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[Intervention Protocol]

Interventions for unexplained subfertility: a systematic review and network meta-analysis

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ABSTRACT

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

We aim to assess the comparative effectiveness and/or safety of interventions currently being used to treat couples with unexplained subfertility.

BACKGROUND

Description of the condition

Up to 1 in 10 couples who try to achieve a pregnancy, fail to do so after 12 months of unprotected intercourse (Boivin 2007; Gnoth 2003). These couples will undergo routine fertility investigations comprising an assessment of ovulation, tubal patency and semen analysis. Of these couples, approximately a quarter will be diagnosed with unexplained subfertility, when no abnormality is found after these investigations (Brandes 2010; Hull 1985). Most of these couples still have a good chance of achieving a pregnancy without treatment (Brandes 2011).

Description of the intervention

Clinical guidelines for the management of unexplained subfertility recommend starting with the least invasive intervention before moving on to more aggressive treatments (ASRM 2006; NICE 2013; NVOG 2010). In clinical practice this has led to a wide range of interventions that are used: expectant management (i.e. sexual intercourse), timed intercourse, ovarian stimulation (i.e. gonadotropins, aromatase-inhibitors or anti-estrogens), intrauterine insemination (IUI) with or without ovarian stimulation, in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI).

Expectant management or timed intercourse

Couples following 'expectant management' still have a good chance of achieving a pregnancy without treatment. A cumulative ongoing pregnancy rate of 27% has been reported after 12 months of unprotected intercourse following the completion of the fertility investigations in a large prospective cohort (Hunault 2005; van Eekelen 2017).

IUI

Delivery rates of approximately 8% per cycle have been reported for subfertile couples with varying causes of subfertility (Kupka 2016).

IVF and ICSI

Clinical pregnancy rates of 29% per cycle have been reported after IVF and 28% per cycle after ICSI for subfertile couples with varying causes of subfertility (Kupka 2016).

How the intervention might work

In couples with unexplained subfertility, a biological cause for their involuntary childlessness has not been detected. For each possible treatment for these couples there are hypotheses regarding their working mechanisms.

The concept behind timed intercourse is to aid couples in having intercourse at the best time for fertilisation through the use of cycle monitoring. Ovarian stimulation is used to stimulate follicular growth to increase the number of mature oocytes available for fertilisation. IUI brings the spermatozoa closer to the oocyte for fertilisation at the appropriate time.

IVF bypasses several steps in the process of conception, such as cervical factors and problems with transport of spermatozoa. ICSI could overcome subtle abnormalities of the sperm that hinder the sperm-oocyte interaction.

Why it is important to do this review

There are various reviews of interventions for couples with unexplained subfertility (Athaullah 2002; Gunn 2016; Hughes 2010; Pandian 2015; Veltman-Verhulst 2016). These reviews have included head to head comparisons of two interventions at the same time, yet as there is a wide range of available treatments, they ultimately do not answer the question which one of the many interventions is the most effective and safe. Network meta-analysis could provide a way of identifying the most effective and safe intervention by not only incorporating head to head direct comparisons but also by using indirect comparison techniques for treatments that have not been directly assessed in randomised controlled trials. The network meta-analysis could also be used to identify gaps in research.

OBJECTIVES

We aim to assess the comparative effectiveness and/or safety of interventions currently being used to treat couples with unexplained subfertility.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials comparing the comparative effectiveness and/or safety of one of the interventions compared to the other intervention. We will exclude quasi-randomised and non-randomised studies. Cross-over trials will be included, but only data from the first phase will be used.

Types of participants

Couples who have been trying to conceive for at least one year, the woman having at least one patent fallopian tube, an ovulatory cycle and no or mild endometriosis (American Fertility Society (AFS) criteria I) and the man having a prewash total motile sperm count > 3 * 106.

Types of interventions

We will consider all trials where one of these interventions is compared.

- Expectant management.
- Timed intercourse.
- Ovarian stimulation using gonadotropins, aromatase-inhibitors or anti-estrogens.
- Intrauterine insemination (IUI) without ovarian stimulation.
- IUI with ovarian stimulation.
- In vitro fertilisation (IVF) with either a single embryo transfer, dual embryos transferred, in a modified natural cycle or combined with intracytoplasmic injection (ICSI).

The interventions of expectant management and timed intercourse will be combined, if no invasive techniques are used.

The reported interventions will be compared to each other or to no intervention (i.e. expectant management).

Types of outcome measures

Primary outcomes

1. The primary effectiveness outcome is a composite of cumulative live birth (live birth is defined as the birth of a living child after 24 weeks of gestation) or ongoing pregnancy (defined as a registered embryonic heartbeat on ultrasound at 12 weeks of gestation); cumulative refers to multiple attempts to conceive, i.e. multiple cycles or fresh IVF followed by cryo cycles).
2. The primary safety outcome is multiple pregnancy (defined as two registered embryonic heartbeats on ultrasound).

Secondary outcomes

Secondary outcomes are:
3. clinical pregnancy (defined as a registered embryonic heartbeat on ultrasound); and
4. moderate/severe ovarian hyperstimulation syndrome (defined as increased abdominal discomfort with symptoms of nausea, vomiting or diarrhoea, the presence of ascites on ultrasound, and an ovarian size of at least 8 cm).

Search methods for identification of studies

We will search for all published and unpublished randomised controlled trials (RCTs), without language or date restriction, in consultation with the Cochrane Gynaecology and Fertility Group (CGF) Information Specialist.

Electronic searches

We will search the following electronic databases for relevant trials from inception onwards.

- The Cochrane Gynaecology and Fertility Group (CGF) specialised register of controlled trials (Procite platform) (Appendix 1).
- The Cochrane Central Register of Studies Online (CRSO Web platform) (Appendix 2).
- MEDLINE (Ovid platform) (Appendix 3).
- Embase (Ovid platform) (Appendix 4).
- PsycINFO (Ovid platform) (Appendix 5).
- CINAHL (Ebsco platform) (Appendix 6).

The MEDLINE search will be combined with the Cochrane highly sensitive search strategy for identifying randomized trials, which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Version 5.1.0, chapter 6, 6.4.11). The Embase, PsycINFO and CINAHL searches will be combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/methodology/filters.html#random).
Other electronic sources of trials will include:

- trial registers for ongoing and registered trials:
  - www.clinicaltrials.gov (a service of the US National Institutes of Health);
  - www.who.int/trialsearch/Default.aspx (The World Health Organisation International Trials Registry Platform search portal);
- the Virtual Health Library Regional Portal (VHL) (bvsalud.org/portal/?lang=en) which includes LILACS; and
- PubMed and Google Scholar (for recent trials not yet indexed in the major databases).

Searching other resources

We will handsearch reference lists of relevant trials and systematic reviews retrieved by the search and contact experts in the field to obtain additional data. We will also handsearch relevant journals and conference abstracts that are not covered in the CGFG register, in liaison with the Information Specialist.

Data collection and analysis

Selection of studies

Two investigators (RT and RW) will independently assess trial eligibility, according to the Criteria for considering studies for this review. We will resolve disagreements through discussion with a third investigator (MW). A PRISMA flow diagram will be drawn to show the results of the search and the number of included and excluded trials. The reasons for excluding any potentially-eligible studies identified by the search from the (network) meta-analysis will be documented.

Data extraction and management

For all included trials two authors (RT and RW) will independently extract data using a data abstraction form and summarise trial characteristics in tables. From each included study we will extract baseline characteristics of the couples (i.e. female age, duration of subfertility, body mass index, prior treatment), study settings, methods, the types of interventions (used dose, type of preparation, regimens, co-interventions) and the outcomes. Where studies have multiple publications the authors will collate multiple reports of the same study under a single study identifier with multiple references. We will correspond with study investigators for further data on methods and results, as required.

Assessment of risk of bias in included studies

Two authors (RT and RW) will independently assess the risk of bias for each eligible study by using the Cochrane 'Risk of bias'

assessment tool (Higgins 2011) which includes six domains: 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. Disagreements will be resolved by discussion with a third investigator (MW). We will describe all judgements fully and present the conclusions in the 'Risk of bias' table, which will be incorporated into the interpretations 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

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 (ORs). We will present 95% confidence intervals 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). 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. When more than two studies compared the same treatments, a random-effects pooled OR will be calculated. The random-effects model incorporates the between study variability and is more conservative than the fixed-effect model.

For each pairwise comparison we will present a 95% predictive interval; this can be interpreted as the 95% interval of the expected treatment effect in a new trial with this comparison (Salanti 2011). Furthermore we will calculate the probability that an intervention is ranked first, second and so on. We will display this ranking graphically for the primary and secondary outcomes using the surface under the cumulative ranking (SUCRA), where the SUCRA values can range from zero (i.e. the intervention is certain to be the worst) to one (i.e. the intervention is certain to be the best).

Unit of analysis issues

The primary analysis will be cumulative rates of each outcome per woman randomised. 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.

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). Attempts will be made to obtain missing data from the original trialists. Where data are unobtainable, we will undertake imputation of individual values only for the primary outcome of live birth or ongoing pregnancy: an event 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

Clinical and methodological heterogeneity

To evaluate the presence of clinical and methodological heterogeneity, we will generate descriptive statistics for trial and study population characteristics across all eligible trials that compare each pair of interventions. We will assess the presence of clinical and methodological heterogeneity within each pairwise comparison by comparing these characteristics. Additionally, we will consider whether there is sufficient similarity of the studied interventions and characteristics of the couples across all included studies for the network meta-analysis (i.e. the assumption of transitivity in network meta-analyses). We will explore the distribution of potential effect modifiers across the different pairwise interventions, i.e. female age, duration of subfertility, primary/secondary subfertility and if the women are treatment naive. In this study we expect the transitivity assumption will hold assuming the following.

1. The common intervention used to compare with different interventions indirectly is similar when it appears in different RCTs (e.g. IUI is used in a similar way in an RCT comparing IUI with expectant management as in an RCT comparing IUI with IVF).
2. All pairwise comparisons do not differ with respect to the distribution of effect modifiers (e.g. the design and study characteristics of an RCT comparing IUI versus expectant management are similar to an RCT comparing IUI versus IVF).

Statistical heterogeneity and inconsistency

Within each pairwise comparison 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).

Another key assumption for performing a network meta-analysis is the consistency of the network, i.e. the agreement between the direct and indirect sources of evidence. We will assess the agreement between the various sources of evidence in the network through two approaches: loop consistency and the design-by-treatment method for the whole network. Loop inconsistency

should be considered if the included studies have different treatment comparisons, study populations or contexts (i.e. settings, study periods) which could be substantially different in ways that might affect the effect size of the comparison. We will furthermore assess the assumption of consistency for the whole network using the design-by-treatment method (Higgins 2012). This approach allows for a global statistical test for the presence of inconsistency of the whole network.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we 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 comparison-adjusted funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies) (Chaimani 2013).

Data synthesis

We will compare interventions using ORs with their respective 95% confidence intervals. When more than two studies compared the same treatments, a random-effects summary OR will be calculated.

We will conduct a network meta-analysis based on all investigated comparisons between treatments and the indirect analysis can be performed utilising all the possible pathways provided by the network. An indirect estimate of A versus B can be calculated by comparing direct comparisons of A versus C with trials of B versus C. In this way the OR for comparing A and B can be calculated using the following principle: ln(ORAvsB) = ln(ORAvsC) − ln(ORBvsC). The direct and indirect evidence will be combined for each comparison using the abovementioned analysis for direct and indirect comparisons. We will use STATA for the analyses.

Subgroup analysis and investigation of heterogeneity

We will assess subgroup differences by interaction tests. We will report the results of subgroup analysis quoting the Chi^2 statistic and P value, and the interaction test I^2 value. If we detect substantial heterogeneity, we will explore possible explanations in subgroup analyses (e.g. differing populations) and/or sensitivity analyses (e.g. differing risk of bias). We will take any statistical heterogeneity into account when interpreting the results, especially if there is any variation in the direction of effect.

Where data are available from at least two studies, we will conduct subgroup analyses for the primary outcomes only to determine the separate evidence within the following subgroups.

1. Younger women (=< 38 years) versus older women (> 38 years).
2. Treatment naïve couples versus couples who have received prior treatment.
3. Short duration of subfertility (<= 2 years) versus long duration of subfertility (> 2 years).
4. IVF with single embryo transfer versus IVF with dual or more embryo transfer.
5. IUI with follicle stimulating hormone (FSH) versus IUI with clomiphene citrate (CC).

Sensitivity analysis

We will conduct sensitivity analyses for the primary outcomes to determine whether the conclusions are robust to arbitrary decisions made regarding the eligibility and analysis. These analyses will include consideration of whether the review conclusions would have differed if:

1. eligibility had been restricted to studies with no domains at high risk of bias;
2. alternative imputation strategies had been implemented;
3. eligibility had varied by publication type (abstract versus full text); or
4. we had included only studies with the outcome live birth.

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

We will prepare a 'Summary of findings' (SoF) table using GRADEpro software. We will follow the approach suggested by the GRADE Working Group (Puhan 2014). The SoF table will evaluate the overall quality of the body of evidence for the main review outcomes (live birth or ongoing pregnancy, multiple pregnancy, clinical pregnancy, moderate/severe ovarian hyperstimulation syndrome) for each comparison. We will provide estimates of the direct and indirect evidence and of the network meta-analysis. 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.

ACKNOWLEDGEMENTS

None.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Group (CGF) search strategy

From inception to present
Procite platform
Keywords CONTAINS "unexplained and endometriosis related infertility" or "unexplained infertility" or "unexplained subfertility" or "idiopathic infertility "or "idiopathic male infertility" or "idiopathic subfertility" or Title CONTAINS "unexplained and endometriosis related infertility" or "unexplained infertility" or "unexplained subfertility" or "idiopathic infertility" or "idiopathic male infertility" or "idiopathic subfertility"

Appendix 2. Cochrane Central Register of Studies Online (CRSO) search strategy

From inception to present
CRSO web platform
#1 MESH DESCRIPTOR Infertility EXPLODE ALL TREES
#2 unexplained:TI,AB,KY
#3 idiopathic:TI,AB,KY
#4 #2 OR #3
#5 #1 AND #4
#6 (unexplain* adj5 infertil*):TI,AB,KY
#7 (unexplain* adj5 subfertil*):TI,AB,KY
#8 (idiopathic adj5 subfertil*):TI,AB,KY
#9 (idiopathic adj5 infertil*):TI,AB,KY
#10 (unknown adj5 subfertil*):TI,AB,KY
#11 (unknown adj5 infertil*):TI,AB,KY
#12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

Appendix 3. MEDLINE search strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print, In Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily, and Ovid MEDLINE (R) 1946-Present

1 exp Infertility/ and unexplained.tw.
2 exp Infertility/ and idiopathic.tw.
3 (unexplain* adj5 infertil*).tw.
4 (unexplain* adj5 subfertil*).tw.
5 (idiopathic adj5 subfertil*).tw.
6 (idiopathic adj5 infertil*).tw.
7 (unknown adj3 infertil*).tw.
8 (unknown adj3 subfertil*).tw.
9 (unexplained adj3 steril*).tw.
10 (idiopathic adj3 steril*).tw.

11 (unknown adj3 steril*).tw.
12 or/1-11
13 exp Clomiphene/
14 clomifene.tw.
15 clomiphene.tw.
16 Serophene.tw.
17 clomid.tw.
18 selective estrogen receptor modulators/ or exp raloxifene hydrochloride/ or exp tamoxifen/
19 selective estrogen receptor modulator*.tw.
20 (SERMs or SERM).tw.
21 (raloxifene or tamoxifen).tw.
22 or/13-21
23 Aromatase Inhibitors/
24 Aromatase inhibitor*.tw.
25 letrozole.tw.
26 (femara or anastrozole).tw.
27 (anti-?estrogen* or anti?estrogen*).tw.
28 or/23-27
29 exp follicle stimulating hormone/ or exp follicle stimulating hormone, beta subunit/ or exp glycoprotein hormones, alpha subunit/ or exp menotropins/ or exp urofollitropin/
30 Follicle Stimulating Hormone*.tw.
31 (FSH or rFSH or recFSH).tw.
32 (uFSH or rhFSH).tw.
33 (hpFSH or pFSH).tw.
34 (follitropin or Gonal F).tw.
35 (menotropin* or menopur).tw.
36 corifollitropin.tw.
37 (urofollitropin or pergonal or bravelle* or follitrin).tw.
38 Follistim*.tw.
39 (Puregon or humegon or menogon).tw.
40 human menopausal gonadotrop?in.tw.
41 growth hormone.tw.
42 HMG.tw.
43 gonadotrop?in*.tw.
44 or/29-43
45 expectant management.tw.
46 watchful waiting.tw.
47 (watch and wait).tw.
48 Coitus/
49 coitus.tw.
50 intercourse.tw.
51 sex*.tw.
52 or/45-51
53 exp Insemination, Artificial/
54 intrauterine insemination*.tw.
55 artificial insemination*.tw.
56 superovulat*.tw.
57 IUI.tw.
58 or/53-56
59 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/
60 embryo transfer*.tw.
61 vitro fertili?ation.tw.
62 ivf.tw.

63 icsi.tw.
64 intracytoplasmic sperm injection*.tw.
65 (blastocyst adj2 transfer*).tw.
66 exp reproductive techniques, assisted/ or exp insemination, artificial/ or exp ovulation induction/
67 assisted reproduct*.tw.
68 ovulation induc*.tw.
69 (ovar* adj2 stimulat*).tw.
70 ovarian hyperstimulation.tw.
71 COH.tw.
72 (ovar* adj2 induc*).tw.
73 (modified adj3 cycle*).tw.
74 (natural adj3 cycle*).tw.
75 MNC IVF.tw.
76 (NCIVF or NC-IVF).tw.
77 unstimulated ivf.tw.
78 (unstimulated adj2 in vitro fertili?ation).tw.
79 (artificial adj3 cycle$).tw.
80 or/59-79
81 22 or 28 or 44 or 52 or 58 or 80
82 12 and 81
83 randomised controlled trial.pt.
84 controlled clinical trial.pt.
85 randomized.ab.
86 randomised.ab.
87 placebo.tw.
88 clinical trials as topic.sh.
89 randomly.ab.
90 trial.ti.
91 (crossover or cross-over or cross over).tw.
92 or/83-91
93 exp animals/ not humans.sh.
94 92 not 93
95 82 and 94

Appendix 4. Embase search strategy

From 1980 to present
Ovid platform
1 (exp infertility/ or exp infertility therapy/) and unexplained.tw.
2 (exp infertility/ or exp infertility therapy/) and idiopathic.tw.
3 (unexplain* adj5 infertil*).tw.
4 (unexplain* adj5 subfertil*).tw.
5 (idiopathic adj5 subfertil*).tw.
6 (idiopathic adj5 infertil*).tw.
7 (unknown adj3 infertil*).tw.
8 (unknown adj3 subfertil*).tw.
9 (unexplained adj3 steril*).tw.
10 (idiopathic adj3 steril*).tw.
11 (unknown adj3 steril*).tw.
12 or/1-11
13 exp clomifene/
14 clomifene.tw.

15 clomiphene.tw.
16 Serophene.tw.
17 clomid.tw.
18 exp selective estrogen receptor modulator/
19 exp raloxifene/
20 exp tamoxifen citrate/ or exp tamoxifen/
21 selective estrogen receptor modulator*.tw.
22 (SERMs or SERM).tw.
23 (raloxifene or tamoxifen).tw.
24 or/13-23
25 exp aromatase inhibitor/
26 Aromatase inhibitor*.tw.
27 letrozole.tw.
28 (femara or anastrozole).tw.
29 (anti-?estrogen* or anti?estrogen*).tw.
30 or/25-29
31 exp follitropin/
32 exp human menopausal gonadotropin/
33 exp urofollitropin/
34 Follicle Stimulating Hormone*.tw.
35 (FSH or rFSH or recFSH).tw.
36 (uFSH or rhFSH).tw.
37 (hpFSH or pFSH).tw.
38 (follitropin or Gonal F).tw.
39 (menotropin* or menopur).tw.
40 corifollitropin.tw.
41 (urofollitropin or pergonal or bravelle* or follitrin).tw.
42 Follistim*.tw.
43 (Puregon or humegon or menogon).tw.
44 human menopausal gonadotrop?in.tw.
45 growth hormone.tw.
46 HMG.tw.
47 gonadotrop?in*.tw.
48 or/31-47
49 expectant management.tw.
50 watchful waiting.tw.
51 (watch and wait).tw.
52 exp coitus/
53 coitus.tw.
54 intercourse.tw.
55 sex*.tw.
56 or/49-55
57 exp artificial insemination/
58 intrauterine insemination*.tw.
59 artificial insemination*.tw.
60 superovulat*.tw.
61 IUI.tw.
62 or/49-61
63 exp fertilization in vitro/
64 exp embryo transfer/
65 exp intracytoplasmic sperm injection/
66 embryo transfer*.tw.
67 vitro fertili?ation.tw.

68 ivf.tw.
69 icsi.tw.
70 intracytoplasmic sperm injection*.tw.
71 (blastocyst adj2 transfer*).tw.
72 exp infertility therapy/
73 exp artificial insemination/
74 exp ovulation induction/
75 assisted reproduct*.tw.
76 ovulation induc*.tw.
77 (ovar* adj2 stimulat*).tw.
78 ovarian hyperstimulation.tw.
79 COH.tw.
80 (ovar* adj2 induc*).tw.
81 (modified adj3 cycle*).tw.
82 (natural adj3 cycle*).tw.
83 MNC IVF.tw.
84 (NCIVF or NC-IVF).tw.
85 unstimulated ivf.tw.
86 (unstimulated adj2 in vitro fertili?ation).tw.
87 (artificial adj3 cycle$).tw.
88 or/63-87
89 24 or 30 or 48 or 56 or 62 or 88
90 Clinical Trial/
91 Randomized Controlled Trial/
92 exp randomization/
93 Single Blind Procedure/
94 Double Blind Procedure/
95 Crossover Procedure/
96 Placebo/
97 Randomi?ed controlled trial$.tw.
98 Rct.tw.
99 random allocation.tw.
100 randomly.tw.
101 randomly allocated.tw.
102 allocated randomly.tw.
103 (allocated adj2 random).tw.
104 Single blind$.tw.
105 Double blind$.tw.
106 ((treble or triple) adj blind$).tw.
107 placebo$.tw.
108 prospective study/
109 or/90-108
110 case study/
111 case report.tw.
112 abstract report/ or letter/
113 or/110-112
114 109 not 113
115 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
116 114 not 115
117 12 and 89 and 116

Appendix 5. PsycINFO search strategy

From 1806 to present
Ovid platform
1 exp INFERTILITY/ and unexplained.tw.
2 exp INFERTILITY/ and idiopathic.tw.
3 (unexplain* adj5 infertil*).tw.
4 (unexplain* adj5 subfertil*).tw.
5 (idiopathic adj5 infertil*).tw.
6 (unknown adj3 infertil*).tw.
7 (unexplained adj3 steril*).tw.
8 (idiopathic adj3 steril*).tw.
9 (unknown adj3 steril*).tw.
10 or/1-9
11 random*.ti,ab,hw,id.
12 trial*.ti,ab,hw,id.
13 controlled stud*.ti,ab,hw,id.
14 placebo*.ti,ab,hw,id.
15 ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)).ti,ab,hw,id.
16 (cross over or crossover or factorial* or latin square).ti,ab,hw,id.
17 (assign* or allocat* or volunteer*).ti,ab,hw,id.
18 treatment effectiveness evaluation/
19 mental health program evaluation/
20 exp experimental design/
21 or/11-20
22 10 and 21

Appendix 6. CINAHL search strategy

From 1982 to present
Ebsco platform

#	Query
S23	S10 AND S22
S22	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21
S21	TX allocat* random*
S20	(MH “Quantitative Studies”)
S19	(MH “Placebos”)
S18	TX placebo*
S17	TX random* allocat*
S16	(MH “Random Assignment”)

(*Continued*)

S15	TX randomi* control* trial*
S14	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*))
S13	TX clinic* n1 trial*
S12	PT Clinical trial
S11	(MH "Clinical Trials+")
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
S9	TX(idiopathic N3 steril*)
S8	TX(unknown N3 subfertil*)
S7	TX(unknown N3 infertil*)
S6	TX(idiopathic N5 infertil*)
S5	TX(idiopathic N5 subfertil*)
S4	TX(unexplain* N5 subfertil*)
S3	TX (unexplain* N5 infertil*)
S2	(MM "Infertility") and TX idiopathic
S1	(MM "Infertility") and TX unexplained

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