Heparin for assisted reproduction (Protocol)

Akhtar M, Sur S, Raine-Fenning N, Jayaprakasan K, Thornton JG, Quenby S

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[Intervention Protocol]

Heparin for assisted reproduction

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Editorial group: Cochrane Menstrual Disorders and Subfertility Group.
Publication status and date: New, published in Issue 11, 2011.

Citation: Akhtar M, Sur S, Raine-Fenning N, Jayaprakasan K, Thornton JG, Quenby S. Heparin for assisted reproduction. *Cochrane Database of Systematic Reviews* 2011, Issue 11. Art. No.: CD009452. DOI: 10.1002/14651858.CD009452.

ABSTRACT

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

To evaluate the risks and benefits of periconceptual heparin in women undergoing an ART cycle.

BACKGROUND

Description of the condition

Infertility is the failure of a couple of reproductive age to conceive after having regular unprotected sexual intercourse for a period of 12 months or more. Primary infertility refers to couples who have never conceived, and secondary infertility refers to couples who have previously conceived but are unable to do so again after a year of trying.

Infertility affects 15% of couples and is becoming increasingly common. Of these couples, 70% will have primary and 30% secondary infertility. Assisted reproduction techniques (ART) have been employed to help some of these couples achieve a pregnancy. Assisted reproduction has significant physical, social, psychological and financial implications. The success of assisted reproductive treatment is determined by clinical pregnancy and the live birth of a child. Live birth rates with ART vary from 5% to 60%; hence various adjuncts have been employed during assisted reproduction to increase the likelihood of pregnancy and live birth. The effectiveness of these adjuncts remains to be determined in many cases. Heparin, given as an adjunct to women with or without a known thrombophilia, is one such therapy and has been suggested as being efficacious in improving implantation (attachment of the fertilised egg to the wall of the uterus) and achieving pregnancy.

This Cochrane review will provide evidence-based knowledge of the efficacy of heparin given in the periconceptual period (around the time of conception) to reduce implantation failure in women who have a history of infertility and are undergoing assisted reproduction treatments. In this review we will not be assessing the efficacy of heparin as an antithrombophilic agent (preventing blood clots) later in pregnancy or in women with a history of recurrent miscarriage.

Heparan sulphates have an important role in conception and early pregnancy events. The role of heparin (a structural analogue of Heparan) in assisted conception is, however, not clear. Heparin is a linear polydisperse polysaccharide consisting of 1-4 linked pyranosyluronic acid and 2-amino-deoxyglucopyranose (glucosamine) residues (Comper 1981). Owing to their highly anionic nature, heparin and heparan sulphate have high binding affinity to antithrombin, growth factors, growth factor receptors, viral envelope proteins and extracellular matrix molecules.

Heparan sulphate proteoglycans (HSPGs) are expressed throughout the reproductive tract and are involved in the regulation of endometrial cycling (Potter et al 1992; Kelly et al 1995, San Martin et al 2004; Germeyer et al 2007; Lai et al 2007; Xu et al 2007).

Description of the intervention

When heparin is used as an adjunct treatment during assisted reproduction, there is no consensus regarding the optimum type of heparin, either unfractionated heparin or low molecular weight heparin, or the dose. This is an area which will be considered in the review.

Low molecular weight heparins (LMWH) are derived from heparin by enzymatic (for example tinzaparin) or chemical (for example dalteparin, nadroparin and enoxaparin) depolymerization of unfractionated heparin (UFH), which in itself cannot be synthesized in vitro.

UFH and LMWHs facilitate the anticoagulant effect of antithrombin (Bick et al 2005) but, compared with UFH, LMWH has reduced antifactor IIa activity leading to inefficient inhibition of thrombin by antithrombin. However, the smaller LMWH fragments inactivate factor Xa with equal efficacy. LMWH has a longer half-life, a more predictable antithrombotic response, and a substantially lower risk of heparin-induced thrombocytopenia (HIT) (Warkentin et al 1995; Warkentin and Greinacher et al 2004) and osteoporosis (Murray et al 1995), which has obvious clinical benefits.

LMWHs have a mean molecular weight of 4300 to 5000 kDa (range 1000 to 10 000 kDa), compared to 15,000 kDa for UFH (Nelson and Greer et al 2008).

How the intervention might work

Implantation is a complex, dynamic process which involves coordination of various interactions at an intra and intercellular level. The interaction between the developing embryo and the endometrium is still not fully understood; however heparin can potentially modulate many of the known mechanisms that underlie the successful implantation of the developing embryo.

Traditionally, the role of heparin in early pregnancy was believed to be in the prevention of blood clotting during implantation and placentation in women with inherited and acquired thrombophilias. However, more recent work suggests a possible therapeutic role for heparin in other mechanisms fundamental to implantation. UFH as well as LMWH are able to modulate the process of decidualisation, whereby the cells in the lining of the womb prepare for pregnancy. This positive effect on decidualisation is a potential mechanism by which heparin improves implantation in ART (Corvinus et al 2003, Poehlmann et al 2005, Fluhr H et al 2010).

Heparin also has the ability to bind with and modulate a wide variety of proteins, which can alter a number of physiological processes that are involved in implantation and trophoblastic development. These processes include adhesion of the blastocyst to the endometrial surface (Wang et al 2002), trophoblastic differentiation and invasion (Erden et al 2006, Quenby et al 2004, Di Simone et al 2007a, Leach et al 2004, Arai et al 1994,; Moller et al 2006, Weigert et al 2001, Nelson and Greer et al 2008, d'Souza et al 2007)

Why it is important to do this review

Heparin is often offered to couples as an adjunct in an attempt to improve live birth rates, its presumed effect being to improve implantation. Clinicians may be using heparin as an adjunct based on biological plausibility rather than evidence of efficacy.
A systematic review is required to determine the efficacy of heparin to increase pregnancy and live birth rates and reduce adverse perinatal outcomes for all women undergoing assisted reproduction.

OBJECTIVES

To evaluate the risks and benefits of periconceptual heparin in women undergoing an ART cycle.

METHODS

Criteria for considering studies for this review

Types of studies

Truly randomised controlled trials (RCTs).
Only trials that are either clearly randomised or claim to be randomised and do not have evidence of inadequate sequence generation such as date of birth or hospital number will be included.

Types of participants

All women undergoing assisted reproduction treatment (ART) with a history of infertility. Women undergoing stimulated or unstimulated intrauterine insemination (IUI) will not be included. Women with a previously known thrombophilia will not be excluded.

Types of interventions

1. Heparin versus no treatment
2. Heparin versus placebo
3. Heparin versus aspirin
4. Heparin versus heparin and aspirin
5. Unfractionated heparin (UFH) versus low molecular weight heparin (LMWH)

Studies will be included if heparin was administered in the periconceptual period (from the day of egg collection or embryo transfer to 14 days later).

Types of outcome measures

Primary outcomes

1. Live birth rate per woman
- Number of live births divided by the number of randomised women (live birth is defined as delivery of one or more live infants)
2. Adverse effects of heparin e.g. any bleeding, bruising, heparin-induced thrombocytopenia (HIT), anaphylaxis and any other unexpected side effects

Secondary outcomes

1. Clinical pregnancy rate per woman
- Number of clinical pregnancies divided by the number of randomised women

The presence of a gestational sac with fetal heart beat on ultrasound scan defines a clinical pregnancy.

2. Pregnancy rate per woman

Number of women achieving a pregnancy divided by the number of randomised women

3. On-going pregnancy rate per woman
- Number of women achieving an on-going pregnancy divided by the number of randomised women (pregnancies going beyond 12 weeks duration)

4. Multiple pregnancy rate per woman
- Incidence of multiple pregnancy per randomised women

The demonstration of more than one sac with a fetal pole on ultrasound scan defines multiple pregnancies.

5. Maternal pregnancy complications including first trimester miscarriage, second trimester miscarriage, preterm delivery, pre-eclampsia, pregnancy-induced hypertension, any maternal bleeding

6. Fetal complications during pregnancy including intrauterine growth restriction, placenta previa, placental abruption

Additional outcomes not appropriate for statistical pooling

Data per cycle, per pregnancy or per embryo transfer (ET) are not appropriate for pooling because of what statisticians refer to as 'unit of analysis errors'. Simple group comparison tests for categorical data require that observations are statistically independent. The use of multiple observations per woman leads to unpredictable bias in the estimate of treatment difference (Vail et al 2003). However, due to the frequency with which this form of data is reported in subfertility research it will be entered into the 'table of comparisons' for the following outcomes:

• implantation rate, the number of fetal sacs divided by the number of embryos transferred;
• incidence of miscarriage per total number of pregnancies;
• incidence of multiple pregnancies per total number of pregnancies.

Search methods for identification of studies

A comprehensive and exhaustive search strategy has been developed in consultation with the Trials Search Coordinator of the Cochrane Menstrual Disorders and Subfertility Group. The strategy will be used in an attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress). Relevant trials will be identified from both electronic databases and other resources.
Completion of the review is expected within one year of publication of the protocol on *The Cochrane Library*. It is also the intention of the review authors that a new search for RCTs will be performed every two years. When an important study is published we will update the review accordingly.

Electronic searches

We will search the following electronic databases, from inception to the present with the Cochrane highly sensitive search strategy for identifying randomised trials, which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (version 5.1.0; chapter 6, 6.4.11) (Higgins 2011).
1. The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* latest issue) (see Appendix 1).
2. English language electronic databases: MEDLINE, EMBASE and PsycINFO (see Appendix 2, Appendix 3, Appendix 4).
3. *The Cochrane Library* (www.cochrane.org/index.htm) for DARE, the Database of Abstracts of Reviews of Effects (reference lists from non-Cochrane reviews on similar topics).
4. Current Controlled Trials (www.controlled-trials.com).
5. The World Health Organization International Trials Registry Platform search portal (www.who.int/trialsearch/Default.aspx).

Searching other resources

We will search the references lists of all included studies and relevant reviews to identify further relevant articles.
If required, we will contact authors and experts in the relevant field for potential studies.
We will do a search for grey literature.

Data collection and analysis

We will perform statistical analysis in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Review Manager 5.1 will be used for input of data.

Selection of studies

The title, abstract, and keywords of every record retrieved will be scrutinized independently by two review authors to determine which studies require further assessment. The full text will be retrieved when the information given in the titles, abstracts, and keywords suggest that the randomised controlled study intervention is heparin as an adjunct to assisted reproduction therapy.
If there are any doubts regarding these criteria, from scanning the titles and abstracts, the full article will be retrieved for clarification. Disagreements will be resolved by discussion with a third review author (Professor S Quenby), if necessary. The authors of trials will be contacted to provide missing data, if required.

Data extraction and management

The following information will be extracted from the studies included in the review. It will be presented in the table 'Characteristics of included studies'.

Trial characteristics

These will include:
1. method of generating randomisation sequence;
2. allocation concealment;
3. trial design;
4. number of women screened for eligibility then randomised, excluded, and finally analysed;
5. duration, timing, and location of the trial;
6. source of funding.

Baseline characteristics of the studied groups

1. Age of the women
2. Duration of infertility
3. Type of ART
4. Previous fertility treatments

Intervention

1. Type of intervention and control group
2. Dose regimen and timing

Outcomes

1. Outcomes
2. How outcomes were defined
3. How outcomes were measured
4. Timing of outcome measurement

All data will be extracted independently by two review authors using forms designed according to Cochrane guidelines. Additional information will be sought from the authors on trial methodology and trial data for trials that appear to meet the eligibility criteria but have aspects of methodology that are unclear or data in an unsuitable form for meta-analysis.
Differences of opinion are to be noted and resolved by consensus.

Assessment of risk of bias in included studies

Assessment of risk of bias in the included studies will be independently performed by two review authors; disagreements will be noted and resolved by a third review author.

The risk of bias table will be included in the table 'Characteristics of included studies'.

The following risk of bias domains will be assessed according to modification of the quality criteria specified by the *Cochrane Handbook for Systematic Reviews of Interventions* 5.1.0.

1. Random sequence generation method (e.g. computer generated, random number tables, or drawing lots)
2. Allocation concealment: adequate (e.g. third party, sealed envelopes); inadequate (e.g. open list of allocation codes); not clear (e.g. not stated).
3. Blinding of participants, personnel, and outcome assessors.
4. Whether an intention-to-treat analysis was performed or not.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Any other sources of bias not included in this protocol.

Measures of treatment effect

All outcomes are expected to be dichotomous. We will use the numbers of events in the control and intervention groups of each study to calculate odds ratios (OR) with 95% confidence intervals (CI).

Unit of analysis issues

The primary analysis will be per woman randomised. Reported data that do not allow valid analysis (for example, 'per cycle' rather than 'per woman', where women contribute more than one cycle) will be briefly summarised in an additional table and will not be used in meta-analysis. Multiple live births (for example, twins or triplets) will be counted as one live birth event.

In cross-over trials, only first cycle data will be included in the analysis.

Dealing with missing data

We will contact the authors of the RCTs to source any missing data or to resolve any queries that may arise.

If required we will extract data to allow an intention-to-treat analysis (this analysis will include all the participants in the original randomly assigned groups). If the participant numbers randomised and the numbers analysed are inconsistent then the percentage loss to follow up will be calculated and reported in an additional table.

Assessment of heterogeneity

The review authors will check to see if the participants, interventions, and outcomes in the included studies are similar enough to consider pooling in a meta-analysis.

Tests for statistical heterogeneity in pooled data will be carried out using the Chi^2 test, with significance set at $P < 0.1$. The I^2 statistic will be used to estimate the total variation across studies that is due to heterogeneity, where < 25% is considered as low-level, 25% to 50% as moderate-level, and > 50% as high-level heterogeneity. If high levels of heterogeneity (I^2 > 50%) are seen for primary outcomes, we will explore possible sources of heterogeneity using sensitivity and subgroup analyses described below.

Assessment of reporting biases

Potential publication bias will be assessed using a funnel plot, or other corrective analytical methods, depending on the number of included studies (Egger et al 1997).

Data synthesis

Meta-analyses will be performed, as appropriate, where data are available from multiple studies investigating the same treatment, and where the outcome has been measured in a standard way between the studies. A fixed-effect model will be used. We will undertake this meta-analysis according to methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). An increase in the odds of a particular outcome, which may be beneficial (for example, live birth) or detrimental (for example, 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.

Subgroup analysis and investigation of heterogeneity

Where data are available, we will conduct subgroup analyses to investigate the following.

1. Efficacy of heparin with different ART excluding IUI.
2. Efficacy of adjunct therapy of heparin with or without thrombophilia for women undergoing ART.
3. Duration, dose, timing and type of heparin therapy during ART.
4. Any other adjunct therapy used in addition with heparin during ART.
5. Efficacy of heparin during ART according to age.
6. Efficacy of heparin during ART according to number of implantation failures.
7. Efficacy of heparin with fresh versus frozen embryo transfer.

Factors such as length of follow-up and use of adjusted or unadjusted analysis will be considered in interpretation of any heterogeneity.

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of the following factors on effect size:

1. Publication status of studies (published or unpublished)
2. Study quality, such as allocation concealment, blinding, and numbers lost to follow up (considered separately).

ACKNOWLEDGEMENTS

We thank Jane Clarke and Helen Nagels (Managing Editors), Marian Showell (Trials Search Coordinator), and the editorial board of the Cochrane Menstrual Disorders and Subfertility Group (MDSG) for their invaluable assistance in developing this protocol.

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Bick et al 2005
Bick RL, Frenkel EP, Walenga J, Fareed J, Hoppensteadt DA. Unfractionated heparin, low molecular weight heparins, and pentasaccharide: basic mechanism of actions, pharmacology and clinical use. *Hematology Oncology Clinics of North America* 2005;**19**:1–51.

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Comper WD. *Heparin (and related polysaccharides) structural and functional properties*. Gordon and Breach Publication group, 1981.

Corvinus et al 2003
Corvinus FM, Fitzgerald JS, Friedrich K, Markert UR. Evidence for a correlation between trophoblast invasiveness and STAT3 activity. *American Journal of Reproductive Immunology* 2003;**50**:316–21.

Di Simone et al 2007a
Di Simone N, Di Nicuolo F, Sanguinetti M, Ferrazzani S, D'Alessio MC, Castellani R, et al.Low-molecular weight heparin induces in vitro trophoblast invasiveness: role of matrix metalloproteinases and tissue inhibitors. *Placenta* 2007;**a 28**:298–304.

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Egger et al 1997
Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315 (7109)**:629–34.

Erden et al 2006
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Fluhr H et al 2010
Fluhr H, Spratte J, Ehrhardt J, Steinmüller F, Licht P, Zygmunt, M. Heparin and low-molecular-weight heparins modulate the decidualization of human endometrial stromal cells. *Fertility and Sterility* 2010;**93**:2581–7.

Germeyer et al 2007
Germeyer A, Klinkert MS, Huppertz A-G, Clausmeyer S, Popovici RM, Strowitzki T, et al.Expression of syndecans, cell-cell interaction regulating heparan sulfate proteoglycans, within the human endometrium and their regulation throughout the menstrual cycle. *Fertility and Sterility* 2007; **87**:657–63.

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Murray et al 1995
Murray WJ, Lindo VS, Kakkar VV, Melissari E. Long-term administration of heparin and heparin fractions and osteoporosis in experimental animals. *Blood Coagulation & Fibrinolysis* 1995;**6**:113–8.

Nelson and Greer et al 2008
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Poehlmann et al 2005
Poehlmann TG, Fitzgerald JS, Meissner A, Wengenmayer T, Schleussner E, FriedrichK, Markert UR. Trophoblast invasion: tuning through LIF, signalling via Stat3. *Placenta* 2005;**26 Suppl**:37–41.

Potter et al 1992
Potter SW, Morris JE. Changes in histochemical distribution of cell surface heparan sulfate proteoglycan in mouse uterus during the estrous cycle and early pregnancy. *The Anatomical Record* 1992;**234**:383–90.

Quenby et al 2004
Quenby S, Mountfield S, Cartwright JE, Whitley GS, Vince G. Effects of low-molecular-weight and unfractionated heparin on trophoblast function. *Obstetrics & Gynecology* 2004;**104**:354–61.

San Martin et al 2004
San Martin S, Soto-Suazo M, Zorn TMT. Perlecan and syndecan-4 in uterine tissues during the early pregnancy in mice. *American Journal of Reproductive Immunology* 2004; **52**:53–9.

Vail et al 2003
Vail A, Gardener E. Common statistical errors in the design and analysis of subfertility trials.. *Human Reproduction* 2003;**18**:1000–4.

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Weigert et al 2001
Weigert C, Brodbeck K, Haring HU, Gambaro G, Schleicher ED. Low-molecular-weight heparin prevents high glucose- and phorbol ester-induced TGF-beta 1 gene activation. *Kidney International* 2001;**60**:935–43.

Xu et al 2007
Xu X, Ding J, Rao G, Shen J, Prinz RA, Rana N, Dmowski WP. Estradiol induces heparanase-1 expression and heparan sulphate proteoglycan degradation in human endometrium. *Human Reproduction* 2007;**22**:927–37.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

Menstrual Disorders and Subfertility Group Specialised Register (inception to present)
Ovid the Cochrane Central Register of Controlled Trials (CENTRAL) (inception to present)
There is no language restriction in these search.

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/
2 embryo transfer$.tw.
3 in vitro fertilisation.tw.
4 ivf-et.tw.
5 (ivf or et).tw.
6 icsi.tw.
7 intracytoplasmic sperm injection$.tw.
8 (blastocyst adj2 transfer$).tw.
9 (assist$ adj2 reproducti$).tw.
10 exp insemination, artificial/ or exp reproductive techniques, assisted/
11 artificial$ inseminat$.tw.
12 iui.tw.

13 intrauterine insemination.tw.
14 nidation.tw.
15 reproductive technique$.tw.
16 reproduct$ technolog$.tw.
17 exp Embryo Implantation/
18 (implant$ adj2 fail$).tw.
19 reproduct$ technique$.tw.
20 exp Infertility, Female/
21 ((Female$ or women) adj2 infertil$).tw.
22 ((Female$ or women) adj2 subfertil$).tw.
23 exp Abortion, Habitual/
24 recurrent miscarriage$.tw.
25 or/1-24 (8324)
26 exp heparin/ or exp heparin, low-molecular-weight/ or exp heparinoids/
27 heparin$.tw.
28 LMWH$.tw.
29 liquemin.tw.
30 enoxaparin.tw.
31 heparinic acid.tw.
32 dalteparin.tw.
33 tinzaparin.tw.
34 clexane.tw.
35 lovenox.tw.
36 indenox.tw.
37 xaparin.tw.
38 or/26-37
39 25 and 38

Appendix 2. MEDLINE search strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1950 to present)

The MEDLINE search was combined with the Cochrane highly sensitive search strategy for identifying randomized trials which appears in the *Cochrane Handbook of Systematic Reviews of Interventions (version 5.0.2; chapter 6, 6.4.11)*

There is no language restriction in this search

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/
2 embryo transfer$.tw.
3 in vitro fertilisation.tw.
4 ivf-et.tw.
5 (ivf or et).tw.
6 icsi.tw.
7 intracytoplasmic sperm injection$.tw.
8 (blastocyst adj2 transfer$).tw.
9 (assist$ adj2 reproducti$).tw.
10 exp insemination, artificial/ or exp reproductive techniques, assisted/
11 artificial$ inseminat$.tw.
12 iui.tw.
13 intrauterine insemination.tw.
14 nidation.tw.
15 reproductive technique$.tw.
16 reproduct$ technolog$.tw.
17 exp Embryo Implantation/

18 (implant$ adj2 fail$).tw.
19 reproduct$ technique$.tw.
20 exp Infertility, Female/
21 ((Female$ or women) adj2 infertil$).tw.
22 ((Female$ or women) adj2 subfertil$).tw.
23 exp Abortion, Habitual/
24 recurrent miscarriage$.tw.
25 or/1-24
26 exp heparin/ or exp heparin, low-molecular-weight/ or exp heparinoids/
27 heparin$.tw.
28 LMWH$.tw.
29 liquemin.tw.
30 enoxaparin.tw.
31 heparinic acid.tw.
32 dalteparin.tw.
33 tinzaparin.tw.
34 clexane.tw.
35 lovenox.tw.
36 indenox.tw.
37 xaparin.tw.
38 or/26-37
39 25 and 38
40 randomized controlled trial.pt.
41 controlled clinical trial.pt.
42 randomized.ab.
43 placebo.tw.
44 clinical trials as topic.sh.
45 randomly.ab.
46 trial.ti.
47 (crossover or cross-over or cross over).tw.
48 or/40-47
49 exp animals/ not humans.sh.
50 48 not 49
51 39 and 50

Appendix 3. EMBASE search strategy

Ovid EMBASE (01.01.10 to present)
EMBASE is only searched one year back as the UKCC has hand searched EMBASE to this point and these trials are already in CENTRAL.
The EMBASE search is combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/mehodology/filters.html#random
There is no language restriction in this search
1 exp embryo transfer/ or exp female infertility/ or exp fertilization in vitro/
2 embryo transfer$.tw.
3 in vitro fertilisation.tw.
4 ivf-et.tw.
5 (ivf or et).tw.
6 icsi.tw.
7 intracytoplasmic sperm injection$.tw.
8 (blastocyst adj2 transfer$).tw.
9 (assist$ adj2 reproducti$).tw.

10 exp artificial insemination/
11 artificial$ inseminat$.tw.
12 reproductive technique$.tw.
13 reproduct$ technolog$.tw.
14 exp nidation/
15 (implant$ adj2 fail$).tw.
16 reproduct$ technique$.tw.
17 ((Female$ or women) adj2 infertil$).tw.
18 ((Female$ or women) adj2 subfertil$).tw.
19 exp recurrent abortion/
20 recurrent miscarriage.tw.
21 iui.tw.
22 intrauterine insemination.tw.
23 nidation.tw.
24 exp intracytoplasmic sperm injection/
25 or/1-24
26 exp HEPARIN/ or exp LOW MOLECULAR WEIGHT HEPARIN/
27 heparin$.tw.
28 LMWH$.tw.
29 liquemin.tw.
30 enoxaparin.tw.
31 heparinic acid.tw.
32 dalteparin.tw.
33 tinzaparin.tw.
34 clexane.tw.
35 lovenox.tw.
36 indenox.tw.
37 xaparin.tw.
38 or/26-37
39 25 and 38
40 Clinical Trial/
41 Randomized Controlled Trial/
42 exp randomization/
43 Single Blind Procedure/
44 Double Blind Procedure/
45 Crossover Procedure/
46 Placebo/
47 Randomi?ed controlled trial$.tw.
48 Rct.tw.
49 random allocation.tw.
50 randomly allocated.tw.
51 allocated randomly.tw.
52 (allocated adj2 random).tw.
53 Single blind$.tw.
54 Double blind$.tw.
55 ((treble or triple) adj blind$).tw.
56 placebo$.tw.
57 prospective study/
58 or/40-57
59 case study/
60 case report.tw.
61 abstract report/ or letter/
62 or/59-61

63 58 not 62
64 39 and 63
65 (2010$ or 2011$).em.
66 64 and 65

Appendix 4. PsycINFO search strategy

Ovid PsycINFO (1806 to present)
There is no language restriction in this search

1 exp Reproductive Technology/
2 exp Infertility/
3 exp Embryo/
4 embryo transfer$.tw.
5 in vitro fertili?ation.tw.
6 ivf-et.tw.
7 (ivf or et).tw.
8 icsi.tw.
9 intracytoplasmic sperm injection$.tw.
10 (blastocyst adj2 transfer$).tw.
11 (assist$ adj2 reproducti$).tw.
12 artificial$ inseminat$.tw.
13 iui.tw.
14 intrauterine insemination.tw.
15 nidation.tw.
16 reproductive technique$.tw.
17 reproduct$ technolog$.tw.
18 (implant$ adj2 fail$).tw.
19 reproduct$ technique$.tw.
20 ((Female$ or women) adj2 infertil$).tw.
21 ((Female$ or women) adj2 subfertil$).tw.
22 exp Spontaneous Abortion/
23 recurrent miscarriage$.tw.
24 or/1-23
25 exp Heparin/
26 heparin$.tw.
27 LMWH$.tw.
28 liquemin.tw.
29 enoxaparin.tw.
30 heparinic acid.tw.
31 dalteparin.tw.
32 tinzaparin.tw.
33 clexane.tw.
34 lovenox.tw.
35 indenox.tw.
36 xaparin.tw.
37 or/25-36
38 24 and 37

HISTORY

Protocol first published: Issue 11, 2011

CONTRIBUTIONS OF AUTHORS

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All correspondence with drafting of the protocol, develop a search strategy, search for trials, obtain copies of trials, select which trials to include, extract data from trials, enter data into RevMan, carry out the analysis, interpret the analysis, draft the final review and update the review.

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DECLARATIONS OF INTEREST

The authors have no commercial interest to disclose.

SOURCES OF SUPPORT

Internal sources

- Cochrane Menstrual Disorders and Subfertilty Group, New Zealand.
- Department of Obstetrics and Gynaecology, University of Auckland, New Zealand.
- Clinical Reproductive Medicine Unit, University Hospitals Coventry & Warwickshire NHS Trust, UK.
- Division of Obstetrics & Gynaecology, School of Clinical Sciences, University of Nottingham, UK.
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External sources

- No sources of support supplied