulation.tw.
26 or/8-25
27 7 and 26
28 random.tw.
29 control.tw.
30 double-blind.tw.
31 clinical trials/
32 placebo/
33 exp Treatment/
34 or/28-33
35 27 and 34

Appendix 6. AMED search strategy

OVID platform
From 1985 to present
1 exp Obesity/
2 (obesity or obese or overweight).tw.
3 exp Body weight/
4 BMI.tw.
5 body mass index.tw.
6 weight.tw.
7 or/1-6
8 exp Fertility/
9 exp Infertility female/
10 exp Ovarian disease/
11 (infertil$ adj5 female$).tw.
12 (infertil$ adj5 wom?n).tw.
13 (subfertil$ adj5 wom?n).tw.
14 (subfertil$ adj5 female$).tw.
15 Polycystic Ovar$.tw.
16 PCOS.tw.
17 exp Amenorrhea/
18 amenorrh?ea.tw.
19 oligomenorrh$.tw.
20 exp Menstruation disorders/
21 hyperandrogenism.tw.
22 (ivf or icsi).tw.
23 intrauterine insemination$.tw.
24 iui.tw.
25 ovar$ hyperstimulation.tw.
26 or/8-25
27 7 and 26

Appendix 7. CINAHL search strategy

From 1982 to present
EBSCO platform

#	Query
S35	S20 AND S34
S34	S21 OR S22 or S23 or S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33
S33	TX allocat* random*
S32	(MH "Quantitative Studies")
S31	(MH "Placebos")
S30	TX placebo*

(*Continued*)

S29	TX random* allocat*
S28	(MH "Random Assignment")
S27	TX randomi* control* trial*
S26	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S25	TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S24	TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S23	TX clinic* n1 trial*
S22	PT Clinical trial
S21	(MH "Clinical Trials+")
S20	S9 AND S19
S19	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18
S18	TX intrauterine insemination
S17	(MH "Fertilization in Vitro") OR (MH "Fertility")
S16	TX (ivf or icsi)
S15	TX hyperandrogenism
S14	TX subfertil*
S13	TX infertil*
S12	TX Polycystic Ovar*
S11	(MM "Polycystic Ovary Syndrome")
S10	(MM "Infertility")
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S8	TX weight
S7	TX BMI
S6	TX Body Mass Index

(*Continued*)

S5	(MM "Body Mass Index")
S4	TX overweight
S3	TX obese
S2	TX Obesity
S1	(MH "Obesity+")

WHAT'S NEW

Date	Event	Description
29 April 2017	Amended	Correction to affiliation of 2 authors

CONTRIBUTIONS OF AUTHORS

All authors contributed to writing this protocol.

DECLARATIONS OF INTEREST

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