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Assisted reproductive technology: an overview of Cochrane Reviews (Review)

Farquhar C, Rishworth JR, Brown J, Nelen WLDM, Marjoribanks J

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[Overview of Reviews]

Assisted reproductive technology: an overview of Cochrane Reviews

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ABSTRACT

Background

As many as one in six couples will encounter problems with fertility, defined as failure to achieve a clinical pregnancy after regular intercourse for 12 months. Increasingly, couples are turning to assisted reproductive technology (ART) for help with conceiving and ultimately giving birth to a healthy live baby of their own. Fertility treatments are complex, and each ART cycle consists of several steps. If one of the steps is incorrectly applied, the stakes are high as conception may not occur. With this in mind, it is important that each step of the ART cycle is supported by good evidence from well-designed studies.

Objectives

To summarise the evidence from Cochrane systematic reviews on procedures and treatment options available to couples with subfertility undergoing assisted reproductive technology (ART).

Methods

Published Cochrane systematic reviews of couples undergoing ART (in vitro fertilisation or intracytoplasmic sperm injection) were eligible for inclusion in the overview. We also identified Cochrane reviews in preparation, for future inclusion.

The outcomes of the overview were live birth (primary outcome), clinical pregnancy, multiple pregnancy, miscarriage and ovarian hyperstimulation syndrome (secondary outcomes). Studies of intrauterine insemination and ovulation induction were excluded.

Selection of systematic reviews, data extraction and quality assessment were undertaken in duplicate. Review quality was assessed by using the AMSTAR tool. Reviews were organised by their relevance to specific stages in the ART cycle. Their findings were summarised in the text and data for each outcome were reported in 'Additional tables'.

Main results

Fifty-nine systematic reviews published in *The Cochrane Library* up to July 2015 were included. All were high quality. Thirty-two reviews identified interventions that were effective (n = 19) or promising (n = 13), 14 reviews identified interventions that were either ineffective (n = 2) or possibly ineffective (n = 12), and 13 reviews were unable to draw conclusions due to lack of evidence.

An additional 11 protocols and five titles were identified for future inclusion in this overview.

Authors' conclusions

This overview provides the most up to date evidence on ART cycles from systematic reviews of randomised controlled trials. Fertility treatments are costly and the stakes are high. Using the best available evidence to optimise outcomes is best practice. The evidence from this overview could be used to develop clinical practice guidelines and protocols for use in daily clinical practice, in order to improve live birth rates and reduce rates of multiple pregnancy, cycle cancellation and ovarian hyperstimulation syndrome.

PLAIN LANGUAGE SUMMARY

Assisted reproductive technology: an overview of Cochrane Reviews

Background

As many as one in six couples encounter problems with fertility, defined as failure to achieve a clinical pregnancy after regular intercourse for 12 months. Increasingly, couples are turning to assisted reproductive technology (ART) for help with conceiving and ultimately giving birth to a healthy live baby of their own. Fertility treatments are complex and costly, and each assisted reproduction cycle consists of several steps. If one of the steps is incorrectly applied, the stakes are high as conception may not occur. With this in mind, it is important that each step involved in ART is supported by good evidence from well-designed studies. Cochrane reviewers examined the evidence from Cochrane systematic reviews on ART published in *The Cochrane Library*.

Study characteristics

We included 59 Cochrane systematic reviews on various stages in the ART cycle. All were high quality. Reviews of in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) were included in the overview. Reviews of intrauterine insemination and ovulation induction were not included. This overview provides the most up to date evidence from randomised controlled trials for ART cycles.

Key results

Thirty-two reviews identified interventions that were effective or promising, 14 reviews identified interventions that were ineffective or possibly ineffective, and 13 reviews were unable to draw conclusions due to lack of evidence. Use of the evidence from this overview to guide clinical practice should help to improve live birth rates and reduce rates of multiple pregnancy, cycle cancellation and ovarian hyperstimulation syndrome.

BACKGROUND

Description of the condition

As many as one in six couples will encounter problems with fertility, defined as failure to achieve a clinical pregnancy after regular intercourse for 12 months (Boivin 2007; Zegers-Hochschild 2009). Increasingly, couples are turning to assisted reproductive technology (ART) for help with conceiving and ultimately giving birth to a healthy live baby of their own. Fertility treatments are complex, and each assisted reproduction cycle consists of several steps. If one of the steps is incorrectly applied, the stakes are high as conception may not occur. With this in mind, it is important that each step involved in assisted fertility treatment is supported by good evidence from well-designed studies.

This review summarises the evidence for the different steps in ART.

Description of the interventions

Assisted reproductive technology (ART) consists of procedures that involve the in vitro handling of both human oocytes and sperm, or of embryos, with the objective of establishing a pregnancy (Zegers-Hochschild 2009).

Once couples have been prepared for treatment, the following are the steps that make up an ART cycle.

1. Drugs are initiated to stimulate growth of multiple ovarian follicles, while at the same time other medications are given to suppress the natural menstrual cycle and down-regulate the pituitary gland.

2. After initiation of ovarian stimulatory drugs, monitoring is undertaken at intervals to assess the growth of the follicles.

3. When the follicles have reached an appropriate size, the next step involves giving a drug to bring about final maturation of the eggs (known as ovulation triggering).

4. The next step involves egg collection (usually with a transvaginal ultrasound probe to guide the pickup) and, in some cases of male infertility, sperm retrieval.

5. Next is the fertilisation process, which is usually completed by in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI).

6. Laboratory procedures follow for embryo culture: culture media, oxygen concentration, co-culture, assisted hatching etc.

7. The embryos are then placed into the uterus. Issues of importance here include endometrial preparation, the best timing for embryo transfer, how many embryos to transfer, what type of catheter to use, the use of ultrasound guidance, need for bed rest etc.

8. Then there is luteal phase support, for which several options are available including administration of progesterone, estrogen (E_2), and human chorionic gonadotropin (hCG).

Finally, adverse effects, such as ovarian hyperstimulation syndrome, can be associated with the assisted reproduction process.

How the intervention might work

Assisted reproductive technology (ART) treats a variety of causes of infertility by collecting gametes, creating embryos from these in the laboratory, and transferring the most viable embryo into the uterus.

Why it is important to do this overview

The significance of this process of reviewing reviews on ART is that it provides evidence indicating the best methods for each step in the ART cycle, which can lead to simplifying and improving the process. The outcome should be an increase in live birth rates from assisted reproduction, along with a reduction in adverse events such as ovarian hyperstimulation syndrome and multiple pregnancy.

OBJECTIVES

To summarise the evidence from Cochrane systematic reviews on procedures and treatment options available to couples with subfertility undergoing ART.

METHODS

Criteria for considering reviews for inclusion

Only published Cochrane systematic reviews were considered in this overview. Cochrane reviews in preparation (published protocols and titles) were identified for future inclusion.

Participants

Participants in eligible studies were couples with subfertility seeking a pregnancy and undergoing ART. Specifically, participants included women with endometriosis, women with a previous poor response or recurrent pregnancy losses, and couples undergoing frozen embryo replacement cycles, oocyte donation cycles or both.

Interventions

Reviews of in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI) were considered. Reviews of intrauterine insemination and ovulation induction were excluded from the overview.

Outcomes

The primary outcome of this overview was live birth.

Secondary outcomes were clinical pregnancy, multiple pregnancy, miscarriage, and ovarian hyperstimulation syndrome.

Search methods for identification of reviews

The *Cochrane Database of Systematic Reviews* was searched in July 2015, using the term: 'Assisted Reproductive Technology'. The search term was limited to title, abstract, or keywords. No other databases were searched.

Data collection and analysis

Selection of reviews

Reviews addressing the stages or steps of ART interventions were selected. These reviews were identified by one review author and confirmed by a second review author. Disagreements were resolved by consensus or by discussion with a third party.

The reviews were separated into the following topics.

1. Indication for ART.
2. Pre-ART and adjuvant strategies

2.1 for unselected populations:

- lifestyle advice,
- surgical therapy,
- medical therapy,
- alternative therapy;

2.2 for selected populations (e.g. tubal pathology, endometriosis, polycystic ovary syndrome).

3. Down-regulation with agonists or antagonists.
4. Ovarian stimulation:
4.1 medication type;
4.2 monitoring;
4.3 interventions for poor responders;
4.4 natural cycle IVF.
5. Ovulation triggering.
6. Oocyte retrieval.
7. Sperm retrieval.
8. Laboratory phase.
9. Embryo transfer:
9.1 developmental stage;
9.2 number of embryos;
9.3 transfer techniques and procedures.
10. Luteal phase support.
11. Prevention of ovarian hyperstimulation syndrome (OHSS).
12. Frozen embryo replacement cycles.

Data extraction and management

Data on the above outcomes were extracted independently by two review authors (from JR, JB, CF, WN, JM) using an Excel spreadsheet. Disagreements were resolved by consensus. In cases where significant data were missing, the original review authors were contacted for assistance. Information was extracted and reported in additional tables concerning the following.

1. Population demographics: participant characteristics.
2. Review characteristics: the number of included trials; the number of participants; the date that the review was assessed as up to date; interventions and comparisons; all outcomes; and limitations of the review.
3. Statistical summary: the summary effects from relevant comparisons and outcomes.

We used the same effect measures as the original reviews, in most cases odds ratios. Problems can arise if the odds ratio is misinterpreted as a risk ratio. For interventions that increase the chances of events, the odds ratio is larger than the risk ratio, so the misinterpretation will tend to overestimate the intervention effect, especially when events are common (with, say, risks of events more than 20%). For interventions that reduce the chances of events, the odds ratio will be smaller than the risk ratio, so that again misinterpretation overestimates the effect of the intervention (Higgins 2011).

Assessment of methodological quality of included reviews

Quality of included reviews

The quality of the included reviews was assessed using the AMSTAR tool (Shea 2007). We also noted in each case whether the literature search had been conducted or updated within the past three years.

Quality of evidence from primary studies in included reviews

We used the GRADEPro 'Summary of findings' tables from each review (or if necessary we constructed such a table) to indicate the quality of the evidence for the main comparisons. The following criteria were taken into account: study limitations (that is risk of bias), consistency of effect, imprecision, indirectness, and publication bias.

Data synthesis

A narrative description of the included trials was undertaken. A network meta-analysis was not undertaken.

We summarised the main results of the included reviews by categorising their findings in the following framework, organised by topic.

- Effective interventions: indicating that the review found evidence of effectiveness for an intervention.
- Promising interventions (more evidence needed): indicating that the review found some evidence of effectiveness for an intervention, but more evidence is needed.
- Ineffective interventions: indicating that the review found evidence of lack of effectiveness for an intervention.
- Probably ineffective interventions (more evidence needed): indicating that the review found evidence suggesting lack of effectiveness for an intervention, but more evidence is needed.
- No conclusions possible due to lack of evidence: indicating that the review found insufficient evidence to comment on the effectiveness of an intervention.

The choice of category reflected the conclusions of the authors of the individual reviews, in the judgement of the overview authors. Disagreements were resolved by discussion between overview authors.

This approach to summarising the evidence was based on a Cochrane Overview of pain management in labour, which categorises interventions as "What works," "What may work", and "Insufficient evidence to make a judgement" (Jones 2012).

RESULTS

Description of included reviews

Fifty-nine systematic reviews published in *The Cochrane Library* were included in this overview (127,951 participants). See Table 1 for a summary of the characteristics of the 59 included reviews (review title and author, when the review was last assessed as up

to date, how many randomised controlled trials and participants were included, and the interventions and comparisons, outcomes, and the main limitations of each review).
An additional 11 protocols and five titles were identified, which will be added to the overview when they are published as full reviews and the overview is updated. For details see Appendix 1.

Methodological quality of included reviews

1. Quality of systematic reviews

The quality of the included reviews was rated using the AMSTAR tool (Shea 2007).

- All reviews had prespecified their clinical question and inclusion criteria.
- All reviews conducted study selection and data extraction in duplicate.
- All reviews conducted a comprehensive literature search.
- All reviews included searches of grey literature.
- All reviews listed included and excluded studies.
- All reviews described the characteristics of the included studies.
- All reviews assessed study quality.
- All reviews combined the studies using appropriate methods.
- A total of 52/59 reviews addressed the risk of reporting bias, using a statistical test where appropriate.
- All reviews addressed the potential for conflict of interest.

Half of the 59 reviews had conducted a literature search within the past three years (to July 2015) or have been deemed stable (i.e. search not to be updated unless we become aware of new evidence) See Table 2 and Table 3 for details.

2. Quality of evidence from primary studies in included reviews

The quality of the evidence reported by the primary studies in the included reviews was rated using GRADE methods. The quality of the evidence varied widely (by review and also by outcome) and ranged from very low to high. See Table 1; Table 4; Table 5; Table 6; Table 7; Table 8 for details.

Effect of interventions

For the statistical evidence from the reviews for each outcome, which will indicate the extent of the extent of any benefits or harms, please see the following additional tables.

- Table 4: live birth per woman (data from 42 reviews).
- Table 5: clinical pregnancy per woman (data from 54 reviews).
- Table 6: ovarian hyperstimulation syndrome per woman (data from 21 reviews).
- Table 7: multiple pregnancy per woman (data from 24 reviews).
- Table 8: miscarriage per woman (data from 33 reviews).

Summary of the review findings for each stage of the ART pathway

1. Indication for ART

Three reviews were identified.

- Pandian 2012: 'In vitro fertilisation for unexplained subfertility' (ZP672).
- Yossry 2006: 'In vitro fertilisation versus tubal reanastomosis (sterilisation reversal) for subfertility after tubal sterilisation' (AMY731).
- Siristatidis 2009: 'In vitro maturation in subfertile women with polycystic ovarian syndrome undergoing assisted reproduction' (CS1400).

Pandian 2012 reported that IVF may be more effective than intrauterine insemination (IUI) plus ovarian stimulation. However, due to the lack of randomised controlled trial evidence the effectiveness of IVF compared with expectant management, clomiphene citrate or IUI alone has not been proven. The trials failed to adequately address issues of adverse events and cost effectiveness.
Neither Yossry 2006 nor Siristatidis 2009 identified any randomised controlled trial evidence to support their review questions.

2. Pre-ART and adjuvant strategies

2.1. Strategies for unselected populations

Seven reviews were identified.

- Anderson 2010: 'Preconception lifestyle advice for people with subfertility' (KA992).
- Nastri 2015: 'Endometrial injury in women undergoing assisted reproductive techniques' (WM1504).
- Showell 2014: 'Antioxidants for male subfertility' (MGS1510).
- Showell 2013: 'Antioxidants for female subfertility' (JC1630).
- Duffy 2010: 'Growth hormone for in vitro fertilisation' (KH291).
- Siristatidis 2011: 'Aspirin for in vitro fertilisation' (VJP951).

- Cheong 2013: 'Acupuncture and assisted reproductive technology' (IRS911).
- Gutarra-Vilchez 2014: 'Vasodilators for women undergoing fertility treatment' (RBG1760)

2.1.1 Lifestyle advice

Anderson 2010 identified a single trial that compared smoking cessation advice with standard clinical advice in women attending an infertility clinic. Live birth was not reported as an outcome. There was no evidence identified regarding the effect of pre-conception advice on the chance of a live birth outcome.

2.1.2 Surgical therapy

Endometrial injury

Nastri 2015 reported that endometrial injury performed between day 7 of the previous cycle and day 7 of the embryo transfer (ET) cycle was associated with an improvement in live birth or ongoing pregnancy rates and in clinical pregnancy rates in women with more than two previous embryo transfers. There was no evidence of an effect on miscarriage, multiple pregnancy or bleeding. The evidence suggested that endometrial injury on the day of oocyte retrieval was associated with lower clinical and ongoing pregnancy rates.

2.1.3 Medical therapy

Antioxidants

Showell 2014 included three RCTs with 111 male partners of women undergoing ART, and reported live birth and pregnancy rates in this subgroup. A single study suggested that antioxidant supplementation in subfertile males may improve live birth rates but there was no evidence of a difference in clinical pregnancy rates when two studies were pooled.
Showell 2013 included nine studies of 1326 women undergoing ART and reported live birth and pregnancy rates in this subgroup. Antioxidants for females were not associated with a significantly increased live birth or clinical pregnancy rate.

Growth hormone

Duffy 2010 reported no evidence of an overall benefit in fertility outcomes for growth hormone compared with placebo during an IVF protocol. For a subgroup of women who were considered to be 'poor responders' there was a statistically significant increase in live birth rate and in clinical pregnancy rate, in favour of adjuvant growth hormone compared with placebo. The results were based on a small number of trials with relatively small sample sizes and the review authors recommend that the evidence is interpreted with caution.

Aspirin

Siristatidis 2011 found no evidence of a benefit for aspirin compared with placebo or no treatment for any of the fertility outcomes reported (live birth rate, clinical pregnancy rate, miscarriage rate). The review authors concluded that aspirin was not recommended for women undergoing IVF due to lack of evidence from adequately powered randomised controlled trials.
Vasodilators
Gutarra-Vilchez 2014 found insufficient evidence to show that vasodilators influenced the live birth rate in women undergoing fertility treatment. However, low-quality evidence suggested that vasodilators may increase clinical pregnancy rates in comparison with placebo or no treatment. Data were insufficient to support any conclusions regarding adverse effects.

2.1.4 Alternative therapy

Acupuncture

Cheong 2013 reported that there was no evidence of overall benefit of acupuncture for improving live birth rate regardless of whether acupuncture was performed around the time of oocyte retrieval or around the day of embryo transfer. There was no evidence that acupuncture had any effect on pregnancy or miscarriage rates, or had significant side effects.

2.2 Strategies for selected populations

Four reviews were identified.
- Johnson 2010: 'Surgical treatment for tubal disease in women due to undergo in vitro fertilisation' (NJ472).
- Benschop 2010: 'Interventions for women with endometrioma prior to assisted reproductive technology' (SG1241).
- Tso 2014: 'Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome' (LDT1201).
- McDonnell 2014: 'Ovarian cyst aspiration prior to in vitro fertilization treatment for subfertility' (SH1141)

2.2.1 Tubal pathology

Johnson 2010 found that both laparoscopic salpingectomy and tubal occlusion prior to IVF increased the chances of clinical

pregnancy. The review authors concluded that surgical treatment should be considered for all women with hydrosalpinges prior to IVF treatment. Previous evidence supported only unilateral salpingectomy for a unilateral hydrosalpinx (bilateral salpingectomy for bilateral hydrosalpinges). Johnson 2010 indicated that laparoscopic tubal occlusion is an alternative to laparoscopic salpingectomy in improving pregnancy rates in women with hydrosalpinges undergoing IVF. There is currently insufficient evidence to assess the value of aspiration of hydrosalpinges prior to or during IVF procedures and also the value of tubal restorative surgery as an alternative (or as a preliminary) to IVF.

2.2.2 Endometriosis

Benschop 2010 reported that there was no evidence of a difference in clinical pregnancy rates between gonadotrophin-releasing hormone (GnRH) agonists and antagonists administered for endometrioma prior to ART, and no evidence of a difference in clinical pregnancy outcomes between surgery (cystectomy or aspiration) prior to ART and expectant management, or between pre-ART ablation and cystectomy in women with endometrioma.

2.2.3 Polycystic ovary syndrome (PCOS)

Tso 2014 found no conclusive evidence that metformin treatment before or during ART cycles improved live birth rates in women with PCOS. However, the use of this insulin-sensitising agent increased clinical pregnancy rates and decreased the risk of OHSS.

2.2.4 Ovarian cysts

McDonnell 2014 found insufficient evidence to determine whether drainage of functional ovarian cysts prior to COH influences clinical pregnancy rates. None of the studies reported live birth. The review authors concluded that there is no supportive evidence for cyst drainage, in view of the requirement for anaesthesia, extra cost, psychological stress and risk of surgical complications.

3. Down-regulation with agonists or antagonists

Four reviews were identified for inclusion.

- Sallam 2006: 'Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis' (HNS881).
- Albuquerque 2013: 'Depot versus daily administration of gonadotrophin-releasing hormone agonist protocols for pituitary down regulation in assisted reproduction cycles' (LA541).
- Al-Inany 2011: 'Gonadotrophin-releasing hormone antagonists for assisted reproductive technology' (HA412).
- Maheshwari 2011: 'Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproductive treatment' (SD265).

Sallam 2006 reported that the live birth rate per woman was significantly higher in women receiving the gonadotrophin-releasing hormone (GnRH) agonist than in the control group. The administration of GnRH agonists for a period of three to six months prior to IVF or ICSI in women with endometriosis increased the odds of clinical pregnancy . This evidence is very low quality and the review is being updated.

Albuquerque 2013 found no evidence of a significant difference between depot and daily GnRH agonist use for pituitary down-regulation in IVF cycles using the long protocol, but substantial differences could not be ruled out. Since depot GnRH agonist requires more gonadotrophins and a longer duration of use, it may increase the overall costs of IVF treatment.

Al-Inany 2011 reported no evidence of a difference in live birth rate for GnRH antagonists compared with long GnRH agonist protocols. However, GnRH antagonists were associated with a significant reduction in the cases of OHSS compared with GnRH agonist protocols.

Maheshwari 2011 examined different durations of GnRH agonist protocols for pituitary suppression in ART cycles (long, short, ultra-short). There was no evidence of a difference in the outcome of live birth, however the evidence was based on only three trials out of the 29 identified. Clinical pregnancy rate was significantly increased in the long versus short protocol, but also required significantly more gonadotrophins. There was no evidence of a difference in fertility outcomes between a variety of long protocols. There was no evidence that stopping or reducing GnRHa at the start of the stimulation resulted in a decrease in pregnancy rate.

4. Ovarian stimulation

Nine reviews were identified.

- Gibreel 2012: 'Clomiphene citrate for controlled ovarian stimulation in women undergoing IVF' (AM1335).
- Pouwer 2015: 'Long-acting FSH versus daily FSH for women undergoing assisted reproduction' (AWP1710).
- Mochtar 2007: 'Recombinant Luteinizing Hormone (rLH) for controlled ovarian hyperstimulation in assisted reproductive cycles' (MHM931).
- van Wely 2011: 'Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles' (IOK973).
- Martins 2013: 'FSH replaced by low-dose hCG in the late follicular phase versus continued FSH for assisted reproductive techniques' (WPM1780).
- Smulders 2010: 'Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques' (DHH752).
- Kwan 2014: 'Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI)' (IOK972).
- Pandian 2010: 'Interventions for 'poor responders' to

controlled ovarian hyper stimulation (COH) in in-vitro fertilisation (IVF)' (RSS791).

- Allersma 2013: 'Natural cycle IVF for subfertile couples' (TA1860).

4.1 Medication type

Gibreel 2012 found no evidence to indicate that clomiphene citrate with gonadotropins (with or without GnRH antagonist) differed significantly from gonadotropins in GnRH agonist protocols for women undergoing IVF treatment, in terms of live births or pregnancy rates. Meanwhile, use of clomiphene led to a reduction in the incidence of OHSS. However, as these results were based on data from a small number of underpowered randomised trials with few participants there was insufficient evidence to recommend use of clomiphene citrate in routine IVF practice. Larger trials with adequate power are required.

Pouwer 2015 compared long-acting versus daily FSH and reported no evidence of a difference between the groups in live birth rates or OHSS. In a subgroup analysis of dose of long-acting FSH there was evidence of reduced live birth rate in women who received lower doses (60 to 120 μg) of long-acting FSH compared to daily FSH. There was no evidence of a difference in live birth rates in the medium or high dose subgroups. There was no evidence of effect on any of the other fertility outcomes examined. A medium dose of long-acting FSH appeared to be a safe treatment option and as effective as daily FSH. The review authors indicated that further research is needed to determine whether long-acting FSH is safe and effective for use in hyper-responders or poor responders and in women with all causes of subfertility.

Mochtar 2007 found no evidence of a statistically significant difference in live birth rate between recombinant luteinizing hormone (rLH) plus recombinant follicle stimulating hormone (rFSH) and rFSH alone. There was evidence of statistically more clinical pregnancies in the group receiving rLH plus rFSH compared with rFSH alone.

van Wely 2011 reported no evidence of a statistically significant difference in live birth rate when comparing rFSH to any of the other gonadotrophins irrespective of the down-regulation protocol used. The gonadotrophins compared appeared to be equally effective. The review authors concluded that the clinical choice of gonadotrophin should depend on availability, convenience and costs. Further research on these comparisons is unlikely to identify substantive differences in effectiveness or safety.

Martins 2013 concluded that the effect on live birth of using low-dose hCG to replace FSH during the late follicular phase of controlled ovarian hyperstimulation (COH) in women undergoing ART, compared to the use of conventional COH, was very uncertain. The evidence suggested that this intervention did not reduce the chances of ongoing and clinical pregnancy; and that it was likely to result in an equivalent number of oocytes retrieved, expending less FSH. They suggested that more studies are needed to strengthen the evidence regarding the effect of this intervention on important reproductive outcomes.

Smulders 2010 found no evidence of effect with regard to the number of live births when using a pre-treatment (combined oral contraceptive pill (OCP), progestogen or estrogen). However, there was evidence of improved pregnancy outcomes with progestogen pre-treatment and poorer pregnancy outcomes with a combined OCP pre-treatment. The authors concluded that major changes in ART protocols should not be made at this time, since the number of overall studies was small and reporting of the major outcomes was inadequate.

4.2 Monitoring

Kwan 2014 found no evidence to support cycle monitoring by ultrasound plus serum estradiol compared with ultrasound alone for fertility outcomes in trials of controlled ovarian stimulation monitoring.

4.3 Interventions for poor responders

Pandian 2010 summarised the evidence from 10 randomised controlled trials and suggested that there is insufficient evidence to support the routine use of any one particular intervention in the management of women who are 'poor responders'. Only one of the trials reported on live birth. The evidence was based on comparisons which only contained one randomised trial and the extrapolation of the evidence is limited.

4.4 Natural cycle IVF

Allersma 2013 found no evidence of a significant difference between natural cycle and standard IVF in subfertile couples with regard to live birth rates, OHSS rate, clinical pregnancy rates, ongoing pregnancy rates, number of oocytes retrieved, number of cycles needed to conceive, cumulative pregnancy rates, multiple pregnancies, cycle cancellation rates, gestational abnormalities, cancellations of treatment due to patient motivation or adverse effects.

5. Ovulation triggering

Two reviews were identified that reported on ovulation triggering.

- Youssef 2014 'Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology' (MM1690).

- Youssef 2011: 'Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles' (HA413).

Youssef 2014 reported evidence of a lower live birth rate, reduced ongoing pregnancy rate, and higher miscarriage rate in women who received a GnRH agonist for final oocyte maturation triggering compared to women given hCG, in fresh autologous cycles

(women's own eggs). However, the incidence of OHSS was lower in the GnRH agonist group.
Youssef 2011 reported no evidence of a statistically significant difference between rHCG or rLH and uHCG in achieving final follicular maturation in IVF with regards to pregnancy rates and OHSS incidence. The authors concluded that uHCG remains the best choice for final oocyte maturation triggering in IVF and ICSI treatment cycles due to availability and cost.

6. Oocyte retrieval

Two reviews were identified.

- Kwan 2013: 'Pain relief for women undergoing oocyte retrieval for assisted reproduction' (IOK971).
- Wongtra-ngan 2010: 'Follicular flushing during oocyte retrieval in assisted reproductive techniques' (SW811).

Kwan 2013 compared a variety of head to head and placebo controlled interventions for conscious sedation. Only one study reported live birth, this indicated a higher birth rate following conscious sedation plus electroacupuncture plus paracervical block compared with conscious sedation plus paracervical block. There was no evidence of a difference in clinical pregnancy rate for the same comparison. The review did not support one particular method or technique over another in providing effective conscious sedation and analgesia for pain relief during and after oocyte recovery.
Wongtra-ngan 2010 reported that there was no evidence that follicular aspiration and flushing is associated with improved clinical or ongoing pregnancy rates, nor an increase in oocyte yield. The operative time was significantly longer and more opiate analgesia was required for pain relief during oocyte retrieval. None of the included trials reported on live birth.

7. Sperm retrieval

Two reviews were identified.

- Proctor 2008: 'Techniques for surgical retrieval of sperm prior to intra-cytoplasmic sperm injection (ICSI) for azoospermia' (AMVP611).
- McDowell 2014: 'Advanced sperm selection techniques for assisted reproduction' (SMD1810)

Proctor 2008 reported evidence based on a single trial. The review authors concluded that there was insufficient evidence to recommend any specific sperm retrieval technique for azoospermic men undergoing ICSI. The single trial provided some evidence that microsurgical epididymal sperm aspiration (MESA) achieved a significantly lower pregnancy rate than the micropuncture with perivascular nerve stimulation technique.
McDowell 2014 reported that there was insufficient evidence to determine whether sperm selected by hyaluronic acid binding improves live birth or pregnancy outcomes in ART, or whether there is a difference in efficacy between the hyaluronic acid binding methods SpermSlow and PICSI. No randomised evidence evaluating sperm selection by sperm apoptosis, sperm birefringence or surface charge was found.

8. Laboratory phase

Eight reviews were identified.

- Carney 2012: 'Assisted hatching on assisted conception (in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI))' (MWS391).
- Glujovsky 2014: 'Vitrification versus slow freezing for women undergoing oocyte cryopreservation' (DG1352)
- Van Rumste 2003: 'Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in couples with non-male subfertility' (MVR461).
- Bontekoe 2012: 'Low oxygen concentrations for embryo culture in assisted reproductive technologies' (SB1283).
- Twisk 2006; 'Preimplanation genetic screening for abnormal numbers of chromosomes (aneuploidies) in in vitro fertilisation or intracytoplasmic sperm injection' (SMA991).
- Huang 2013: 'Brief co-incubation of sperm and oocytes for in vitro fertilization techniques' (ZH1093).
- Teixeira 2013: 'Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction' (WPM1800).
- Armstrong 2015: Time-lapse systems for embryo incubation and assessment in assisted reproduction (SCA1950)

Carney 2012 found no evidence of a significant difference in live birth rate following assisted hatching compared with no assisted hatching. While assisted hatching (AH) did appear to offer a significantly increased chance of achieving a clinical pregnancy, the finding only just reached statistical significance. The included trials provided insufficient data to investigate the impact of AH on several important outcomes and most trials failed to report live birth rates. Miscarriage rates per woman were similar in both groups but multiple pregnancy rates were significantly increased in the AH groups.
Glujovsky 2014 found that vitrification probably increased clinical pregnancy rates compared to slow freezing. However the total number of women and of pregnancies was low. No data were available on live birth or adverse events.
Van Rumste 2003 identified that the outcomes of live birth, miscarriage rates or other adverse events were not reported in the single trial in their review. There was no evidence of a difference in clinical pregnancy rate between ICSI and IVF.
Bontekoe 2012 reported that there was evidence of an increase in live birth rate associated with embryo culture using low oxygen concentrations (~5%) compared with atmospheric oxygen concentrations (~20%). This equated to an increase from a 30% success rate to 32% to 42% success using low oxygen concentrations.

Similar results were reported for ongoing and clinical pregnancy rates. There was no evidence of an increase in adverse events (multiple pregnancy, miscarriage) associated with embryo culture using low oxygen concentrations.

Twisk 2006 reported that live birth rate was significantly lower following IVF or ICSI with preimplantation genetic screening using fluorescent in situ hybridization compared with no preimplantation genetic screening, both in women with advanced age and in those with repeated IVF failure. For women with good prognosis there was no evidence of a significant difference between the intervention and control groups. Until further research is available for newer techniques in preimplantation genetic screening the review authors do not recommend the routine offer of screening to couples undergoing IVF or ICSI.

Huang 2013 reported that brief co-incubation of sperm and oocytes may improve the ongoing pregnancy and clinical pregnancy rates for infertile women undergoing IVF cycles, though more randomised controlled trials are required.

Teixeira 2013 reported that there was no evidence of a difference between regular (ICSI) and ultra-high magnification (IMSI) sperm selection with respect to live birth or miscarriage rates, and evidence suggesting that IMSI improved clinical pregnancy was of very low quality. There was no indication that IMSI increased congenital abnormalities.

Armstrong 2015 reported that there is insufficient evidence of any difference in live birth, miscarriage, stillbirth or clinical pregnancy rates to choose between time lapse systems and conventional incubation

9. Embryo transfer

Eight reviews were identified that looked at embryo transfer.

- Glujovsky 2012: 'Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology' (DB551).
- Gunby 2004: 'Day three versus day two embryo transfer following in vitro fertilisation or intracytoplasmic sperm injection' (CO226).
- Pandian 2013: 'Number of embryos for transfer following in vitro fertilisation or intra cytoplasmic sperm injection' (ZP661).
- Bontekoe 2014: 'Adherence compounds in embryo transfer media for assisted reproductive technologies' (DB552).
- Derks 2009: 'Techniques for preparation prior to embryo transfer' (SV602).
- Kroon 2012: 'Antibiotics prior to embryo transfer in ART' (EN1382).
- Brown 2010: 'Ultrasound versus 'clinical touch' for catheter guidance during embryo transfer in women' (JB604).
- Abou-Setta 2014: 'Post-embryo transfer interventions for assisted reproduction technology cycles' (AAS605).

9.1. Developmental stage

Glujovsky 2012 reported evidence of a significant increase in live birth rate favouring blastocyst stage compared with cleavage stage transfer. However, although live birth rates were increased with blastocyst transfer it was also associated with a reduction in the number of embryos transferred and the number for embryo freezing. Cumulative clinical pregnancy rates were increased with cleavage stage transfer.

Gunby 2004 reported that although an increase in clinical pregnancy rate with day three embryo transfer was demonstrated, there was not sufficient good quality evidence to suggest an improvement in live birth when embryo transfer was delayed from day two to day three.

9.2. Number of embryos

Pandian 2013 found that in a single assisted reproduction cycle the live birth rate was lower following single embryo transfer compared with double embryo transfer. Elective single embryo transfer resulted in fewer multiple pregnancies than double embryo transfer. Although the pregnancy and live birth rate per fresh IVF cycle was lower, the cumulative live birth rate associated with single embryo transfer followed by a single frozen and thawed embryo transfer was comparable with that after one cycle of double embryo transfer.

9.3. Transfer techniques and procedures

Bontekoe 2014 reported on the use of adherence compounds in embryo transfer media.

There was evidence of improved live birth and pregnancy rates with the use of functional concentrations of hyaluronic acid, but the multiple pregnancy rate was also increased. The authors suggested that the increased multiple pregnancy rate might be the result of use of an adherence compound together with a policy of transferring more than one embryo

Derks 2009 reported on a variety of techniques that could be used at the time of embryo transfer. There was a lack of evidence on live birth outcomes. There was no evidence of a benefit in fertility outcomes from having a full bladder, removal of cervical mucus, or flushing of the endometrial or endocervical cavity at the time of embryo transfer. No trials were identified for dummy transfer, change of position during transfer, use of a tenaculum, or embryo afterloading.

Kroon 2012 noted that although upper genital tract microbial contamination may have been reduced by the use of antibiotics, the use of amoxicillin plus clavulanic acid did not increase the clinical pregnancy rate compared with no antibiotics. Live births were not reported.

Brown 2010 reported that there was no overall effect on live birth rate with ultrasound guided embryo transfer compared with clinical touch. However, this was based on only three trials that reported this outcome of the 20 included trials in the review. There

was evidence of a significant increase in clinical pregnancy using ultrasound guided embryo transfer compared with clinical touch. There were no significant differences in reporting of adverse events, including multiple pregnancies and miscarriage.
Abou-Setta 2014 concluded that there was insufficient evidence to support a certain amount of time for women to remain recumbent following ET, or to support the use of fibrin sealants. There was limited evidence to support the use of mechanical closure of the cervical canal following embryo transfer.

10. Luteal phase support

Three reviews were identified.

- van der Linden 2015: 'Luteal phase support in ART cycles' (MV263).
- Boomsma 2012: 'Peri-implantation glucocorticoid administration for assisted reproductive technology cycles' (CMB126).
- Akhtar 2013: 'Heparin for assisted reproduction' (MA1441).

van der Linden 2015 reported that progesterone appeared to be the best method of providing luteal phase support, as it was associated with higher rates of live birth or ongoing pregnancy than placebo, and lower rates of OHSS than hCG. Moreover, addition of one or more doses of GnRH agonists to progesterone was associated with higher live birth and ongoing pregnancy rates than progesterone alone. Overall, addition of other substances such as oestrogen or hCG did not seem to improve outcomes, and hCG was associated with higher risk of OHSS. The route of progesterone administration did not seem to matter.
Boomsma 2012 reported no overall differences between peri-implantation glucocorticoids and no glucocorticoids on fertility outcomes. However, a subgroup analysis indicated that for couples undergoing IVF there was evidence of a significantly higher clinical pregnancy rate for peri-implantation glucocorticoids compared with no glucocorticoids. The difference was not observed in couples undergoing ICSI. The review authors do however urge caution when extrapolating conclusions from this subgroup analysis.
Akhtar 2013 reported that peri-implantation low molecular weight heparin in ART cycles may improve the live birth rate in women undergoing assisted reproduction. However, the evidence was very poor quality. There were side effects reported with the use of heparin and no reliable data on long-term effects. The authors concluded that their results do not justify use of heparin outside of well-conducted research trials.

11. Prevention of ovarian hyperstimulation syndrome (OHSS)

Four reviews were identified that examined prevention of OHSS. [See also Al-Inany 2011 'Gonadotrophin-releasing hormone (GnRH) antagonists for ART' in Section 3; and Youssef 2014 'GnRHa versus hCG for oocyte triggering in antagonist ART cycles' in Section 5]

- Tang 2012: 'Cabergoline for preventing ovarian hyperstimulation syndrome' (TH1338).
- D'Angelo 2007: 'Embryo freezing for preventing ovarian hyperstimulation syndrome' (ADA561).
- D'Angelo 2011: 'Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome' (ADA563).
- Youssef 2011a: 'Intra-venous fluids for the prevention of severe ovarian hyperstimulation syndrome' (PMA481).

Tang 2012 reported evidence that there was a statistically significant reduction in the risk of OHSS in high risk women with the use of cabergoline compared with placebo. This was particularly so for women with moderate OHSS. There was no evidence that the use of cabergoline affected the pregnancy outcome (clinical pregnancy rate, miscarriage rate), nor was there an increased risk of adverse events. Caution is required as the evidence was only based on two trials (n = 230 women). Live birth rate or multiple pregnancy rates were not reported in either trial.
D'Angelo 2007 identified only two randomised trials. The review authors concluded that there was insufficient evidence to support routine cryopreservation and insufficient evidence for the relative merits of intravenous albumin versus cryopreservation in the reduction of OHSS. There was also a lack of reported fertility outcomes such as live birth.
D'Angelo 2011 found very low quality evidence from a single small trial suggesting a benefit from withholding gonadotrophins (coasting) after ovulation in IVF. Moderate to severe OHSS was less common in the coasting group than the no coasting group. There was no difference between the groups for other outcomes, and nor was there any difference between the groups when coasting was compared with other interventions (early unilateral follicular aspiration, GnRH agonist). The evidence was limited by the small number of included trials.
Youssef 2011a reported no evidence of a difference in the incidence of severe OHSS between women receiving intravenous human albumin and a group receiving placebo or no treatment. There was evidence of a statistically significant decrease in severe OHSS incidence with administration of hydroxyethyl starch. There was no evidence of statistical difference in the pregnancy rate between both groups of treatment. None of the trials reported on live birth

12. Frozen embryo replacement cycles

Two reviews were identified that examined frozen cycles.

- Ghobara 2008: 'Cycle regimens for frozen-thawed embryo transfer (FET)' (TG691).
- Glujovsky 2010: 'Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes' (DG1351).

Ghobara 2008 reported that there was insufficient evidence to support the use of one menstrual cycle regimen over another (nat-

ural cycle, artificial cycle, and ovulation induction cycle) in frozen-thawed embryo transfer (FET). The review authors suggested that women with regular spontaneous cycles may be offered any of the cycle regimens to prepare the womb lining for FET. If artificial cycles are used there is some evidence to support the use of an additional drug that suppresses hormone production by the ovaries (GnRH agonist). Again, there was a lack of reporting of live births as a fertility outcome.

Glujovsky 2010 reported insufficient evidence to be able to identify one particular intervention for endometrial preparation that clearly improves the treatment outcome for women receiving embryo transfers with either frozen embryos or embryos derived from donated oocytes. However, there was evidence of a lower pregnancy rate and a higher cycle cancellation rate when the progesterone supplementation was commenced prior to oocyte retrieval in oocyte donation cycles. Adequately powered studies are needed to evaluate each treatment more accurately.

DISCUSSION

Summary of main results

We have summarised the main results of the included reviews by categorising their findings in the following framework.

- Effective interventions: indicating that the review found evidence of effectiveness (or improved safety) for an intervention.
- Promising interventions (more evidence needed): indicating that the review found some evidence of effectiveness (or improved safety) for an intervention, but more evidence is needed.
- Ineffective interventions: indicating that the review found evidence of lack of effectiveness (or reduced safety) for an intervention.
- Possibly ineffective interventions (more evidence needed): indicating that the review found evidence suggesting lack of effectiveness (or reduced safety) for an intervention, but more evidence is needed.
- No conclusions possible due to lack of evidence: indicating that the review found insufficient evidence to comment on the effectiveness or safety of an intervention.

1. Indication for ART

Promising interventions (more evidence needed)

- In vitro fertilisation for unexplained subfertility: in vitro fertilisation (IVF) may be more effective than intra-uterine insemination (IUI) plus ovarian stimulation (low quality evidence). (Pandian 2012)

No conclusions possible due to lack of evidence

- IVF versus tubal reanastomosis (sterilisation reversal) for subfertility after tubal sterilisation: no randomised controlled trials (RCTs) found. (Yossry 2006)
- In vitro maturation in subfertile women with polycystic ovarian syndrome (PCOS) undergoing assisted reproduction: no RCTs found. (Siristatidis 2011)

2. Pre-ART and adjuvant strategies

Effective interventions

- Endometrial injury in women undergoing assisted reproductive techniques (ART): endometrial injury performed in the month prior to ovulation induction for ART appeared to increase both the live birth or ongoing pregnancy rate and the clinical pregnancy rate (moderate quality evidence). There was no evidence of a difference between the groups in miscarriage, multiple pregnancy or bleeding rates. Evidence suggested that endometrial injury on the day of oocyte retrieval was associated with a lower live birth or ongoing pregnancy rate (low quality evidence). (Nastri 2015)
- Growth hormone for IVF: the use of growth hormone in poor responders was associated with a significant improvement in live birth rates (moderate quality evidence). (Duffy 2010)
- Metformin treatment before and during IVF or ICSI in women with PCOS: there was no conclusive evidence that metformin treatment before or during ART cycles improved live birth rates (low quality evidence). However, the use of this insulin-sensitising agent increased clinical pregnancy rates and decreased the risk of OHSS (moderate quality evidence). (Tso 2014)
- Surgical treatment for tubal disease in women due to undergo IVF: laparoscopic tubal occlusion is an alternative to laparoscopic salpingectomy in improving IVF pregnancy rates in women with hydrosalpinges (moderate quality evidence). (Johnson 2010)

Promising interventions (more evidence needed)

- Antioxidants for male subfertility: oral antioxidants given to the men in couples with male factor or unexplained subfertility may improve live birth rates, but more evidence is needed (low quality evidence). (Showell 2014)
- Vasodilators for women undergoing fertility treatment: Gutarra-Vilchez 2014 found that vasodilators may increase clinical pregnancy rates in women undergoing ART. No clear

effect was found on live birth rates, but few studies reported this outcome (low quality evidence).

Possibly ineffective interventions (more evidence needed)

- Acupuncture and ART: there was no evidence that acupuncture improves live birth or pregnancy rates in assisted conception (low quality evidence). (Cheong 2013)
- Interventions for women with endometrioma prior to ART: there was no evidence of an effect on reproductive outcomes in any of the four included trials. Therapies considered included surgery, medicines and expectant management (low quality evidence). (Benschop 2010)
- Antioxidants for female subfertility: antioxidants were not associated with an increased live birth rate or clinical pregnancy rate, though more evidence is needed (low quality evidence). (Showell 2013)
- Ovarian cyst aspiration prior to in vitro fertilization treatment for subfertility: there was no evidence that cyst aspiration was associated with increased clinical pregnancy rates (low quality evidence). None of the studies reported live birth. (McDonnell 2014)

No conclusions possible due to lack of evidence

- Preconception lifestyle advice for people with subfertility: there was insufficient evidence to reach a conclusion, with only one RCT. (Anderson 2010)
- Aspirin for IVF: there was insufficient evidence from adequately powered RCTs to reach a conclusion. (Siristatidis 2011)

3. Down-regulation with agonists or antagonists

Effective interventions

- Gonadotropin releasing hormone agonist (GnRHa) protocols for pituitary suppression in assisted reproductive technology cycles: the pregnancy rate was higher when GnRHa was used in a long protocol as compared to a short or ultra-short protocol (low quality evidence). (Maheshwari 2011)
- Gonadotrophin-releasing hormone (GnRH) antagonists for ART: the use of antagonist compared with long GnRHa protocols was associated with a large reduction in OHSS and there was no evidence of a difference in live birth rates (moderate quality evidence). (Al-Inany 2011)
- Long-term pituitary down-regulation before IVF for women with endometriosis: the administration of GnRHa for a period of three to six months prior to IVF or ICSI in women with endometriosis increased the odds of clinical pregnancy (very low quality evidence). (Sallam 2006)

Possibly ineffective interventions (more evidence needed)

- Depot versus daily administration of GnRHa protocols for pituitary desensitisation in assisted reproduction cycles: there was no evidence of a significant difference in live birth or pregnancy outcomes between depot and daily GnRHa use for pituitary down-regulation in IVF cycles using the long protocol, but substantial differences could not be ruled out (moderate quality evidence). (Albuquerque 2013)

4. Ovarian stimulation

Effective interventions

- Recombinant versus urinary gonadotrophin for ovarian stimulation in ART cycles: it appeared that all available gonadotrophins were equally effective and safe. The choice of one or the other product will depend upon the availability of the product, the convenience of its use, and the associated costs. Any specific differences are likely to be too small to justify further research (high quality evidence). (van Wely 2011)
- Long-acting FSH versus daily FSH for women undergoing assisted reproduction: the use of a medium dose (150 to 180 μg) of long-acting FSH appeared to be a safe treatment option and as effective as daily FSH in women with unexplained subfertility. There was evidence of reduced live birth rate in women receiving a low dose (60 to 120 μg) of long-acting FSH compared to daily FSH (moderate quality evidence). (Pouwer 2015)

Promising interventions (more evidence needed)

- Recombinant luteinizing hormone (rLH) for controlled ovarian hyperstimulation in assisted reproductive cycles: there was no evidence that the co-administration of rLH to rFSH in GnRHa down-regulated women resulted in more live births than controlled ovarian hyperstimulation (COH) with rFSH alone. Nevertheless, all pooled pregnancy estimates, although not significantly different, pointed towards a beneficial effect of co-treatment with rLH, in particular with respect to pregnancy loss (low quality evidence). (Mochtar 2007)
- Clomiphene citrate for controlled ovarian stimulation in women undergoing IVF: this review suggested that regimens with clomiphene could be used in controlled ovarian stimulation for IVF treatment without a reduction in pregnancy rates. However, further evidence is required before they can be recommended with confidence as alternatives to gonadotropins alone in GnRH long or short protocols (low quality evidence). (Gibreel 2012)
- FSH replaced by low-dose hCG in the late follicular phase versus FSH alone for ARTs: the authors were very uncertain of the effect on live birth, OHSS and miscarriage, but the evidence suggested that this intervention did not reduce the chance of

ongoing and clinical pregnancy and that it was likely to result in an equivalent number of oocytes retrieved, while expending less FSH (very low quality evidence). (Martins 2013)

- Oral contraceptive pill (OCP), progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing ARTs: there was evidence of improved pregnancy outcomes with progestogen pre-treatment and poorer pregnancy outcomes with a combined OCP pre-treatment. (Smulders 2010)
- Natural cycle IVF for subfertile couples: there was no evidence of a significant difference between natural cycle and standard IVF for outcomes including live birth, OHSS, clinical pregnancy and multiple pregnancy (very low quality evidence). (Allersma 2013)

Possibly ineffective interventions (more evidence needed)

- Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI): there was no evidence from RCTs to support cycle monitoring by ultrasound plus serum estradiol as more efficacious than cycle monitoring by ultrasound only on the outcomes of live birth and pregnancy. A large well-designed RCT is needed (low quality evidence). (Kwan 2014)

No conclusions possible due to lack of evidence

- Interventions for 'poor responders' to COH in IVF: there was insufficient evidence to support the routine use of any particular intervention for pituitary down-regulation, ovarian stimulation or adjuvant therapy in the management of poor responders to COH in IVF. (Pandian 2010)

5. Ovulation triggering

Effective interventions

- Recombinant versus urinary hCG for final oocyte maturation triggering in IVF and ICSI cycles: the authors concluded that urinary hCG remains the best choice for final oocyte maturation triggering in IVF and ICSI treatment cycles due to availability and cost (moderate quality evidence). (Youssef 2011)

- GnRHa versus hCG for oocyte triggering in antagonist ART cycles: there was evidence of a lower live birth rate, reduced ongoing pregnancy rate and higher miscarriage rate in women who received a GnRHa. However, there was a reduction in OHSS rates with GnRHa triggering and therefore there is a trade off between benefits and harms (moderate quality evidence). (Youssef 2014)

6. Oocyte retrieval

Effective interventions

- Pain relief for women undergoing oocyte retrieval for assisted reproduction: the various approaches and techniques reviewed (five different categories of conscious sedation and analgesia) appeared to be acceptable and were associated with a high degree of satisfaction in women. The authors proposed that the optimal method may be individualised depending on the preferences of the women and their clinicians, and resource availability (very low quality evidence for most comparisons). (Kwan 2013)

Ineffective interventions

- Follicular flushing during oocyte retrieval in ARTs: there was no evidence that follicular aspiration and flushing was associated with improved clinical or ongoing pregnancy rates, nor an increase in oocyte yield. The operative time was significantly longer and more opiate analgesia was required for pain relief during oocyte retrieval (moderate quality evidence). (Wongtra-ngan 2010)

7. Sperm retrieval

No conclusions possible due to lack of evidence

- Techniques for surgical retrieval of sperm prior to ICSI for azoospermia: there was insufficient evidence to recommend any specific sperm retrieval technique for azoospermic men undergoing ICSI (only one RCT) (low quality evidence). (Proctor 2008)
- Advanced sperm selection techniques for assisted reproduction: there was insufficient evidence to determine whether sperm selected by hyaluronic acid binding improves live birth or pregnancy outcomes in ART, or whether there is a difference in efficacy between the hyaluronic acid binding methods SpermSlow and PICSI. No randomised evidence evaluating sperm selection by sperm apoptosis, sperm birefringence or surface charge was found (low quality evidence). (McDowell 2014)

8. Laboratory phase

Effective interventions

- Low oxygen concentrations for embryo culture in ART: there was evidence of an increase in live birth rates associated with embryo culture using low oxygen concentrations (moderate quality evidence). (Bontekoe 2012)

Promising interventions (more evidence needed)

- Assisted hatching on assisted conception (IVF and ICSI): whilst assisted hatching (AH) appeared to offer an increased chance of achieving a clinical pregnancy, the extent to which it might do so only just reached statistical significance. The 'take home' baby rate was still not proved to be increased by AH, and multiple pregnancy rates were significantly increased in the AH groups (moderate quality evidence). (Carney 2012)
- Brief co-incubation of sperm and oocytes for IVF techniques: brief co-incubation of sperm and oocytes may improve the ongoing pregnancy and clinical pregnancy rates for women undergoing IVF cycles, compared to the standard overnight insemination protocol. More RCTs are required (low quality evidence). (Huang 2013)
- Vitrification probably increases clinical pregnancy rates compared to slow freezing. However the total number of women and of pregnancies was low and no data were available on live birth or adverse events (low quality evidence). (Glujovsky 2014)

Possibly ineffective interventions (more evidence needed)

- Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction: there was no evidence of a difference between ICSI and IMSI with respect to live birth or miscarriage rates, and evidence suggesting that IMSI improved clinical pregnancy was of very low quality (very low quality evidence). (Teixeira 2013)

Ineffective interventions

- Preimplantation genetic screening for abnormal number of chromosomes (aneuploidies) in IVF or ICSI: preimplantation genetic screening using fluorescent in situ hybridization significantly decreased live birth rates in women of advanced maternal age and those with repeated IVF failure. Trials in which PGS was offered to women with a good prognosis suggested similar outcomes (moderate quality evidence). (Twisk 2006)

No conclusions possible due to lack of evidence

- ICSI versus conventional techniques for oocyte insemination during IVF in patients with non-male subfertility: there was insufficient evidence to reach a conclusion, with only one RCT. (Van Rumste 2003)
- Time-lapse systems versus conventional embryo incubation and assessment: there was insufficient evidence of differences in live birth, miscarriage, stillbirth or clinical pregnancy to reach a conclusion. (Armstrong 2015)

9. Embryo transfer

Effective interventions

- Ultrasound versus 'clinical touch' for catheter guidance during embryo transfer in women: there was evidence of a significant increase in clinical pregnancy using ultrasound guided embryo transfer compared with clinical touch (low quality evidence). (Brown 2010)
- Adherence compounds in embryo transfer media for ART: there was evidence of an improved live birth and clinical pregnancy rate with the use of hyaluronic acid. Multiple pregnancy rates were also increased in the intervention group, which the authors suggested might relate to use of an adherence compound together with a policy of transferring more than one embryo (moderate quality evidence). (Bontekoe 2014)
- Number of embryos for transfer following IVF or ICSI: although in a single ART cycle the live birth rate was lower following single embryo transfer compared with double embryo transfer, elective single embryo transfer resulted in fewer multiple pregnancies than double embryo transfer (high quality evidence). The cumulative live birth rate associated with single embryo transfer followed by a single frozen and thawed embryo transfer was comparable with that after one cycle of double embryo transfer (low quality evidence). (Pandian 2013)

Promising interventions (more evidence needed)

- Day three versus day two embryo transfer following IVF or ICSI: there were no differences in rates of live birth or clinical pregnancy between day three and day two embryo transfer. Although an increase in clinical pregnancy rate with day three embryo transfer was demonstrated, there was insufficient good quality evidence to suggest an improvement in live birth when embryo transfer was delayed from day two to day three (low quality evidence). (Gunby 2004)

Possibly ineffective interventions (more evidence needed)

- Techniques for preparation prior to embryo transfer: there was no evidence of benefit with the following interventions at the time of embryo transfer: full bladder, removal of cervical mucus, flushing the endocervical canal or the endometrial cavity. More and larger studies are needed on embryo transfer preparation techniques. (Derks 2009)
- Antibiotics prior to embryo transfer in ART: the administration of amoxicillin and clavulanic acid prior to embryo transfer reduced upper genital tract microbial contamination but did not alter clinical pregnancy rates (moderate quality evidence). There were no data from RCTs to support or refute other antibiotic regimens in this setting. Future research is warranted. (Kroon 2012)

No conclusions possible due to lack of evidence

- Cleavage stage versus blastocyst stage embryo transfer in ART: the margin of benefit between cleavage stage and blastocyst

transfer is unclear. Although live birth rates are increased with blastocyst transfer it is also associated with a reduction in the number of embryos transferred and for embryo freezing. Cumulative clinical pregnancy rates are increased with cleavage stage transfer (moderate quality evidence). Future RCTs should report miscarriage, live birth and cumulative live birth rates to facilitate well-informed decisions on the best treatment option available. (Glujovsky 2012)

- Post-embryo transfer interventions for IVF and ICSI patients: there is insufficient evidence to support a certain amount of time for women to remain recumbent following embryo transfer, or to support the use of fibrin sealants.There is limited evidence to support the use of mechanical closure of the cervical canal following embryo transfer. Further well-designed studies are required. (Abou-Setta 2014)

10. Luteal phase support

Effective interventions

- Luteal phase support in ART cycles: this review concluded that progesterone appears to be the best method of providing luteal phase support, as it is associated with higher rates of live birth or ongoing pregnancy than placebo, and lower rates of OHSS than hCG. Addition of one or more doses of GnRH agonists to progesterone was associated with higher live birth and ongoing pregnancy rates than progesterone alone. Overall, addition of other substances such as oestrogen or hCG did not seem to improve outcomes, and hCG was associated with higher risk of OHSS. The route of progesterone administration did not seem to matter (quality of evidence low for most comparisons). (van der Linden 2015)

Promising interventions (more evidence needed)

- Heparin for assisted reproduction: Akhtar 2013 reported that peri-implantation low molecular weight heparin in ART cycles may improve the live birth rate in women undergoing assisted reproduction. However the results did not justify the use of heparin outside well-conducted research trials, as evidence quality was poor (very low quality evidence).

Possibly ineffective interventions (more evidence needed)

- Peri-implantation glucocorticoid administration for ART cycles: overall, there was no clear evidence that administration of peri-implantation glucocorticoids in ART cycles significantly improved clinical outcomes (low quality evidence). (Boomsma 2012)

11. Prevention of ovarian hyperstimulation syndrome (OHSS)

Effective interventions

- Intravenous fluids for the prevention of severe OHSS: hydroxyethyl starch decreased the incidence of severe OHSS (very low quality evidence) (Youssef 2011a)
- Cabergoline for preventing OHSS: cabergoline appeared to reduce the risk of OHSS in high risk women, especially for moderate OHSS. The use of cabergoline did not appear to affect clinical pregnancy rates or miscarriage rates, nor was there an increased risk of other adverse events (low quality evidence). (Tang 2012)
- Gonadotrophin-releasing hormone (GnRH) antagonists for ART: *as noted in Section 3 above*, the use of antagonist compared with long GnRHa protocols was associated with a large reduction in OHSS and there was no evidence of a difference in live birth rates (moderate quality evidence). (Al-Inany 2011)
- GnRHa versus hCG for oocyte triggering in antagonist ART cycles: *as noted in Section 3 above*, there was evidence of a lower live birth rate, reduced ongoing pregnancy rate and higher miscarriage rate in women who received a GnRHa. However, there was a reduction in OHSS rates with GnRHa triggering and therefore there is a trade off between benefits and harms (moderate quality evidence). (Youssef 2014)

Possibly ineffective interventions (more evidence needed)

- Embryo freezing for preventing OHSS: there was insufficient evidence to support routine cryopreservation and insufficient evidence for the relative merits of intravenous albumin versus cryopreservation (low quality evidence). (D'Angelo 2007)
- Coasting (withholding gonadotrophins) for preventing OHSS: there was insufficient evidence to confirm whether there is any benefit from using coasting to prevent OHSS compared with no coasting or other interventions (very low quality evidence). (D'Angelo 2011)

12. Frozen embryo replacement cycles

No conclusions possible due to lack of evidence

- Cycle regimens for frozen-thawed embryo transfer: at the present time there is insufficient evidence to support the use of one intervention in preference to another. (Ghobara 2008)
- Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes: there is insufficient evidence to recommend any one particular protocol for endometrial preparation over another

with regard to pregnancy rates after embryo transfers. *(*Glujovsky 2010)

Overall completeness and applicability of evidence

This overview summarises published Cochrane systematic reviews of all randomised controlled trials on the different stages of an ART cycle and the different populations undergoing ART. We consider it to be complete, although we also acknowledge that not all systematic reviews in this overview are up to date. We consider that the information in this study can be applied to couples undergoing an ART cycle in most parts of the world, including using low cost strategies such as modified natural cycle IVF.

Quality of the evidence

Each of the reviews has been assessed using the AMSTAR tool for assessing systematic reviews. The results are presented in the table 'AMSTAR assessment' (Table 2). Overall, the quality of the reviews was high with almost all criteria being met. The exception was the assessment of publication bias, which was considered inadequate in seven of the 59 reviews. Half of the reviews have searches more than three years old.

Potential biases in the overview process

No specific biases were identified in the overview process. However it is acknowledged that decisions about effectiveness, possible ineffectiveness and insufficient evidence could be considered subjective. Ideally, these decisions should be made by a larger group of clinical and methodological experts.

Agreements and disagreements with other studies or reviews

There are no reviews comparable with this overview.
Several of the reviews in this overview are currently being used to help develop World Health Organisation fertility guidelines. The National Institute for Health and Care Excellence (NICE) clinical guidelines on the assessment and treatment of people with fertility problems (NICE 2013) also used many of our reviews.

AUTHORS' CONCLUSIONS

Implications for practice

This overview provides the most up to date evidence on ART cycles from systematic reviews of randomised controlled trials. Fertility treatments are costly and the stakes are high. Best practice requires using the best available evidence to optimise outcomes. The evidence from this overview could be used to develop clinical practice guidelines and protocols for use in daily clinical practice, in order to improve live birth rates and reduce rates of multiple pregnancy, cycle cancellation and ovarian hyperstimulation syndrome.

Implications for research

This overview highlights areas where there is insufficient evidence either because of a lack of primary research or a lack of reporting of important outcomes, and it can be used to generate research questions. The most important outcomes are live birth, cumulative live birth, multiple pregnancy, cycle cancellation and ovarian hyperstimulation syndrome.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Review characteristics

Review ID	Date assessed as up to date	Number of included trials	Population	Intervention	Comparison intervention/control	Outcomes	Review limitations
1. Indication for ART							
ZP672 Pandian 2012 In vitro fertilisation for unexplained subfertility	1/07/2011	6 RCTs	733 couples with unexplained subfertility	In vitro fertilisation	Expectant management Intrauterine insemination Intrauterine insemination + ovarian stimulation Clomiphene citrate	Live birth rate Clinical pregnancy rate Multiple pregnancy rate OHSS	Some evidence was based on a single trial. There were limitations in imprecision and heterogeneity for some outcomes
AMY731 Yossry 2006 In vitro fertilisation versus tubal reanastomosis (sterilisation reversal) for subfertility after tubal sterilisation	15/05/2009	No RCTs	N/A	In vitro fertilisation	Tubal re-anastomosis	Live birth rate Clinical pregnancy rate Multiple pregnancy rate OHSS	Empty review with no trials. No longer being updated
CS1400 Siristatidis 2009 In vitro maturation in sub-	17/02/2011	No RCTs	N/A	In vitro maturation	In vitro fertilisation Intra-cytoplasmic sperm	Live birth Cycle cancellation Oocyte fertilisation	Empty review with no trials. No longer

Table 1. Review characteristics (*Continued*)

fertile women with polycystic ovarian syndrome undergoing assisted reproduction					injection	rate OHSS Miscarriage rate Preterm birth Congenital abnormalities	being updated
2. Pre-ART and adjuvant strategies							
2.1 For unselected populations							
KA992 Anderson 2010 Preconception lifestyle advice for people with subfertility	18/11/2009	1 RCT	94 women who perceived that they may be infertile	Smoking cessation advice	Standard clinical advice	Smoking behaviour change Live birth	The trial did not report on fertility outcomes. Evidence was based on a single trial
WM1504 Nastri 2015 Endometrial injury in women undergoing assisted reproductive technology	19/1/2015	14 RCTs	1063 women undergoing ART	Endometrial injury	No endometrial injury Mock procedure	Live birth rate Clinical pregnancy rate Multiple pregnancy rate Miscarriage rate Ongoing pregnancy rate Pain/bleeding Implantation rate	Serious imprecision for most outcomes Adverse events such as miscarriage rate and multiple pregnancy rate were poorly reported
MGS1510 Showell 2014 Antioxidants for male subfertility	31/1/14	3 RCTs*	111 male partners of couples undergoing ART	Antioxidant	Placebo/no treatment Antioxidant	Live birth Pregnancy Adverse events DNA fragmentation Sperm parameters Miscarriage	* A further 45 RCTs in this review included subfertile couples not undergoing ART Lack of a clear description of trial methods and inconsistent, inadequate reporting of live

Table 1. Review characteristics (*Continued*)

							births and clinical pregnancies
JC1630 Showell 2013 Antioxidants for female subfertility	15/4/13	9 RCTs	1326 women undergoing ART	Antioxidant	Placebo/no treatment Antioxidant	Live birth Pregnancy Multiple pregnancy Miscarriage	Not all trials described the sequence generation or allocation concealment methods, and most trials randomly assigned only small numbers of women
IRS911 Cheong 2013 Acupuncture and assisted reproductive technology	22/7/13	20 RCTs	4544 women undergoing ART	Acupuncture Repeated acupuncture	No acupuncture Sham acupuncture Acupuncture plus ART	Live birth Ongoing pregnancy Clinical pregnancy Multiple pregnancy OHSS Miscarriage Adverse effects	Study quality generally low, with over 75% failing to describe an adequate method of allocation concealment
KH291 Duffy 2010 Growth hormone for in vitro fertilisation	01/07/2009	10 RCTs	440 couples undergoing IVF	Growth hormone	Placebo	Live birth rate Pregnancy rate Number of women with at least one oocyte retrieved Embryos transferred Ampoules of gonadotrophin Adverse events	Lack of methodological clarity in reporting of randomisation and allocation concealment
RBG1760 Gutarra-Vilchez 2014 Vasodilators for women undergoing fertility treatment	25/2/2014	10 RCTs	797 women undergoing ART	Vasodilators	Other interventions, placebo or no treatment	Live birth Clinical pregnancy Multiple pregnancy Miscarriage	The main limitations were imprecision and lack of clarity about study methods. Risk

Table 1. Review characteristics (*Continued*)

							of publication bias could not be assessed because of the low number of identified studies
VJP 951 Siristatidis 2011 Aspirin for in vitro fertilisation	15/06/2011	13 RCTs	2653 women undergoing IVF	Aspirin	Placebo No treatment	Live birth Clinical pregnancy Multiple pregnancy Complications of IVF Complications of pregnancy Miscarriage Ongoing pregnancy	Incomplete outcome data not well described. Live birth only reported in 3 trials
2.2. For selected populations							
NJ472 Johnson 2010 Surgical treatment for tubal disease in women due to undergo in vitro fertilisation	28/10/2009	5 RCTs	646 women due to undergo IVF	Surgical treatment for tubal disease	No interventions Head to head	Live birth rate Ongoing pregnancy Clinical pregnancy Ectopic pregnancy Miscarriage rate	None of the trials showed evidence of blinding. Live birth was not reported in the included trials
SG1241 Benschop 2010 Interventions for women with endometrioma prior to assisted reproductive technology	26/11/2010	4 RCTs	312 women undergoing management of endometrioma prior to ART	Surgical or medical treatment prior to ART	Placebo/no treatment Other surgical or medical treatment prior to ART	Live birth rate Clinical pregnancy rate Adverse events Quality of life Pain Recurrence Oestradial levels Number of mature oocytes	No live birth rates reported. Two of the trials were open label
LDT120 Tso 2014 Metformin	15/10/2014	9 RCTs	816 women with polycys-	Metformin	Placebo No treatment	Live birth Clinical pregnancy Miscar-	Half the trials were not blinded

Table 1. Review characteristics (*Continued*)

treatment before and during IVF or ICSI in women with polycystic ovary syndrome			tic ovary syndrome			riage OHSS Adverse events Number of oocytes retrieved Total dose FSH (IU) Number of days gonadotrophin treatment Cycle cancellation rate Serum E2 level (nmol/l	and lacked details on allocation concealment and randomisation
SH1141 McDonnell 2014 Ovarian cyst aspiration prior to in vitro fertilization treatment for subfertility	24/4/14	3 RCTs	339 women with ovarian cysts undergoing ART	Ovarian cyst aspiration	Conservative treatment	Clinical pregnancy Number of follicles recruited Number of oocytes collected Number of cancelled cycles	Live birth not reported by any of the studies Poor reporting of study methods Imprecision Inconsistency
3. Down-regulation with agonists or antagonists							
LA541 Albuquerque 2013 Depot versus daily administration of gonadotrophin releasing hormone agonist protocols for pituitary down regulation in assisted reproduction cycles	3/7/12	16 RCTs	1811 women undergoing IVF	GnRHa depot	GnRHa daily	Clinical pregnancy Pregnancy per oocyte retrieval procedure Pregnancy rate per embryo transferred Number of ampoules of gonadotrophin employed Number of days of go-	Study quality was unclear due to poor reporting. Only four studies reported live births as an outcome and only five described adequate methods for concealment of allocation

Table 1. Review characteristics (*Continued*)

						nadotrophin treatment Number of oocytes retrieved Abortion rate Ongoing/ delivered pregnancy rates per cycle started Multiple pregnancy rates OHSS	
HA412 Al-Inany 2011 Gonadotrophin-releasing hormone antagonists for assisted reproductive technology	01/03/2010	45 RCTs	7511 women undergoing ART	GnRH antagonist	Long course GnRH agonist	Live birth Ongoing pregnancy Clinical pregnancy Miscarriage OHSS Cycle cancellation	Only 9 trials reported live birth Trial methodology limited by lack of blinding
HNS 881 Sallam 2006 Long-term pituitary down- regulation before in vitro fertilization (IVF) for women with endometriosis	17/10/2005	3 RCTs	228 women with endometriosis undergoing ART	GnRH agonist	No GnRH agonist	Clinical pregnancy Dose of FSH/ HMG (ampoule) Duration of FSH administration (days) Number of oocytes	No blinding Unclear allocation concealment in all trials and no reporting of live birth Possible unit of analysis error - review being updated
SD265 Maheshwari 2011 Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in	24/01/2011	29 RCTs	Included women undergoing ART: total number of participants unclear from review	Long protocol Short protocol	Short protocol Ultra short protocol Stop short protocol	Live birth Clinical pregnancy Ongoing pregnancy Number of oocytes Dose of gonadotrophins Cycle cancel-	Only 3 trials reported live birth Methodology limited by lack of blinding and inadequate reporting of out-

Table 1. Review characteristics (*Continued*)

assisted reproductive treatment						lation	come data assessed Overall very limited by methodology.
4. Ovarian stimulation							
4.1 Medication type							
AM1335 Gibreel 2012 Clomiphene citrate in combination with gonadotropins for controlled ovarian stimulation in women undergoing in vitro fertilization	23/3/2012	14 RCTs	2536 (12 trials) Subfertile women undergoing ART	Clomiphene citrate +/- additional treatments	Alternative treatments for controlled ovarian hyperstimulation	Live birth rate Miscarriage rate Ectopic pregnancy Fetal abnormality Ongoing pregnancy rate Cancellation rate OHSS	Live birth only reported in 5 of the trials Most studies suffered from suboptimal methodology and there was insufficient information on some outcomes
AWP1710 Pouwer 2015 Long-acting FSH versus daily FSH for women undergoing assisted reproduction	8/6/15	6 RCTs	3753 women with subfertility	Long acting FSH	Daily FSH	Live birth rate Ongoing pregnancy rate Clinical pregnancy rate OHSS Multiple pregnancy rate Miscarriage rate Adverse events Satisfaction	Limited by risk of attrition bias in some of the primary studies and by serious imprecision
MHM931 Mochtar 2007 Recombinant luteinizing hormone (rLH) for controlled ovarian hyperstimulation in assisted reproductive cycles	14/06/2011	33 RCTs	5624 women with subfertility	Recombinant luteinising hormone plus recombinant follicle stimulating hormone	Recombinant follicle stimulating hormone	Live birth Adverse events Ongoing pregnancy Miscarriage Amount of rFSH used Serum oestradiol used Num-	Live birth was reported in 5 of the trials There was a lack of methodological details provided by the review authors with regards to

Table 1. Review characteristics (*Continued*)

						ber of oocytes retrieved	blinding and inadequate outcome data assessed. Trials were also limited by information on randomisation and allocation concealment
IOK973 van Wely 2011 Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles	20/10/2010	42 RCTs	9606 women undergoing ART	Recombinant follicle stimulating hormone	Urinary gonadotrophins	Live birth/ongoing pregnancy OHSS Clinical pregnancy Multiple pregnancy Miscarriage	The majority of the trials were open labelled.
WPM1780 Martins 2013 FSH replaced by low-dose hCG in the late follicular phase versus continued FSH for assisted reproductive techniques	5/2/13	5 RCTs	351 women undergoing COH for ART.	Low dose human chorionic gonadotrophin in the late follicular phase	Follicle stimulating hormone throughout controlled ovarian hyperstimulation	Live birth OHSS Ongoing pregnancy Clinical pregnancy Miscarriage Total dose of FSH used Oocytes retrieved	Only two studies reported live birth: both were at high risk of attrition bias Low precision due to small overall sample size
DHH752 Smulders 2010 Oral contraceptive pill, progestogen or estrogen pre- treatment for ovarian stimulation protocols	16/11/2008	23 RCTs	2603 women with subfertility	Combined OCP Progesterone Oestrogen	Placebo or no treatment Combined OCP Progesterone Oestrogen	Live birth rate Ongoing pregnancies Clinical/ ongoing pregnancies Oocytes retrieved Gonadotrophin	Live birth reported in 6 trials Methodological limitations: poor reporting of randomisation procedures, high

Table 1. Review characteristics (*Continued*)

for women undergoing assisted reproductive techniques						treatment Pregnancy loss Ovarian cyst formation Multiple pregnancies OHSS	risk of attrition bias in some studies, poor precision due to low sample numbers for individual comparisons
4.2 Monitoring							
IOK972 Kwan 2014 Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI)	30/5/2014	6 RCTs	781 women undergoing ovarian stimulation with gonadotrophins in ART	Ultrasound plus oestradiol	Ultrasound only	Clinical pregnancy Number of oocytes OHSS	No studies reported live birth Study methods inadequately described, serious imprecision
4.3 Interventions for poor responders							
RSS791 Pandian 2010 Interventions for 'poor responders' to controlled ovarian hyper stimulation (COH) in invitro fertilisation (IVF)	16/03/2009	10 RCTs	625 women considered to be 'poor responders' to COH in IVF treatment	Stop protocol GnRHa protocol GnRHa flare up protocol GnRH antagonist Low dose GnHa flare up protocol Multiple dose GnRH antagonist Flare up protocol Long protocol	Long protocol GnRHa flare up protocol Spontaneous natural cycle IVF Mini dose long agonist protocol Modified long protocol	Live birth rate per woman Clinical pregnancy rate per woman Ongoing pregnancy rate per woman Miscarriage rate Ectopic pregnancy Cancellation rate Oocytes retrieved Dose of gonadotrophins Total FSH used	Live birth rate only reported in one trial Methodological limitations in terms of limited blinding, lack of details on addressing incomplete data outcome
4.4 Natural cycle IVF							
TA1860 Allersma 2013	5/3/13	5 RCTs	382 subfertile women	Natural cycle IVF	Controlled ovarian hyper-	Live birth OHSS	Few studies, live birth

Table 1. Review characteristics (*Continued*)

Natural cycle IVF for subfertile couples			and couples undertaking IVF treatment	Modified natural cycle IVF	stimulation IVF	Pregnancy Ongoing pregnancy No of oocytes retrieved Time to live birth Number of cycles required to conceive Cumulative pregnancy/ live birth rate Multiple pregnancy Lack of embryos for cryopreservation Cycle cancellation Gestational abnormalities Cancellation of treatment Cost effectiveness	only reported in one very small trial Inclusion criteria differed
5. Ovulation triggering							
MM1690 Youssef 2014 Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology	8/9/2014	17 RCTs	1847 women undergoing ART	GnRH agonist	HCG	Live birth rate Ongoing pregnancy rate Clinical pregnancy rate Multiple pregnancy rate Miscarriage rate OHSS	Risk of bias in included studies. Limitations included premature termination, failure to clearly report methods, and substantial heterogeneity Adverse events such as multiple pregnancy rate were not well reported
HA413 Youssef 2011 Recombinant versus urinary	20/1/2010	14 RCTs	2306 women undergoing ART	Recombinant hCG Recombinant	Urinary hCG	Live birth OHSS Clinical preg-	Authors combined ongoing pregnancy and

Table 1. Review characteristics (*Continued*)

human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles				hLH		nancy rate Miscarriage rate Oocytes retrieved Tolerance	live births together 6 of 14 trials reported on live birth Four of the trials lacked details on allocation concealment, randomisation and blinding
6. Oocyte retrieval							
IOK971 Kwan 2013 Pain relief for women undergoing oocyte retrieval for assisted reproduction	31/1/13	21 RCTs	2974 women undergoing transvaginal oocyte retrieval during IVF treatment	Intravenous alfentanyl plus PCB Intravenous midazolam Intravenous sedation plus PCB Patient controlled sedation Patient-controlled inhalational Isodesox Conscious sedation Intramuscular pethidine	Electroacupuncture plus PCB General anaesthesia Placebo plus PCB Physician controlled sedation intravenous analgesia Placebo Piroksikam	Pain Patient satisfaction Pregnancy rate Ongoing and live birth rate	Evidence was generally of low quality, mainly due to poor reporting of methods, small sample sizes and inconsistency between the trials Only one study reported live birth rate
SW811 Wongtrangan 2010 Follicular flushing during oocyte retrieval in assisted reproductive techniques	31/03/2010	4 RCTs	208 women undergoing ART	Follicular flushing	Aspiration alone	Clinical /ongoing pregnancy Oocyte retrieval Adverse events Duration of procedure Pain	No reporting of live birth Half trials did not report details of allocation concealment Blinding poorly reported
7. Sperm retrieval							

Table 1. Review characteristics (*Continued*)

AMVP611 Proctor 2008 Techniques for surgical retrieval of sperm prior to intra-cytoplasmic sperm injection (ICSI) for azoospermia	12/12/2012 Review is stable and will no longer be updated	1 RCT	59 men with obstructive or non-obstructive azoospermia	Epididymal or testicular techniques for sperm retrieval	Epidydymal or testicular techniques for sperm retrieval	Pregnancy rate Sperm parameters Fertilisation rate	No live birth reported Based on single RCT Poor methodology
SMD 1810 McDowell 2014 Advanced sperm selection techniques for assisted reproduction	26/5/2014	2 RCTS	581 couples undergoing ART	Sperm selection by hyaluronanic acid binding for ICSI	1.Conventional ICSI 2. Comparison of different hyaluronanic acid binding technique	Live birth Pregnancy Miscarriage	Only one study reported live birth Poor reporting of study methods in one study Data discrepancy in one study Imprecision
8. Laboratory phase							
DG1352 Glujovsky 2014	3/3/14	2 RCTs	106 women undergoing ART and wishing to preserve oocytes	Vitrification	Slow freezing	Clinical pregnancy Ongiong pregnancy	Failure to report live birth Imprecision
MWS391 Carney 2012 Assisted hatching on assisted conception (in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI))	8/8/12	31 RCTs	5728 women undergoing ART	Assisted hatching	No assisted hatching	Live birth Multiple pregnancy Clinical pregnancy Miscarriage Ectopic pregnancy Monozygotic twinning Congenital or chromosomal abnormalities Failure	Few studies described adequate allocation concealment. Most failed to report on live birth rates

Table 1. Review characteristics (*Continued*)

						to transfer any embryos Embryo damage In vitro blastocyst development	
MVR461 Van Rumste 2003 Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in patients with non-male subfertility	24/1/2011 Review no longer being updated	1 RCT	415 couples with non-male factor subfertility	Intracytoplasmic sperm injection	In vitro fertilisation	Clinical pregnancy Adverse events Miscarriage	Evidence based on a single trial with unclear details on blinding
SB1283 Bontekoe 2012 Low oxygen concentrations for embryo culture in assisted reproductive technologies	4/11/2011	7 RCTs	2422 couples undergoing ART	Embryo culture with low oxygen concentrations	Embryo culture with atmospheric oxygen concentrations	Live birth Ongoing pregnancy Clinical pregnancy Multiple pregnancy Miscarriage Congenital abnormalities Implantation rate Embryo development Cryopreservation rate	Only three of the trials reported on live birth outcomes There were unclear methodological details in six of the trials
SMA991 Twisk 2006 Preimplantation genetic screening for abnormal numbers of chromosomes (aneu-	15/07/2010	9 RCTs	1589 women undergoing IVF or ICSI with and without PGS for all suggested indications	IVF/ICSI with preimplantation genetic screening	IVF/ICSI with no preimplantation genetic screening	Live birth Clinical pregnancy Multiple pregnancy Miscarriage Ongoing pregnancy Congenital	Six of the nine trials were open label and other methodological details were unclear

Table 1. Review characteristics (*Continued*)

ploidies) in in vitro fertilisation or intracytoplasmic sperm injection						abnormalities	
ZH1093 Huang 2013 Brief co-incubation of sperm and oocytes for in vitro fertilization techniques	26/3/13	8 RCTs	733 women undergoing ART	Brief co-incubation of gametes for women undergoing IVF	Standard overnight insemination protocol for women undergoing IVF	Live birth Ongoing pregnancy Clinical pregnancy Miscarriage Fertilisation Polyspermy Implantation	The trials provided low quality evidence. Only 3/8 gave information on how the randomization was achieved and all had unclear methods of allocation concealment. No studies reported live birth
WPM1800 Teixeira 2013 Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction	8/5/13	9 RCTs	2014 couples undergoing ART	IMSI	ICSI	Live birth Clinical pregnancy Miscarriage Congenital abnormalities	Only one trial reported live birth. Issues such as risk of bias (differences between number of oocytes transferred), imprecision and strong suspicion of publication bias
SCA1950 Armstrong 2015 Time-lapse systems for embryo incubation and assessment in assisted reproduction	17/11/14	3 RCTs	994 women undergoing ART	TIme lapse systems	Conventional embryo incubation	Live birth Miscarriage Clinical pregnancy Cumulative clinical pregnancy	Evidence limited by methodological weaknesses, imprecision and indirectness

Table 1. Review characteristics (*Continued*)

9. Embryo transfer							
9.1 Developmental stage							
DB551 Glujovsky 2012 Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology	21/02/2012	23 RCTs	3241 women undergoing ART	Cleavage stage transfer	Blastocyst stage transfer	Live birth rate Clinical pregnancy rate Multiple pregnancy rate Miscarriage rate Embryo freezing rate Failure to have a transfer Cumulative pregnancy rate	Many of the trials had inadequate or unclear methodological details
9.2 Number of embryos							
CO266 Gunby 2004 Day three versus day two embryo transfer following in vitro fertilisation or intracytoplasmic sperm injection	15/12/2003	16 trials	2691 (12 studies) couples undergoing ART	Day 3 embryo transfer	Day 2 embryo transfer	Live birth Ongoing pregnancy Clinical pregnancy rate Complication rate Multiple pregnancy rate Miscarriage rate Ectopic pregnancy Foetal abnormalities Womens' evaluation	Live birth reported in only 3 trials Many of the included trials lacked methodological details
ZP661 Pandian 2013 Number of embryos for transfer following in vitro fertilisation or intra cytoplasmic sperm injection	17/07/2012	14 RCTs	2165 couples undergoing ART	Single embryo transfer Double embryo transfer	Double embryo transfer Three embryo transfer Four embryo transfer	Live birth rate Pregnancy rate Multiple pregnancy rate Miscarriage rate	Many of the included studies were small, with half enrolling fewer than 60 participants. There was con-

Table 1. Review characteristics (*Continued*)

							siderable clinical heterogeneity between the studies but little evidence of statistical heterogeneity for most analyses. The methodological quality of the studies was mixed
9.3 Transfer techniques							
DB552 Bontekoe 2014 Adherence compounds in embryo transfer media for assisted reproductive technologies	13/11/13	17 RCTs	3898 women undergoing ART	Embryo transfer media enriched with adherence compounds (hyaluronic acid or fibrin sealant)	Embryo transfer media devoid of , or with a low dose of such adherence compounds	Live birth Ongoing pregnancy Clinical pregnancy Multiple pregnancy Implantation rate Adverse events	There were some methodological limitations and some imprecision
SV602 Derks 2009 Techniques for preparation prior to embryo transfer	18/03/2009	10 RCTs	1693 women (9 RCTs) undergoing IVF	Straightening of the utero-cervical angle Cervical and endometrial preparation Dummy transfer Embryo afterloading	No intervention or no treatment	Live birth Clinical pregnancy Multiple pregnancy Miscarriage Ectopic pregnancy Adverse events - pain/ infection	Only one trial reported on live birth outcomes, methodological procedures were inadequately explained in most of the included trials
EN1382 Kroon 2012 Antibiotics prior to embryo transfer in ART	23/11/2011	1 RCT	350 women undergoing ART	Antibiotics	No treatment	Bacterial contamination rate of catheter Clinical pregnancy rate	Analysis of bacterial contamination was not performed on all participants

Table 1. Review characteristics (*Continued*)

JB604 Brown 2010 Ultrasound versus 'clinical touch' for catheter guidance during embryo transfer in women	9/11/2009	17 RCTs	6524 women with any form of infertility undergoing ART	Ultrasound guided transfer	Clinical touch transfer	Live birth Ongoing pregnancy Clinical pregnancy Multiple pregnancy Miscarriage rate Ectopic pregnancy Foetal abnormalities Complication rate Ease of transfer	Trials lacked methodological details and live birth was not well reported
AAS605 Abou-Setta 2014 Post-embryo transfer interventions for in vitro fertilisation and intra- cytoplasmic sperm injection patients	19/6/14	4 RCTs	1392 women with subfertility of any cause	Bedrest Bladder emptying Mechanical pressure on cervix Fibrin sealant	Different duration of bedrest No intervention	Live birth rate Ongoing pregnancy Clinical pregnancy rate Multiple pregnancy rate Miscarriage rate Ectopic pregnancy rate Adverse events - pain Subjective experience	No live birth reported, lack of blinding
10. Luteal phase support							
MV263 van der Linden 2015 Luteal phase support for ART cycles	25/11/2014	94 RCTs	26198 women with any cause of subfertility undergoing ART	Progesterone hCG	Placebo or no treatment hCG Progesterone + oestrogen Progesterone + GnRH agonist	Live birth rate Clinical pregnancy rate Ongoing pregnancy rate Miscarriage rate OHSS Multiple pregnancy rate	Poor reporting of study methods and imprecision due to small sample sizes

Table 1. Review characteristics (*Continued*)

CMB126 Boomsma 2012 Peri-implantation glucocorticoid administration for assisted reproductive technology cycles	20/09/2011	14 RCTs	1879 couples with any cause of subfertility undergoing ART	Glucocorticoids	No glucocorticoids Placebo	Live birth Ongoing pregnancy Pregnancy Multiple pregnancy Miscarriage Ectopic pregnancy OHSS Implantation rate	Only 3 trials reported live birth Methodology limited by lack of blinding and inadequate reporting of outcome data assessed
MA1441 Akhtar 2013 Heparin for assisted reproduction	6/5/13	3 RCTs	386 subfertile women undergoing ART	Heparin	Placebo No treatment	Live birth Adverse effects Clinical pregnancy Multiple pregnancy Maternal complications Fetal complications	Only three small studies, one of which did not adequately describe allocation concealment. High heterogeneity reflecting differing participant inclusion criteria
11. Prevention of ovarian hyperstimulation syndrome (OHSS)							
TH1338 Tang 2012 Cabergoline for preventing ovarian hyperstimulation syndrome	2/09/2011	2 RCTs	230 women at high risk of OHSS undergoing ART	Cabergoline	Placebo/no treatment Other treatment	OHSS Live birth rate Miscarriage Clinical pregnancy rate Multiple miscarriage rate Adverse events	Allocation concealment not clearly reported. Blinding in one of the trials was not clearly reported and there were issues around incomplete data reporting. No studies reported live birth rate
ADA563 D'Angelo 2011	19/07/2010	4 RCTs	340 women with PCOS down-	Coasting when estradiol levels	Early unilateral follicular aspiration	OHSS Clinical pregnancy	Comparisons based on limited trial data

Table 1. Review characteristics (*Continued*)

Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome			regulated by GnRH-a, undergoing super-ovulation in IVF or ICSI cycles	were > 2500 pg/mL or > 9000 pmol/L Coasting when estradiol levels were > 2500 pg/mL or > 9000 pmol/L	No coasting or other interventions	Number of oocytes retrieved Multiple pregnancy Miscarriage Live birth	Live birth only reported in one trial Trials lacked blinding and half the trials lacked details on allocation concealment and incomplete outcome assessment
ADA561 D'Angelo 2007 Embryo freezing for preventing ovarian hyperstimulation syndrome	26/11/2010 Review is considered to be stable and will not be updated again	2 RCTs	151 women down-regulated by GnRH-a, undergoing superovulation in IVF and or ICSI cycles	Cryopreservation	Fresh embryo transfer Intravenous albumin	OHSS Clinical pregnancy Live birth Admissions	Evidence based on two trials, one for each comparison Live birth only reported in one trial Issues around methodological quality of both trials
PMA481 Youssef 2011a Intra-venous fluids for the prevention of severe ovarian hyperstimulation syndrome	02/11/2010	8 RCTs	1638 women having controlled ovarian hyperstimulation and at risk of severe OHSS	Human albumin Hydroxyethyl starch	Placebo	OHSS Clinical pregnancy	No reporting of live birth Methodological issues especially around incomplete outcome addressed
12. Frozen embryo replacement cycles							
TG691 Ghobara 2008 Cycle regimens for frozen-thawed embryo transfer (FET)	11/10/2007	7 RCTs	1120 women Studies included women with a range of causes of subfertility The review does not provide details of the mean ages	Oestrogen and progesterone GnRHa + day oestrogen + day progesterone Clomiphene + HMG	Natural cycle GnRHa + day oestrogen and progesterone FSH Clomiphene Clomiphene HMG	Live birth per woman Clinical pregnancy per woman Ongoing pregnancy per woman Multiple pregnancy rate Cy-	Of the included studies, randomisation was unclear in six trials. Allocation concealment was adequately re-

Table 1. Review characteristics (*Continued*)

			of the women			cle cancellation rate Miscarriage rate Endometrial thickness	ported in three trials and there was no blinding reported in any of the trials Many of the outcomes associated with the comparisons in the trials are limited to a single trial
DG1351 Glujovsky 2010 Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes	7/10/2009	22 RCTs	3451 women 11 trials used fresh donor oocyte embryo replacement cycles 11 trials used frozen embryo replacement cycles There was no detail on causes of infertility	GnRHa Corticosteroids Low dose aspirin GnRHa Intramuscular progesterone Day of starting progesterone Artificial cycle HCG before retrieval	No treatment GnRHa Vaginal progesterone Day of starting progesterone Non artificial cycle Placebo	Live birth Clinical pregnancy rate Multiple pregnancy rate Cancelled cycle rates Endometrial thickness Pregnancy loss	Only eight trials reported adequate details of allocation concealment Only one trial reported on blinding

HMG - human menopausal gonadotrophin
FSH - follicle stimulating hormone
FET - frozen-thawed embryo transfer
GnRHa - gonadotrophin-releasing hormone agonist
ICSI - intracytoplasmic sperm injection
IVF - in vitro fertilisation

Table 2. AMSTAR assessment

Review no	First author		RE-VIEW TITLE	AMSTAR CRITERIA									
				Pre-specified	Duplicate study	Comprehen-	Grey lit in-	Lists included	Describes	Study quality	Studies com-	Likelihood of	Potential

Table 2. AMSTAR assessment (*Continued*)

				question and inclusion criteria	selection and data extraction	sive lit search	cluded	and excluded studies	characteristics of included studies	assessed	bined using appropriate methods	publication bias considered/ tested	for conflict of interest addressed
AAS605	Abou-Setta 2014		Post-embryo transfer interventions for assisted reproduction technology cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ADA561	D'Angel 2007		Embryo freezing for preventing ovarian hyperstimulation syndrome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ADA563	D'Angel 2011		Coasting (withholding gonadotrop for preventing ovarian hyperstimulation syndrome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

AM1335	Gibreel 2012		Clomiph citrate for controlled ovarian stimulation in women undergoing in vitro fertilization	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AMVP6	Proctor 2008		Techniques for surgical retrieval of sperm prior to intracytoplasmic sperm injection (ICSI) for azoospermia	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AMY731	Yossry 2006		In vitro fertilisation versus tubal reanastomosis (sterilisation reversal) for subfer-	✓	✓	✓	✓	✓	n/a	n/a	n/a	n/a	✓

Table 2. AMSTAR assessment (*Continued*)

			tility after tubal sterilisation										
AWP171	Pouwer 2015		Long-acting FSH versus daily FSH for women undergoing assisted reproduction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CMB12(	Boomsm 2012		Peri-implantation glucocorticoid administration for assisted reproductive technology cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CO266	Gunby 2004		Day three versus day two embryo transfer following in vitro fertilization or in-	✓	✓	✓	✓	✓	✓	✓	✓	x	✓

Table 2. AMSTAR assessment (*Continued*)

			tracyto-plasmic sperm injec-tion									
CS1400	Sirista-tidis 2009		In vitro matu-ration in sub fertile women with poly-cystic ovarian syn-drome under-going assisted repro-duction	✓	✓	✓	✓	✓	n/a	n/a	n/a	n/a	✓
DB551	Glu-jovsky 2012		Cleav-age stage versus blasto-cyst stage embryo transfer in assisted repro-ductive tech-nology	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DB552	Bon-tekoe 2014		Adher-ence com-pounds in embryo transfer media for	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

			assisted reproductive technologies										
DG1351	Glujovsky 2010		Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DG1352	Glujovsky 2014		Vitrification versus slow freezing for women undergoing oocyte cryopreservation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DHH75	Smulders 2010		Oral contraceptive pill, progesto-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

			gen or estrogen pretreatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques										
EN1382	Kroon 2012		Antibiotics prior to embryo transfer in ART	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HA412	Al-Inany 2011		Gonadotrop releasing hormone antagonists for assisted reproductive technology	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
HA413	Youssef 2011		Recombinant versus urinary human	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

			chorionic gonadotrop for final oocyte maturation triggering in IVF/ICSI cycles									
HNS881	Sallam 2006		Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis	✓	✓	✓	✓	✓	✓	✓	✓	x	✓
IOK971	Kwan 2013		Pain relief for women undergoing oocyte retrieval for assisted reproduction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
IOK972	Kwan 2014		Monitoring of stim-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

			ulated cycles in assisted reproduction (IVF and ICSI)										
IOK973	van Wely 2011		Recombinant versus urinary gonadotrop for ovarian stimulation in assisted reproduction technology cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
IRS911	Cheong 2013		Acupuncture and assisted reproductive technology	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
JB604	Brown 2010		Ultrasound versus 'clinical touch' for catheter guidance during	✓	✓	✓	✓	✓	✓	✓	✓	x	✓

Table 2. AMSTAR assessment (*Continued*)

			embryo transfer in women										
JC1630	Showell 2013		Antioxidants for female subfertility	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
KA992	Anderson 2010		Preconception lifestyle advice for people with subfertility	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
KH291	Duffy 2010		Growth hormone for in vitro fertilization	✓	✓	✓	✓	✓	✓	✓	✓	x	✓
LA541	Albuquerque 2013		Depot versus daily administration of gonadotrop releasing hormone agonist protocols for pituitary desen-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

			sitization in assisted reproduction cycles									
LDT120	Tso 2014		Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MA1441	Akhtar 2013		Heparin for assisted reproduction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MGS15	Showell 2014		Antioxidants for male subfertility	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MHM9	Mochtar 2007		Recombinant luteinizing hormone (rLH) for controlled ovarian	✓	✓	✓	✓	✓	✓	✓	✓	x	✓

Table 2. AMSTAR assessment (*Continued*)

			hyperstimulation in assisted reproductive cycles										
MM169	Youssef 2014		Gonadotrop releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MV263	van der Linden 2015		Luteal phase support in ART cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MVR46	Van Rumste 2003		Intracytoplasmic sperm injection versus conventional techniques	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

			for oocyte insemination during in vitro fertilisation in patients with non-male subfertility										
MWS39	Carney 2012		Assisted hatching on assisted conception (IVF and ICSI)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
NJ472	Johnson 2010		Surgical treatment for tubal disease in women due to undergo in vitro fertilisation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PMA481	Youssef 2011a		Intravenous fluids for the prevention of	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

			severe ovarian hyper-stimu-lation syn-drome										
RBG176	Gutarra-Vilchez 2014		Va-sodila-tors for women under-going fertility treat-ment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
RSS791	Pan-dian 2010		Inter-ven-tions for 'poor respon-ders' to con-trolled ovarian hyper stimu-lation (COH) in in-vitro fertili-sation (IVF)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SB1283	Bon-tekoe 2012		Low oxygen con-centra-tions for embryo culture in assisted repro-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

			ductive technologies									
SCA195	Armstrong 2015		Time-lapse systems for embryo incubation and assessment in assisted reproduction	✓	✓	✓	✓	✓	✓	✓	✓	x	✓
SD265	Maheshwari 2011		Gonadotrop releasing hormone agonist protocols for pituitary suppression in assisted reproductive technology cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SG1241	Benschop 2010		Interventions for women with endometrioma	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

			prior to assisted reproductive technology										
SH1141	McDonnell 2014		Ovarian cyst aspiration prior to in vitro fertilization treatment for subfertility	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SMA991	Twisk 2006		Preimplantation genetic screening for abnormal number of chromosomes (aneuploidies) in in vitro fertilisation or intracytoplasmic sperm injection	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SMD18	McDowell 2014		Advanced sperm	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

			selection techniques for assisted reproduction									
SV602	Derks 2009		Techniques for preparation prior to embryo transfer	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SW811	Wongtrangan 2010		Follicular flushing during oocyte retrieval in assisted reproductive techniques	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TA1860	Allersma 2013		Natural cycle IVF for subfertile couples	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TG691	Ghobara 2008		Cycle regimens for frozen-thawed embryo transfer	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

TH1338	Tang 2012		Cabergoline for preventing ovarian hyperstimulation syndrome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
VJP951	Siristatidis 2011		Aspirin for in vitro fertilisation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
WM150	Nastri 2015		Endometrial injury in women undergoing assisted reproductive techniques	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
WPM17	Martins 2013		FSH replaced by low-dose hCG in the late follicular phase versus FSH alone for assisted reproductive techniques	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

WPM18	Teixeira 2013		Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ZH1093	Huang 2013		Brief co-incubation of sperm and oocytes for in vitro fertilization techniques	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ZP661	Pandian 2013		Number of embryos for transfer following in-vitro fertilisation or intracytoplasmic sperm injection	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

ZP672	Pandian 2012		In vitro fertilisation for unexplained subfertility	✓	x	✓	✓	✓	✓	✓	✓	✓	✓

Table 3. Latest search date assessment

Review no	First author	REVIEW TITLE	< 3 yrs since last search (to July 2015 or deemed stable)
AAS605	Abou-Setta 2014	Post-embryo transfer interventions for assisted reproduction technology cycles	✓
ADA561	D'Angelo 2007	Embryo freezing for preventing ovarian hyperstimulation syndrome	Stable
ADA56x3	D'Angelo 2011	Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome	x
AM1335	Gibreel 2012	Clomiphene citrate for controlled ovarian stimulation in women undergoing in vitro fertilization	x
AMVP611	Proctor 2008	Techniques for surgical retrieval of sperm prior to intra-cytoplasmic sperm injection (ICSI) for azoospermia	Stable
AMY731	Yossry 2006	In vitro fertilisation versus tubal reanastomosis (sterilisation reversal) for subfertility after tubal sterilisation	x
AWP1710	Pouwer 2015	Long-acting FSH versus daily FSH for women undergoing assisted reproduction	✓
CMB1261	Boomsma 2012	Peri-implantation glucocorticoid administration for assisted reproductive technology cycles	x
CO266	Gunby 2004	Day three versus day two embryo transfer following in vitro fertilization or intracytoplas-	x

Table 3. Latest search date assessment (*Continued*)

		mic sperm injection	
CS1400	Siristatidis 2009	In vitro maturation in sub fertile women with polycystic ovarian syndrome undergoing assisted reproduction	✓
DB551	Glujovsky 2012	Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology	x
DB552	Bontekoe 2014	Adherence compounds in embryo transfer media for assisted reproductive technologies	✓
DG1351	Glujovsky 2010	Endometrial preparation for women undergoing embryo transfer with frozen embryos or embryos derived from donor oocytes	x
DG1352	Glujovsky 2014	Vitrification versus slow freezing for women undergoing oocyte cryopreservation Review information	✓
DHH752	Smulders 2010	Oral contraceptive pill, progestogen or estrogen pre-treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques	x
EN1382	Kroon 2012	Antibiotics prior to embryo transfer in ART	x
HA412	Al-Inany 2011	Gonadotrophin-releasing hormone antagonists for assisted reproductive technology	x
HA413	Youssef 2011	Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF/ICSI cycles	x
HNS881	Sallam 2006	Long-term pituitary down-regulation before in vitro fertilization (IVF) for women with endometriosis	x
IOK971	Kwan 2013	Pain relief for women undergoing oocyte retrieval for assisted reproduction	x
IOK972	Kwan 2014	Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI)	✓

Table 3. Latest search date assessment (*Continued*)

IOK973	van Wely 2011	Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproduction technology cycles	x
IRS911	Cheong 2013	Acupuncture and assisted reproductive technology	✓
JB604	Brown 2010	Ultrasound versus 'clinical touch' for catheter guidance during embryo transfer in women	✓
JC1630	Showell 2013	Antioxidants for female subfertility	✓
KA992	Anderson 2010	Pre-conception lifestyle advice for people with subfertility	x
KH291	Duffy 2010	Growth hormone for in vitro fertilization	x
LA541	Albuquerque 2013	Depot versus daily administration of gonadotrophin releasing hormone agonist protocols for pituitary desensitization in assisted reproduction cycles	x
LDT1201	Tso 2014	Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome	✓
MA1441	Akhtar 2013	Heparin for assisted reproduction	✓
MGS1510	Showell 2014	Antioxidants for male subfertility	✓
MHM931	Mochtar 2007	Recombinant luteinizing hormone (rLH) for controlled ovarian hyperstimulation in assisted reproductive cycles	x
MM1690	Youssef 2014	Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles	✓
WPM1800	Teixeira 2013	Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction	✓
MV263	van der Linden 2015	Luteal phase support in ART cycles	✓

Table 3. Latest search date assessment (*Continued*)

MVR461	Van Rumste 2003	Intra-cytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in patients with non-male subfertility	✓
MWS391	Carney 2012	Assisted hatching on assisted conception (IVF and ICSI)	✓
NJ472	Johnson 2010	Surgical treatment for tubal disease in women due to undergo in vitro fertilisation	x
PMA481	Youssef 2011a	Intra-venous fluids for the prevention of severe ovarian hyperstimulation syndrome	x
RBG1760	Gutarra-Vilchez 2014	Vasodilators for women undergoing fertility treatment	✓
RSS791	Pandian 2010	Interventions for 'poor responders' to controlled ovarian hyper stimulation (COH) in in-vitro fertilisation (IVF)	x
SB1283	Bontekoe 2012	Low oxygen concentrations for embryo culture in assisted reproductive technologies	✓
SCA1950	Armstrong 2015	Time-lapse systems for embryo incubation and assessment in assisted reproduction	✓
SD265	Maheshwari 2011	Gonadotropin-releasing hormone agonist protocols for pituitary suppression in assisted reproductive technology cycles	✓
SG1241	Benschop 2010	Interventions for women with endometrioma prior to assisted reproductive technology	x
SH1141	McDonnell 2014	Ovarian cyst aspiration prior to in vitro fertilization treatment for subfertility	✓
SMA991	Twisk 2006	Preimplantation genetic screening for abnormal number of chromosomes (aneuploidies) in in vitro fertilisation or intracytoplasmic sperm injection	x
SMD1810	McDowell 2014	Advanced sperm selection techniques for assisted reproduction	✓
SV602	Derks 2009	Techniques for preparation prior to embryo transfer	x

Table 3. Latest search date assessment (*Continued*)

SW811	Wongtra-ngan 2010	Follicular flushing during oocyte retrieval in assisted reproductive techniques	x
TA1860	Allersma 2013	Natural cycle IVF for subfertile couples	✓
TG691	Ghobara 2008	Cycle regimens for frozen-thawed embryo transfer	x
TH1338	Tang 2012	Cabergoline for preventing ovarian hyperstimulation syndrome	x
VJP951	Siristatidis 2011	Aspirin for in vitro fertilisation	x
WM1504	Nastri 2015	Endometrial injury in women undergoing assisted reproductive techniques	✓
WPM1780	Martins 2013	FSH replaced by low-dose hCG in the late follicular phase versus FSH alone for assisted reproductive techniques	✓
ZH1093	Huang 2013	Brief co-incubation of sperm and oocytes for in vitro fertilization techniques	✓
ZP661	Pandian 2013	Number of embryos for transfer following in-vitro fertilisation or intracytoplasmic sperm injection	✓
ZP672	Pandian 2012	In vitro fertilization for unexplained subfertility	x

Table 4. Live birth per woman

Outcome Intervention and comparison intervention	Assumed risk with Comparator	Corresponding risk with intervention	Relative effect (95%CI)	Number of participants (Studies)	Quality of the evidence (GRADE)	Comments
1. Indication for ART						
Pandian 2012 IVF versus expectant management for unexplained subfertility	37 per 1000	458 per 1000 (90 to 879)	OR 22 (2.56 to 189.37)	51 (1 study)	Low	Evidence based on a single study

Table 4. Live birth per woman (*Continued*)

Pandian 2012 IVF versus intrauterine insemination for unexplained subfertility	259 per 1000	407 per 1000 (235 to 604)	OR 1.96 (0.88 to 4.36)	113 (1 study)	Very low	Evidence of imprecision and based on a single trial
Pandian 2012 IVF versus intrauterine insemination + ovarian stimulation for unexplained subfertility (treatment naïve women)	291 per 1000	317 per 1000 (215 to 462)	RR 1.09 (0.74 to 1.59)	234 (2 studies)	Moderate	Both trials lacked an adequate explanation of blinding and one trial did not provide sufficient details on allocation concealment
2. Pre-ART and adjuvant strategies						
2.1 For unselected populations						
Nastri 2015 *See comment Endometrial injury performed between day 7 of the previous cycle and day 7 of the ET cycle vs no injury	260 per 1000	342 per 1000 (281 to 481)	RR 1.42 (1.08 to 1.85	1496 (9 studies)	Moderate	*Outcome is live birth or ongoing pregnancy Serious imprecision
Nastri 2015 * see comment Endometrial injury on the day of oocyte retrieval vs no injury	290 per 1000	90 per 1000	RR 0.31 (0.14 to 0.69)	156 (1 study)	Low	*Outcome is live birth or ongoing pregnancy Very serious imprecision
Showell 2014 Antioxidant versus placebo or no treatment for men	100 per 1000	286 per 1000 (124 to 533)	Peto OR 3.61 (1.27 to 10.29)	90 (2 studies)	Low	Very serious imprecision with only 90 participants and 25 events
Showell 2013 Antioxidant versus placebo or no treatment for women	316 per 1000	172 per 1000 (44 to 180)	OR 0.45 (0.10 to 2.00) (0.19 to 8.26)	37 (1 study)	Very low	Poor reporting of methods and very serious imprecision,

Table 4. Live birth per woman (*Continued*)

						only 9 events in 37 women
Cheong 2013 Acupuncture versus no acupuncture on the day of embryo transfer	281 per 1000	323 per 1000 (254 to 399)	OR 1.22 (0.87 to 1.7)	2505 (8 studies)	Low	Imprecision, inadequate explanation of methods, high statistical heterogeneity (I-squared = 69%)
Cheong 201 Acupuncture versus no acupuncture around the time of oocyte retrieval	357 per 1000	326 per 1000 (247 to 418)	OR 0.87 (0.59 to 1.29)	464 (2 studies)	Low	Imprecision, inadequate explanation of methods, high statistical heterogeneity (I-squared = 69%)
Duffy 2010 Growth hormone versus placebo	146 per 1000	184 per 1000 (64 to 431)	OR 1.32 (0.4 to 4.43)	80 (2 studies)	Moderate	Some evidence of imprecision
Duffy 2010 Growth hormone versus placebo - poor responders	50 per 1000	221 per 1000 (90 to 447)	OR 5.39 (1.89 to 15.35)	165 (4 studies)	Moderate	Some of the studies did not provide adequate explanation of randomisation and/or allocation concealment
Gutarra-Vilchez 2014 Vasodilator compared with placebo	236 per 1000	278 per 1000 (193 to 398)	RR 1.18 (0.82 to 1.69)	350 (3 studies)	Moderate	Studies had low or unclear risk of bias but serious imprecision
Siristatidis 2011 Aspirin versus placebo or no treatment	227 per 1000	211 per 1000 (170 to 266)	RR 0.91 (0.72 to 1.15)	1053 (3 studies)	Moderate	Some evidence of methodological limitations
2.2 For selected populations						
Tso 2014 Metformin versus placebo or no	320 per 1000	395 per 1000 (276 to 530)	OR1.39 (0.81 to 2.40)	551 (5 studies)	Low	Inconsistency: unexplained heterogeneity (I^2 =

Table 4. Live birth per woman (*Continued*)

treatment						52%) Imprecision: total number of events is fewer than 300 There was a data discrepancy in one of these studies. Sensitivity analysis excluding this study yielded an OR of 1.48 (95% CI 0.72 to 3.02) for live birth
3. Down-regulation with agonists or antagonists						
Albuquerque 2013 GnRHa depot versus daily injection	24 per 100	23 per 100 (181 to 292)	OR 0.95 (0.7 to 1.31)	873 (7 studies)	Low	Outcome was live birth or ongoing pregnancy Most of the studies were classified as at unclear risk of bias for all domains. The total number of events was fewer than 300. There were insufficient studies to assess publication bias
Al-Inany 2011 GnRH antagonist versus long course GnRH agonist	314 per 1000	282 per 1000 (240 to 331)	OR 0.86 (0.69 to 1.08)	1515 (9 studies)	Moderate	Lack of detail for some trials on methodological details and a lack of blinding due to the nature of the interventions
Maheshwari 2011 Long versus short protocol for pituitary suppression	134 per 1000	218 per 1000 (124 to 351)	OR 1.8 (0.92 to 3.5)	251 (3 studies)	Very low	Serious methodological limitations in the included studies and only 3 of 29

Table 4. Live birth per woman (*Continued*)

in ART						studies reported on live birth
Maheshwari 2011 Long versus ultra-short protocol for pituitary suppression in ART	122 per 1000	198 per 1000 (91 to 376)	OR 1.78 (0.72 to 4.36)	150 (1 study)	Very low	Evidence based on a single trial with wide confidence intervals and methodological limitations
4. Ovarian stimulation						
4.1 Medication type						
Gibreel 2012 Clomiphene citrate with gonadotropins (with or without mid-cycle GnRH antagonist) versus gonadotropins with GnRH agonists protocols in IVF and ICSI cycles	220 per 1000	208 per 1000 (163 to 259)	OR 0.93 (0.69 to 1.24)	1079 (5 studies)	Low	Wide 95% confidence intervals Method of allocation concealment was either not described or not mentioned at all in some included trials
Pouwer 2015 Long acting FSH (any dose) versus daily FSH	347 per 1000	330 per 1000 (273 to 348)	RR 0.95 (0.84 to 1.07)	2363 (5 studies)	Moderate	Two studies at high risk of attrition bias
Pouwer 2015 Long acting FSH (low dose) versus daily FSH	352 per 1000	246 per 1000 (183 to 327)	RR 0.70 (0.52 to 0.93)	645 (4 studies)	Moderate	Serious imprecision, with low event rate
Pouwer 2015 Long acting FSH (medium dose) versus daily FSH	255 per 1000	263 per 1000 (229 to 301)	RR 1.03 (0.9 to 1.18)	1685 (3 studies)	Moderate	Two studies at high risk of attrition bias
Pouwer 2015 Long acting FSH (high dose) versus daily FSH	375 per 1000	161 per 1000 (45 to 570)	RR 0.43 (0.12 to 1.52)	33 (1 study)	Very low	Serious imprecision due to very low event rate, plus high risk of attrition bias

Table 4. Live birth per woman (*Continued*)

Mochtar 2007 Recombinant luteinizing hormone + recombinant follicle stimulating hormone (rFSH) versus rFSH alone for controlled ovarian hyperstimulation	233 per 1000	247 per 1000 (194 to 307)	OR 1.14 (0.84 to 1.54)	963 (5 studies)	Low	Some methodological detail was unclear and one of the studies was open label. Heterogeneity was >50% (I-squared)
van Wely 2011 rFSH versus urinary gonadotrophins	237 per 1000	232 per 1000 (213 to 251)	OR 0.97 (0.87 to 1.08)	7339 (28 studies)	High	Outcome is live birth or ongoing pregnancy There was a lack of blinding
Martins 2013 FSH replaced by low-dose hCG in the late follicular phase versus continued FSH for assisted reproductive techniques	140 per 1000	220 per 1000 (100 to 450)	RR 1.56 (0.75 to 3.25)	130 (2 studies)	Very low	Very serious imprecision, high risk of bias
Smulders 2010 Combined oral contraceptive plus antagonist versus antagonist	292 per 1000	150 per 1000 (43 to 417)	OR 0.43 (0.11 to 1.74)	45 (1 study)	Very low	Serious risk of imprecision, risk of bias
Smulders 2010 Combined oral contraceptive plus antagonist versus agonist	187 per 1000	187 per 1000 (99 to 325)	OR 1 (0.48 to 2.1)	182 (1 study)	Very low	Serious risk of imprecision, risk of bias
4.3 Interventions for poor responders						
Pandian 2010 Low dose GnRHa flare up versus spontaneous	85 per 1000	86 per 1000 (26 to 245)	OR 1.01 (0.29 to 3.5)	129 (1 study)	Low	Evidence based on a single trial with evidence of

Table 4. Live birth per woman (*Continued*)

natural cycle IVF						imprecision
4.4 Natural cycle IVF						
Allersma 2013 Natural cycle versus standard IVF	125 per 1000	28 per 1000 (1 to 393)	OR 0.20 (0.01 to 4.54)	30 (1 study)	Very low	High risk of performance bias. Very serious imprecision
5. Ovulation triggering						
Youssef 2014 GnRH agonist versus HCG	313 per 1000	176 per 1000 (124 to 242)	OR 0.47 (0.31 to 0.70)	532 (5 studies)	Moderate	One of the studies at high risk of bias because of premature termination, substantial heterogeneity: I^2 = 56%.
Youssef 2011 rhCG versus uhCG	400 per 1000	409 per 1000 (345 to 477)	OR 1.04 (0.79 to 1.37)	1019 (6 studies)	Moderate	2 of the trials were open label and one of the trials lacked details on randomisation, allocation concealment and blinding
Youssef 2011 rhLH versus uhCG	199 per 1000	189 per 1000 (110 to 304)	OR 0.94 (0.5 to 1.76)	280 (2 studies)	Low	One of the trials lacked adequate methodological details and there was evidence of imprecision
6. Oocyte retrieval						
Kwan 2013 Conscious sedation (IV alfentanyl) plus paracervical block versus electroacupuncture plus paracervical block	176 per 1000	334 per 1000 (184 to 601)	OR 2.35 (1.09 to 5.05)	149 (1 study)	Low	Evidence based on a single trial
7. Sperm retrieval						

Table 4. Live birth per woman (*Continued*)

McDowell 2014 HA culture dish (PICSI) compared with viscous medium containing HA (SpermSlow) for infertility requiring intracytoplasmic sperm injection	300 per 1000	350 per 1000 (190 to 550)	RR 1.16 (0.65 to 2.05)	99 (1 study)	Low	Serious risk of bias: study methods not reported in adequate detail Serious imprecision: confidence intervals compatible with substantial benefit or harm from the intervention, or with no effect
8. Laboratory phase						
Carney 2012 Assisted hatching versus no assisted hatching	305 per 1000	311 per 1000 (271 to 356)	OR 1.03 (0.85 to 1.26)	1921 (9 studies)	Moderate	Many of the trials had some methodological limitations or missing information
Bontekoe 2012 Embryo culture with low oxygen concentrations versus atmospheric oxygen concentration	309 per 1000	383 per 1000 (332 to 440)	OR 1.39 (1.11 to 1.76)	1291 (3 studies)	Moderate	In one of the trials there was no allocation concealment and in another trial the method of allocation concealment was unclear
Twisk 2006 Preimplantation genetic screening versus no screening in women with advanced age	259 per 1000	171 per 1000 (133 to 221)	OR 0.59 (0.44 to 0.81)	1062 (5 studies)	Moderate	Only one of the studies described an adequate method of allocation concealment
Twisk 2006 Preimplantation genetic screening versus no screening in women with good prognosis	416 per 1000	263 per 1000 (130 to 461)	OR 0.5 (0.21 to 1.2)	388 (3 studies)	Very low	Methodological details were unclear or inadequate, heterogeneity was high >60%, evidence of imprecision

Table 4. Live birth per woman (*Continued*)

Teixeira 2013 Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection	380 per 1000	440 per 1000 (300 to 630)	RR 1.14 (0.79 to 1.64)	168 (1 study)	Low	Serious imprecision
Armstrong 2015 TLS with or without cell-tracking algorithms versus conventional incubation for embryo incubation in assisted reproduction	500 per 1000	526 per 1000 (310 to 732)	OR 1.11 (0.45 to 2.73)	76 (1 study)	Moderate	Serious risk of imprecision secondary to small sample size and wide confidence intervals
9. Embryo transfer						
9.1 Developmental stage						
Glujovsky 2012 Blastocyst stage versus cleavage stage embryo transfer in assisted reproductive technology	312 per 1000	389 per 1000 (339 to 441)	OR 1.4 (1.13 to 1.74)	1510 (12 studies)	Moderate	Some methodological details were unclear or inadequate
Gunby 2004 Day 3 versus Day 2 embryo transfer	315 per 1000	330 per 1000 (279 to 387)	OR 1.07 (0.84 to 1.37)	1200 (3 studies)	Low	Heterogeneity >60% and evidence of imprecision
9.2 Number of embryos						
Pandian 2013 Single embryo transfer versus double (one cycle only)	450 per 1000	282 per 1000 (242 to 329))	OR 0.48 (0.39 to 0.60)	1564 (9 studies)	High	36% of women noncompliant with treatment allocation in one study: however no heterogeneity detected (I^2 = 0%).

Table 4. Live birth per woman (*Continued*)

Pandian 2013 Repeated single embryo transfer versus double embryo transfer	420 per 1000	373 per 1000 (310 to 441)	OR 0.82 (0.62 to 1.09)	811 (3 studies)	Low	None of studies describe adequate allocation concealment, imprecision
Pandian 2013 Double embryo transfer versus three embryo transfers	273 per 1000	130 per 1000 (33 to 410)	OR 0.4 (0.09 to 1.85)	45 (1 study)	Very low	Randomisation and blinding were unclear, evidence is based on a single trial with evidence of imprecision
Pandian 2013 Double embryo transfer versus four embryo transfers	536 per 1000	288 per 1000 (113 to 548)	OR 0.35 (0.11 to 1.05)	56 (1 study)	Very low	Randomisation, allocation concealment and blinding were unclear, evidence is based on a single trial with evidence of imprecision
9.3 Transfer techniques and procedures						
Bontekoe 2014 Transfer medium enriched with high level of hyaluronic acid versus medium with low level or no hyaluronic acid	374 per 1000	458 per 1000 (412 to 503)	OR 1.41 (1.17 to 1.69)	1950 (6 studies)	Moderate	All studies except one at high risk of bias in one or more domains
Brown 2010 Ultrasound guidance versus clinical touch for embryo transfer	213 per 1000	236 per 1000 (201 to 273)	OR 1.14 (0.93 to 1.39)	2264 (3 studies)	Low	No reporting of blinding and evidence of heterogeneity >60%
Derks 2009 Cervical dilatation versus no intervention	190 per 1000	97 per 1000 (60 to 155)	OR 0.46 (0.27 to 0.78)	288 (1 study)	Moderate	Evidence based on a single trial

Table 4. Live birth per woman (*Continued*)

10. Luteal phase support						
van der Linden 2015 *See comment hCG versus placebo/no treatment	119 per 1000	183 per 1000 (108 to 296)	OR 1.67 (0.90 to 3.12)	527 (3 studies)	Very low	*Outcome is live birth or ongoing pregnancy Serious imprecision, inadequate reporting of methods, findings no longer significant when random effects model used
van der Linden 2015 *See comment Progesterone versus placebo/no treatment	216 per 1000	327 per 1000 (231 to 440)	OR 1.77 (1.09 to 2.86)	642 (5 studies)	Very low	*Outcome is live birth or ongoing pregnancy Serious imprecision, inadequate reporting of methods, findings no longer significant when restricted to live births
van der Linden 2015 *See comment Progesterone versus hCG regimens	278 per 1000	268 per 1000 (200 to 347)	OR 0.95 (0.65 to 1.38)	833 (5 studies)	Low	*Outcome is live birth or ongoing pregnancy Serious imprecision, inadequate reporting of methods.
van der Linden 2015 *See comment Progesterone versus progesterone + oestrogen	420 per 1000	448 per 1000 (397 to 500)	OR 1.12 (0.91 to 1.38)	1651 (9 studies)	Low	*Outcome is live birth or ongoing pregnancy Serious imprecision inadequate reporting of methods.
van der Linden 2015 *See comment Progesterone ver-	355 per 1000	254 per 1000 (209 to 308)	OR 0.62 (0.48 to 0.81)	2861 (9 RCTs)	Very low	Inadequate reporting of methods, serious inconsistency (I^2=69%),

Table 4. Live birth per woman (*Continued*)

sus progesterone + GnRH agonist						only 3 studies reported live birth
Boomsma 2012 Peri-implantation glucocorticoids versus no glucocorticoids	115 per 1000	136 per 1000 (80 to 222)	OR 1.21 (0.67 to 2.19)	424 (3 studies)	Low	Lacked details around methodology and there was evidence of imprecision
Akhtar 2013 Heparin versus control or no heparin	173 per 1000	271 per 1000 (183 to 378)	OR 1.77 (1.07 to 2.90)	386 (3 studies)	Very low	Selection Bias found in one study. High Heterogeneity. Results sensitive to choice of statistical model
11. Prevention of ovarian hyperstimulation syndrome (OHSS)						
D'Angelo 2007 Cryopreservation versus fresh embryo transfer	373 per 1000	380 per 1000 (229 to 558)	OR 1.03 (0.5 to 2.12)	125 (1 study)	Low	Evidence based on a single open label study with insufficient methodological details provided. Evidence of imprecision
D'Angelo 2011 Coasting versus no coasting	265 per 1000	148 per 1000 (48 to 369)	OR 0.48 (0.14 to 1.62)	68 (1 study)	Very low	Evidence based on a single conference abstract, evidence of imprecision, there were insufficient methodological details provided
12. Frozen embryo replacement cycles						
Ghobara 2008 Oestrogen + progesterone frozen thawed embryo transfer (FET) versus GnRHa, oestrogen and progesterone preparations FET	197 per 1000	85 per 1000 (40 to 170)	OR 0.38 (0.17 to 0.84)	234 (1 study)	Low	Evidence based on a single trial and open label

Table 4. Live birth per woman (*Continued*)

Glujovsky 2010 GnRH agonists versus control for endometrial preparation for embryo transfer with frozen embryos or donor oocytes	85 per 1000	197 per 1000 9100 to 351)	OR 2.62 (1.19 to 5.78)	234 (1 study)	Very low	Evidence based on a single, open label trial. Evidence of imprecision
Glujovsky 2010 Intramuscular progesterone versus vaginal progesterone for endometrial preparation for embryo transfer with frozen embryos or donor oocytes	214 per 1000	326 per 1000 (188 to 501)	OR 1.77 (0.85 to 3.68)	153 (1 study)	Very low	Evidence based on a single, open label trial. Insufficient methodological details provided. Evidence of imprecision

Table 5. Clinical pregnancy per woman

Outcome Intervention and comparison intervention	Assumed risk with Comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (Studies)	Quality of the evidence (GRADE)	Comments
1. Indication for ART						
Pandian 2012 IVF versus expectant management for unexplained subfertility	122 per 1000	310 per 1000 (129 to 576)	OR 3.24 (1.07 to 9.8)	86 (2 studies)	Very low	Methodological design limitations including inadequate details of blinding in both trials. One trial also had inadequate details of allocation concealment and high attrition bias. Heterogeneity was high at 80%

Table 5. Clinical pregnancy per woman *(Continued)*

Pandian 2012 IVF versus intrauterine insemination + ovarian stimulation for unexplained subfertility (treatment naïve women	224 per 1000	241 per 1000 (148 to 370)	OR 1.1 (0.6 to 2.03)	232 (2 studies)	Moderate	The trials lacked adequate methodological details
2. Pre-ART and adjuvant strategies						
2. 1 For unselected populations						
Nastri 2015 Endometrial injury performed between day 7 of the previous cycle and day 7 of the ET cycle vs no injury	211 per 1000	298 per 1000 (386 to 480)	RR 1.34 (1.12 to 1.61)	1972 (13 studies)	Moderate	Serious imprecision
Nastri 2015 Endometrial injury on the day of oocyte retrieval vs no injury	330 per 1000	120 per 1000	RR 0.36 (0.18 to 0.71)	156 (1 study)	Low	Very serious imprecision
Showell 2014 Antioxidant versus placebo or no treatment for men	150 per 1000	318 per 1000 (142 to 567)	2.64 (0.94 to 7.41)	90 (2 studies)	Low	Very serious imprecision with only 90 participants and 28 events, confidence intervals cross line of no effect
Showell 2013 Antioxidant versus placebo or no treatmentfor women	279 per 1000	272 per 1000 (222 to 329)	0R 0.97 (0.74 to 1.27)	1173 (7 studies)	Very low	Very serious imprecision, some methodological details were unclear
Duffy 2010 Growth hormone compared	273 per 1000	401 per 1000 (155 to 709)	OR 1.78 (0.49 to 6.5)	42 (1 study)	Moderate	Evidence based on a single trial

Table 5. Clinical pregnancy per woman *(Continued)*

with placebo						and some evidence of imprecision
Duffy 2010 Growth hormone compared with placebo - poor responders	122 per 1000	313 per 1000 (195 to 463)	OR 3.28 (1.74 to 6.2)	279 (8 studies)	High	Adequate description of methodology, no evidence of imprecision or heterogeneity
Gutarra-Vilchez 2014 Vasodilator compared with placebo	274 per 1000	340 per 1000 (274 to 526)	RR 1.38 (1.00 to 1.92)	717 (8 studies)	Low	Studies had low or unclear risk of bias but very serious risk of imprecision
Siristatidis 2011 Aspirin versus placebo or no treatment	299 per 1000	317 per 1000 (290 to 347)	RR 1.03 (0.91 to 1.17)	2142 (10 studies)	Low	All of the trials failed to provide adequate information on incomplete outcome data. There was also inadequate details on allocation concealment and blinding in some of the trials
Cheong 2013 Acupuncture versus no acupuncture on or around the day of embryo transfer	375 per 1000	399 per 1000 (343 to 460)	OR 1.11 (0.87 to 1.42)	3632 (14 studies)	Very low	Only 3/14 studies described adequate allocation concealment, serious heterogeneity (I-squared =66%), imprecision
Cheong 2013 Acupuncture versus no acupuncture around the time of oocyte retrieval	346 per 1000	372 per 1000 (292 to 461)	OR 1.12 (0.78 to 1.62)	912 (6 studies)	Low	Inadequate description of study methods, serious imprecision

Table 5. Clinical pregnancy per woman *(Continued)*

2.2 For selected populations						
Johnson 2010 Salpingectomy versus no surgical treatment	189 per 1000	359 per 1000 (258 to 441)	OR 2.2 (1.26 to 3.82)	329 (3 studies)	Moderate	No evidence of blinding in any of the trials. Heterogeneity: I-squared 52%
Johnson 2010 Tubal occlusion versus no surgical treatment	123 per 1000	396 per 1000 (234 to 585)	OR 4.66 (2.17 to 10.01)	209 (2 studies)	Moderate	Randomisation methods not fully described
Johnson 2010 Aspiration of hydro salpingeal fluid versus no surgical treatment	188 per 1000	313 per 1000 (125 to 592)	OR 1.97 (0.62 to 6.29)	64 (1 study)	Very low	Evidence based on a single trial with imprecision
Benschop 2010 Aspiration of endometrioma versus expectant management prior to ART	200 per 1000	244 per 1000 (101 to 476)	Peto OR 1.29 (0.45 to 3.64)	81 (1 study)	Low	Evidence was based on a single trial, wide confidence intervals which cross line of no effect
Benschop 2010 Cystectomy of endometrioma versus expectant management prior to ART	317 per 1000	348 per 1000 (194 to 542)	Peto OR 1.15 (0.52 to 2.55)	109 (1 study)	Low	Evidence was based on a single trial, wide confidence intervals which cross line of no effect
Benschop 2010 GnRH antagonist versus GnRH agonist prior to ART	242 per 1000	206 per 1000 (77 to 448)	Peto OR 0.81 (0.26 to 2.54)	67 (1 study)	Low	Evidence was based on a single trial, wide confidence intervals which cross line of no effect
Benschop 2010 Ablation versus cystectomy prior to ART	366 per 1000	293 per 1000 (126 to 545)	Peto OR 0.72 (0.25 to 2.08)	65 (1 study)	Very low	Unclear risk of bias related to sequence generation. Single small

Table 5. Clinical pregnancy per woman *(Continued)*

						study, wide confidence intervals cross line of no effect
Tso 2014 Metformin versus placebo or no treatment in women with polycystic ovary syndrome	307 per 1000	403 per 1000 (322 to 488)	OR 1.52 (1.07 to 2.15)	775 (8 studies)	Moderate	Imprecision: total number of events is fewer than 300 There was a data discrepancy in one of these studies. Sensitivity analysis excluding this study did not substantially change the findings
McDonnell 2014 Ovarian cyst aspiration prior to in vitro fertilization treatment for subfertility	53 per 1000	72 per 1000 (36 to 140)	OR 1.40 (0.67 to 2.94)	339 (3 studies)	Low	None of the studies described their method of randomisation or allocation concealment Imprecision: Low event rate (n=33)
3. Down-regulation with agonists or antagonists						
Albuquerque 2013 GnRHa depot versus daily injection	30 per 100	29 per 100 (25 to 35)	OR 0.96 (0.75 to 1.23)	1259 (11 studies)	Moderate	Most of the studies were classified as at unclear risk of bias for all domains
Al-Inany 2011 GnRH antagonist versus long course GnRH agonist	315 per 1000	279 per 1000 (257 to 302)	OR 0.84 (0.75 to 0.94)	6571 (41 studies)	Moderate	Lack of detail for some trials on methodological details and a lack of blinding due to the nature of the interventions
Sallam 2006 Ultra-	Not calculated	Not calculated	OR 4.28 (2.00 to 9.15)	149 (3 studies)	Very low	All of the trials were subject

Table 5. Clinical pregnancy per woman *(Continued)*

long GnRH agonist versus conventional stimulation protocols						to methodological limitations, the outcome is an intermediate outcome and there was evidence of lack of precision. Risk of unit of analysis error; review being updated
Maheshwari 2011 Long versus short protocol for pituitary suppression in ART	177 per 1000	244 per 1000 (200 to 293)	OR 1.5 (1.16 to 1.93)	1437 (20 studies)	Low	There were serious methodological limitations associated with many of the included trials
Maheshwari 2011 Long versus ultra-short protocol for pituitary suppression in ART	154 per 1000	220 per 1000 (127 to 354)	OR 1.55 (0.8 to 3.01)	230 (2 studies)	Low	There were serious methodological limitations associated with both trials
4. Ovarian stimulation						
4.1 Medication type						
Gibreel 2012 Clomiphene citrate with gonadotropins (with or without mid-cycle GnRH antagonist) versus gonadotropins with GnRH agonists protocols in IVF and ICSI cycles	238 per 1000	250 per 1000 (210 to 293)	OR 1.07 (0.85 to 1.33)	1864 (10 studies)	Moderate	Method of allocation concealment was either not described or not mentioned at all in some included trials
Mochtar 2007 Recombinant luteiniz-	260 per 1000	300 per 1000 (268 to 335)	OR 1.22 (1.04 to 1.43)	3209 (15 studies)	Moderate	Some of the trials lacked suf-

Table 5. Clinical pregnancy per woman *(Continued)*

ing hormone + recombinant follicle stimulating hormone (rFSH) versus rFSH alone for controlled ovarian hyperstimulation						ficient methodological details
van Wely 2011 rFSH versus urinary gonadotrophins	282 per 1000	280 per 1000 (263 to 299)	OR 0.99 (0.91 to 1.09)	9482 (41 studies)	Moderate	No evidence of blinding conducted in most of the studies
Martins 2013 FSH replaced by low-dose hCG in the late follicular phase versus continued FSH for assisted reproductive techniques	350 per 1000	410 per 1000 (320 to 540)	RR 1.19 (0.92 to 1.55	351 (5 studies)	Low	Imprecision, high risk of bias
Smulders 2010 Combined oral contraceptive plus agonist versus agonist	333 per 1000	373 per 1000 (209 to 571)	OR 1.19 (0.53 to 2.66)	102 (1 study)	Very low	Single study. Wide confidence intervals which cross line of no effect
Smulders 2010 Combined oral contraceptive plus antagonist versus antagonist	255 per 1000	191 per 1000 (146 to 248)	OR 0.69 (0.5 to 0.96)	847 (4 studies)	Low	Imprecision, high risk of bias
Smulders 2010 Combined oral contraceptive plus antagonist versus agonist	245 per 1000	210 per 1000 (147 to 290)	OR 0.82 (0.53 to 1.26)	472 (3 studies)	Low	Imprecision, one study does not describe satisfactory method of sequence generation, one does not describe satisfactory method of allocation con-

Table 5. Clinical pregnancy per woman *(Continued)*

						cealment, one at high risk of attrition bias
4.2. Monitoring						
Kwan 2014 Ultrasound + estradiol versus ultrasound only	337 per 1000	361 per 1000 (287 to 439)	OR 1.05 (0.79 to 1.54)	617 (4 studies)	Low	Methods of allocation concealment inadequately described in the four trials; none of the trials adequately described blinding. Serious imprecision with wide confidence intervals
4.3 Interventions for poor responders						
Pandian 2010 Cessation of GnRHa on stop protocol versus conventional GnRHa long protocol	176 per 1000	138 per 1000 (43 to 370)	OR 0.75 (0.21 to 2.74)	70 (1 study)	Low	Evidence based on a single trial with no blinding
Pandian 2010 GnRH antagonist versus conventional GnRHa long protocol	67 per 1000	167 per 1000 (34 to 529)	OR 2.8 (0.5 to 15.73)	60 (1 study)	Very low	Evidence based on a single trial with lack of methodological detail and evidence of imprecision
Pandian 2010 GnRH a flare up versus GnRHa long protocol	286 per 1000	77 per 1000 (16 to 304)	OR 0.21 (0.04 to 1.09)	54 (1 study)	Very low	Evidence based on a single trial with lack of methodological detail and evidence of imprecision
Pandian 2010 GnRH antagonist versus	163 per 1000	163 per 1000 (62 to 363)	OR 1 (0.34 to 2.92)	98 (2 studies)	Low	Lack of methodological details

Table 5. Clinical pregnancy per woman *(Continued)*

GnRH a flare up protocol						and evidence of imprecision
Pandian 2010 Low dose GnRHa flare up protocol versus spontaneous natural cycle IVF	119 per 1000	101 per 1000 (35 to 252)	OR 0.83 (0.27 to 2.5)	129 (1 study)	Low	Evidence based on a single trial with evidence of imprecision
Pandian 2010 Multiple dose GnRH agonist versus mini dose long agonist protocol	244 per 1000	227 per 1000 (99 to 439)	OR 0.91 (0.34 to 2.42)	89 (1 study)	Low	No allocation concealment or blinding, evidence based on a single trial with evidence of imprecision
Pandian 2010 Flare up protocol versus modified long protocol	381 per 1000	142 per 1000 (36 to 429)	OR 0.27 (0.06 to 1.22)	42 (1 study)	Low	Evidence based on a single trial with evidence of imprecision
Pandian 2010 Long protocol versus modified long protocol	381 per 1000	105 per 1000 (18 to 398)	OR 0.19 (0.03 to 1.06)	40 (1 study)	Low	Evidence based on a single trial with evidence of imprecision
4.4 Natural cycle IVF						
Allersma 2013 Natural cycle versus standard IVF	112 per 1000	86 per 1000 (36 to 194)	OR 0.75 (0.3 to 1.91)	219 (3 studies)	Low	1/3 studies did not report adequate allocation concealment, risk of performance bias, wide confidence intervals
5. Ovulation triggering						
Youssef 2014 GnRH agonist versus HCG	256 per 1000	194 per 1000 (157 to 238)	OR 0.7 (0.54 to 0.91)	1198 (11 studies)	Low	Outcome = ongoing pregnancy rather than clinical pregnancy Substantial heterogeneity: I^2 =

Table 5. Clinical pregnancy per woman *(Continued)*

						59% to 66%. 5/11 studies at high risk of bias because of early termination and/or inadequate allocation concealment. None clearly reported blinded outcome assessment
Youssef 2011 rHCG versus UhCG	312 per 1000	367 per 1000 (312 to 428)	OR 1.28 (1 to 1.65)	1206 (8 studies)	High	Overall well designed trials included
Youssef 2011 rhLH versus uhCG	265 per 1000	251 per 1000 (160 to 370)	OR 0.93 (0.53 to 1.63)	280 (2 studies)	Low	One of the trials lacked adequate methodological details and there was evidence of imprecision
6. Oocyte retrieval						
Kwan 2013 Conscious sedation versus conscious sedation + electro-acupuncture (VAS)	241 per 1000	594 per 1000 (326 to 815)	OR 4.59 (1.52 to 13.87)	61 (1 study)	Very low	One small study
Kwan 2013 Conscious sedation versus conscious sedation + acupuncture (VAS)	241 per 1000	344 per 1000	OR 1.65 (0.54 to 5.05)	61 (1 study)	Very low	One small study
Kwan 2013 Conscious sedation and analgesia versus general anaesthesia	200 per 1000	100 per 1000	OR 1 (0.25 to 4)	50 (1 study)	Very low	One small study
Kwan 2013 Conscious sedation+paracervical block versus	375 per 1000	296 per 1000	OR 0.7 (0.22 to 1.26	51 (1 study)	Very low	One small study

Table 5. Clinical pregnancy per woman *(Continued)*

general anaesthesia						
Kwan 2013 Conscious sedation+paracervical block versus spinal anaesthesia	375 per 1000	358 per 1000	OR 0.93 (0.24 to 3.65)	38 (1 study)	Very low	One small study
Kwan 2013 Conscious sedation + paracervical block versus paracervical block only	253 per 1000	240 per 1000	OR 0.93 (0.44 to 1.96)	150 (1 study)	Very low	One small study
Kwan 2013 Conscious sedation+paracervical block versus electro-acupuncture+paracervical block	367 per 1000	358 per 1000	OR 0.96 (0.72 to 1.29)	783 (4 studies)	High	Adequate methodology, low heterogeneity
Kwan 2013 Conscious sedation and analgesia: pt controlled vs physician controlled	182 per 1000	168 per 1000	OR 0.91 (0.45 to 1.83)	218 (2 studies)	Moderate	Adequate methodology, low heterogeneity, sample size suboptimal
Wongtra-ngan 2010 Follicular flushing versus no flushing	229 per 1000	258 per 1000 (145 to 414)	OR 1.17 (0.57 to 2.38)	164 (3 studies)	Moderate	Trials lacked sufficient methodological details
7. Sperm retrieval						
Proctor 2008 Microsurgical epididymal sperm aspiration versus epididymal micropuncture with perivascular nerve stimulation	233 per 1000	55 per 1000 (12 to 202)	OR 0.19 (0.04 to 0.83)	59 (1 study)	Low	Evidence based on a single trial with insufficient methodological detail

Table 5. Clinical pregnancy per woman *(Continued)*

McDowell 2014 Conventional sperm selection versus hyaluronan sperm selection (HA-ICSI)	470 per 1000	480 per 1000 (390 to 570)	RR 0.99 (0.82 to 1.20)	482 (1 study)	Low	Serious risk of bias: discrepancy in reporting of pregnancy losses Serious imprecision: confidence intervals compatible with substantial benefit or harm from the intervention, or with no effect
McDowell 2014 HA culture dish (PICSI) compared with viscous medium containing HA (SpermSlow) for infertility requiring intracytoplasmic sperm injection	400 per 1000	430 per 1000 (250 to 620)	RR 1.07 (0.67 to 1.71)	99 (1 study)	Low	Serious risk of bias: study methods not reported in adequate detail Serious imprecision: confidence intervals compatible with substantial benefit or harm from the intervention, or with no effect
8. Laboratory phase						
Carney 2012 Assisted hatching versus no assisted hatching	332 per 1000	360 per 1000 (334 to 387)	OR 1.13 (1.01 to 1.27)	5728 (31 studies)	Moderate	There were methodological limitations or missing information in most of the trials
Glujovsky 2014 Vitrification versus slow freezing for women undergoing oocyte cryopreservation	116 per 1000	449 per 1000	RR 3.86 (1.63 to 9.11)	106 (2 studies)	Moderate	Live birth not reported, wide CIs
Van Rumste 2003 Intracytoplasmic sperm injection versus in vitro fertilisa-	252 per 1000	329 per 1000 (242 to 428)	OR 1.45 (0.95 to 2.22)	415 (1 study)	Low	Details of blinding were unclear and the evidence is based on a single trial

Table 5. Clinical pregnancy per woman *(Continued)*

tion						
Bontekoe 2012 Embryo culture with low oxygen concentrations versus atmospheric oxygen concentration	369 per 1000	442 per 1000 (387 to 494)	OR 1.35 (1.08 to 1.67	1382 (4 studies)	Moderate	In one of the trials there was no allocation concealment and in another trial the method of allocation concealment was unclear
Twisk 2006 Preimplantation genetic screening versus no screening in women with advanced age	291 per 1000	187 per 1000 (144 to 235)	OR 0.59 (0.44 to 0.81)	1062 (5 studies)	Moderate	Only one of the studies described an adequate method of allocation concealment
Huang 2013 Brief co-incubation versus standard insemination	177 per 1000	337 per 1000 (238 to 453)	OR 2.36 (1.45 to 3.85)	372 (3 studies)	Low	One trial lacked adequate explanation for methods of randomization. Allocation concealment not mentioned in any trial
Teixeira 2013 Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction	330 per 1000	430 per 1000 (360 to 520)	RR 1.29 (1.06 to 1.55)	2014 (9 studies)	Very low	High risk of bias (differences within studies between number of oocytes transferred), inconsistency across studies, publication bias strongly suspected
Armstrong 2015 TLS with or without cell-tracking algorithms versus conventional incubation for embryo incubation in assisted repro-	558 per 1000	609 per 1000 (548 to 668)	OR 1.23 (0.96 to 1.59)	994 (3 RCTs)	Low	Overall high risk of selection, performance, attrition and reporting bias The largest study used donor and autologous

Table 5. Clinical pregnancy per woman *(Continued)*

duction						oocytes, whereas the remaining two studies used autologous oocytes only. Donor oocytes were generally from young women, which may behave differently to the usual population of oocytes and embryos of couples undergoing ART
9. Embryo transfer						
9.1 Developmental stage						
Glujovsky 2012 Blastocyst stage transfer versus cleavage stage transfer	388 per 1000	420 per 1000 (386 to 456)	OR 1.14 (0.99 to 1.32)	3241 (23 studies)	Moderate	Some methodological details were unclear or inadequate. Significant heterogeneity but I2 < 50% *NB* *Cumulative pregnancy* from fresh and frozen transfers was lower in the blastocyst stage group (0.63, 95% CI 0.44 to 0.90, 4 RCTs, n=527)
9.3 Transfer techniques						
Gunby 2004 Day 2 versus Day 3 embryo transfer	404 per 1000	392 per 1000 (363 to 423)	OR 0.95 (0.84 to 1.08)	3980 (13 studies)	Low	Heterogeneity >60%, lack of details regarding blinding
Bontekoe 2014 Transfer medium en-	350 per 1000	428 per 1000 (394 to 462)	OR 1.39 (1.21 to 1.6)	3542 (14 studies)	Moderate	All studies except one were at high risk of bias

Table 5. Clinical pregnancy per woman *(Continued)*

riched with high level of hyaluronic acid versus medium with low level or no hyaluronic acid						in at least one domain, moderate heterogeneity I^2=46%
Brown 2010 Ultrasound guidance versus clinical touch for embryo transfer	279 per 1000	336 per 1000 (313 to 361)	OR 1.31 (1.18 to 1.46)	6415 (17 studies)	Moderate	Subjects were unable to be blinded but no reporting of blinding of researchers or outcome assessors was reported
Kroon 2012 Antibiotics prior to embryo transfer versus no antibiotics	355 per 1000	359 per 1000 (266 to 465)	1.02 (0.66 to 1.58)	350 (1 study)	Moderate	Imprecise, single study
Derks 2009 Cervical dilatation versus no intervention	232 per 1000	124 per 1000 (78 to 189)	OR 0.47 (0.28 to 0.77)	288 (1 study)	Moderate	Evidence based on a single study
Derks 2009 Straightening the endocervical angle versus no intervention	271 per 1000	267 per 1000 (175 to 384)	OR 0.98 (0.57 to 1.68)	273 (2 studies)	Moderate	Evidence of imprecision
Derks 2009 Removal of cervical mucus versus no intervention	327 per 1000	320 per 1000 (169 to 522)	OR 0.97 (0.42 to 2.25)	97 (1 study)	Low	Lack of methodological details, evidence of imprecision and evidence based on a single trial
Derks 2009 Flushing the endocervical canal versus no intervention	413 per 1000	445 per 1000 9360 to 533)	OR 1.14 (0.8 to 1.62)	537 (3 studies)	Low	Lack of methodological details, heterogeneity >50%
Derks 2009 Flushing the endometrial cavity	519 per 1000	584 per 1000 (437 to 718)	OR 1.3 (0.72 to 2.36)	181 (1 study)	Low	Lack of methodological details,

Table 5. Clinical pregnancy per woman *(Continued)*

versus no intervention						evidence of imprecision and evidence based on a single trial
Abou-Setta 2014 Mechanical pressure versus no intervention	478 per 1000	637 per 1000 (561 to 706)	OR 1.92 (1.4 to 2.63)	639 (1 study)	Very low	Evidence based on a single trial, method of randomisation was unclear and the trial was open label
Abou-Setta 2014 Fibrin sealant versus no intervention	291 per 1000	287 per 1000 (181 to 422)	OR 0.98 (0.54 to 1.78)	211 (1 study)	Low	Evidence based on a single trial with inadequate allocation concealment
Abou-Setta 2014 More bed rest versus less bed rest	302 per 1000	276 per 1000 (206 to 362)	OR 0.88 (0.6 to 1.31	542 (2 studies)	Moderate	One of the trials was open label
10. Luteal phase support						
van der Linden 2015 hCG versus placebo/no treatment	197 per 1000	242 per 1000 (181 to 316)	OR 1.3 (0.9 to 1.88)	746 (5 studies)	Very low	Poor reporting of study methods, very serious imprecision
van der Linden 2015 Progesterone versus placebo/no treatment	140 per 1000	236 per 1000 (175 to 310)	OR 1.89 (1.3 to 2.75)	841 (7 studies)	Low	Poor reporting of study methods, very serious imprecision
van der Linden 2015 Progesterone versus hCG regimens	284 per 1000	300 per 1000 (263 to 340)	OR 1.08 (0.9 to 1.3)	2355 (16 studies)	Moderate	Poor reporting of study methods
van der Linden 2015 Progesterone versus progesterone	433 per 1000	391 per 1000 (355 to 443)	OR 0.86 (0.72 to 1.04)	2169 (14 studies)	Low	Poor reporting of study methods, serious inconsistency

Table 5. Clinical pregnancy per woman *(Continued)*

+ oestrogen						
van der Linden 2015 Progesterone versus progesterone + GnRH agonist	424 per 1000	327 per 1000 (273 to 384)	OR 0.66 (0.51 to 0.85)	2435 (8 studies)	Low	Poor reporting of study methods, serious inconsistency
Boomsma 2012 Peri-implantation glucocorticoids versus no glucocorticoids	290 per 1000	320 per 1000 (275 to 369)	OR 1.15 (0.93 to 1.43)	1759 (13 studies)	Moderate	Most of the studies lacked adequate blinding
Akhtar 2013 Heparin versus placebo or no treatment	250 per 1000	271 per 1000 (256 to 458)	OR 1.61 (1.03 to 2.53)	386 (3 studies)	Low	Imprecise, sensitive to choice of statistical model: estimate using random effects model: OR 1.66, 95% CI 0.94 to 2.90
11. Prevention of ovarian hyperstimulation syndrome (OHSS)						
D'Angelo 2007 Cryopreservation versus fresh embryo transfer	463 per 1000	482 per 1000 (318 to 654)	OR 1.08 (0.54 to 2.19)	125 (1 study)	Low	Evidence based on a single open label study with insufficient methodological details provided. Evidence of imprecision
D'Angelo 2007 Cryopreservation versus intravenous albumin	385 per 1000	36 per 1000 (0 to 423)	OR 0.06 (0 to 1.17)	26 (1 study)	Low	Evidence based on a single, open label trial with evidence of imprecision
Youssef 2011a Intravenous human albumin versus no treatment or placebo	71 per 1000	64 per 1000 (43 to 95)	OR 0.89 (0.58 to 1.37)	1354 (6 studies)	Low	Insufficient methodological details provided and evidence of imprecision

Table 5. Clinical pregnancy per woman *(Continued)*

Youssef 2011a Intravenous hydroxyethyl starch versus placebo	120 per 1000	141 per 1000 (63 to 286)	OR 1.2 (0.49 to 2.93)	168 (1 RCT)	Very low	Very serious imprecision with low event rate, poor reporting of methods
D'Angelo 2011 Coasting versus no coasting	353 per 1000	234 per 1000 (98 to 471)	OR 0.56 (0.2 to 1.63)	68 (1 study)	Very low	Evidence based on a single trial. Insufficient methodological details provided and evidence of imprecision
Tang 2012 Cabergoline versus placebo/no treatment	429 per 1000	403 per 1000 (240 to 682)	OR 0.94 (0.56 to 1.59)	230 (2 studies)	Low	Allocation concealment inadequately reported in both trials. One trial provided insufficient details on blinding both trials had issues for incomplete outcome data reporting
12. Frozen embryo replacement cycles						
Ghobara 2008 Oestrogen + progesterone frozen thawed embryo transfer (FET) versus natural cycle FET	205 per 1000	214 per 1000 (93 to 419)	OR 1.06 (0.4 to 2.8)	100 (1 study)	Very low	Evidence based on a single trial, insufficient methodological details provided, open label and evidence of imprecision
Ghobara 2008 Oestrogen + progesterone frozen thawed embryo transfer (FET) versus GnRHa, oestrogen and progesterone preparations FET	215 per 1000	173 per 1000 (125 to 232)	OR 0.76 (0.52 to 1.1)	725 (4 studies)	Low	Heterogeneity >50%, included open label trials, some of the trials failed to provide adequate methodological details

Table 5. Clinical pregnancy per woman *(Continued)*

Ghobara 2008 Oestrogen + progesterone frozen thawed embryo transfer (FET) versus FSH ovulation induction FET	128 per 1000	109 per 1000 949 to 228)	OR 0.84 (0.35 to 2.02)	194 (1 study)	Very low	Evidence based on a single trial, there were insufficient methodological details provided and the trial was open label. There was also evidence of imprecision
Ghobara 2008 Clomiphene frozen thawed embryo transfer (FET) versus oestrogen and progesterone FET	96 per 1000	75 per 1000 (22 to 228)	OR 0.76 (0.21 to 2.77)	119 (1 study)	Very low	Evidence based on a single trial, there were insufficient methodological details provided. There was also evidence of imprecision
Ghobara 2008 Clomiphene frozen thawed embryo transfer (FET) versus GnRHa + oestrogen and progesterone FET	162 per 1000	75 per 1000 (23 to 221)	OR 0.42 (0.12 to 1.47)	104 (1 study)	Very low	Evidence based on a single trial, there were insufficient methodological details provided. There was also evidence of imprecision
Ghobara 2008 Clomiphene + HMG frozen thawed embryo transfer (FET) versus HMG FET	275 per 1000	148 per 1000	OR 0.46 (0.23 to 0.92)	209 (1 study)	Low	Evidence based on a single trial, there were insufficient methodological details provided
Glujovsky 2010 GnRH agonists versus control for endometrial preparation for embryo transfer with frozen embryos or donor oocytes	215 per 1000	246 per 1000 (167 to 347)	OR 1.19 (0.73 to 1.94)	778 (5 studies)	Moderate	All of the trials were open label and there was insufficient methodological details in many of the studies

Table 5. Clinical pregnancy per woman *(Continued)*

Glujovsky 2010 Intramuscular progesterone versus vaginal progesterone for endometrial preparation for embryo transfer with frozen embryos or donor oocytes	282 per 1000	361 per 1000 (278 to 452)	OR 1.44 (0.98 to 2.1)	655 (4 studies)	Moderate	All of the trials were open label and there was insufficient methodological details in many of the studies. Wide confidence interval crosses the line of no effect

Table 6. OHSS per woman

Outcome Intervention and comparison intervention	Assumed risk with Comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (Studies)	Quality of the evidence (GRADE)	Comments
1. Indication for ART						
Pandian 2012 IVF versus intrauterine insemination + ovarian stimulation for unexplained subfertility (treatment naïve women	34 per 1000	51 per 1000 (9 to 250)	OR 1.53 (0.25 to 9.49)	118 (1 study)	Low	Evidence lacked precision and there was a inadequate explanation of blinding
2. Pre-ART and adjuvant strategies						
Tso 2014 Metformin versus placebo or no treatment	270 per 1000	97 per 1000 (62 to 153)	OR 0.29 (0.18 to 0.49)	798 (8 studies)	Moderate	Imprecision: total number of events is fewer than 300
3. Down-regulation with agonists or antagonists						
Albuquerque 2013 GnRHa depot versus daily injection	3 per 100	2 per 100 (1 to 6)	OR 0.84 (0.29 to 2.42)	570 (5 studies)	Low	Most of the studies were classified as at unclear risk of bias for all domains. The total num-

Table 6. OHSS per woman (*Continued*)

						ber of events was fewer than 300. There were insufficient studies to assess publication bias.
Al-Inany 2011 GnRH antagonist versus long course GnRH agonist	66 per 1000	30 per 1000 (23 to 39)	OR 0.43 (0.33 to 0.57)	5417 (29 studies)	Low	Methodological limitations including lack of blinding and heterogeneity was 68%
Al-Inany 2011 rhCG versus uhCG	27 per 1000	40 per 1000 (169 to 331)	OR 0.39 (0.25 to 0.61)	374 (3 studies)	Moderate	One of the trials lacked methodological details on randomisation, allocation concealment and blinding
Al-Inany 2011 rhLH versus uhCG	125 per 1000	105 per 1000 (53 to 194)	OR 0.82 (0.39 to 1.69)	280 (2 studies)	Low	One of the trials lacked adequate methodological details and there was evidence of imprecision
Boomsma 2012 Peri-implantation glucocorticoids versus no glucocorticoids	194 per 1000	159 per 1000 (64 to 392)	OR 0.82 (0.33 to 2.02)	151 (2 studies)	Low	Methodological limitations and evidence of imprecision
4. Ovarian stimulation						
4.1 Medication type						
Gibreel 2012 Clomiphene citrate with gonadotropins (with or without mid-cycle GnRH antagonist) versus gonadotropins with GnRH ago-	50 per 1000	12 per 1000 (5 to 27)	OR 0.23 (0.1 to 0.52)	1559 (5 studies)	Low	Few participants. Small number of events in outcome. Very wide 95% confidence interval crossing the thresh-

Table 6. OHSS per woman (*Continued*)

nists protocols in IVF and ICSI cycles						old points of appreciable benefit or harm, which is 25%
Pouwer 2015 Long acting FSH (low dose) versus daily FSH	47 per 1000	57 per 1000 (26 to 125)	RR 1.22 (0.56 to 2.66)	645 (3 studies)	Moderate	Serious imprecision. Low events
Pouwer 2015 Long acting FSH (medium dose) versus daily FSH	63 per 1000	60 per 1000 (45 to 85)	RR 0.96 (0.68 to 1.35)	3075 (5 studies)	Low	Imprecision: confidence intervals compatible with clinically meaningful benefit in either arm or with no effect, plus high risk of attrition bias in two studies. Low events
Pouwer 2015 Long acting FSH (high dose) versus daily FSH	0 per 1000	0 per 1000 (0 to 0)	RR 1.73 (0.09 to 32.75)	33 (1 study)	Very low	Serious imprecision due to very low event rate, plus a high risk of attrition bias
Mochtar 2007 Recombinant luteinizing hormone + recombinant follicle stimulating hormone (rFSH) versus rFSH alone for controlled ovarian hyperstimulation	20 per 1000	27 per 1000 (12 to 59)	OR 1.34 (0.58 to 3.09)	986 (7 studies)	Low	Some methodological details were unclear and there is evidence of imprecision
Martins 2013 FSH replaced by low-dose hCG in the late follicular phase versus continued FSH for assisted reproductive techniques	3 per 100	1 per 100 (0 to 4)	OR 0.30 (0.06 to1.59)	351 (5 studies)	Very low	Very serious imprecision, inconsistency, high risk of bias

Table 6. OHSS per woman (*Continued*)

Smulders 2010 Combined oral contraceptive pill plus antagonist versus antagonist	17 per 1000	25 per 1000 (5 to 133)	OR 1.5 (0.26 to 8.8)	234 (1 study)	very low	Single study. Wide confidence intervals which cross line of no effect. High risk of attrition bias
Smulders 2010 Combined oral contraceptive pill plus antagonist versus agonist	55 per 1000	35 per 1000 (12 to 100)	OR 0.63 (0.21 to 1.92)	290 (2 studies)	very low	Single study. Wide confidence intervals which cross line of no effect. One study has high risk of attrition bias
4.2 Monitoring						
Kwan 2014 Ultrasound + estradiol versus ultrasound only	36 per 1000	36 per 1000 (18 to 75)	OR 1.03 (0.48 to 2.20)	781 (6 studies)	Low	Methods of randomisation inadequately described in three of the six trials, allocation concealment inadequately described in all the six trials and blinding inadequately described in five of the six trials No definition of OHSS provided by authors of these 6 studies Serious imprecision with wide confidence intervals
4.4 Natural cycle IVF						
Allersma 2013 Natural cycle versus stan-	67 per 1000	13 per 1000 (1 to 393)	OR 0.10 (0.01 to 4.06)	60 (1 study)	Very low	Allocation concealment method not re-

Table 6. OHSS per woman (*Continued*)

dard IVF						ported, very serious imprecision
5. Ovulation triggering						
Youssef 2014 GnRH agonist versus HCG	5 per 1000	1 per 1000 (0 to 2)	OR 0.15 (0.05 to 0.47)	989 (8 studies)	Moderate	All studies at high risk of bias in 1 or more domains. None clearly reported blinded outcome assessment
Wongtra-ngan 2010 rFSH versus urinary gonadotrophins	19 per 1000	22 per 1000 (16 to 30)	OR 1.18 (0.86 to 1.61)	7740 (32 studies)	High	There was a lack of blinding
Youssef 2011 rhCG versus uhCG	27 per 1000	40 per 1000 (169 to 331)	OR 0.39 (0.25 to 0.61)	374 (3 studies)	Moderate	One of the trials lacked methodological details on randomisation, allocation concealment and blinding
Youssef 2011 rhLH versus uhCG	125 per 1000	105 per 1000 (53 to 194)	OR 0.82 (0.39 to 1.69)	280 (2 studies)	Low	One of the trials lacked adequate methodological details and there was evidence of imprecision
10. Luteal phase support						
van der Linden 2015 hCG versus placebo/no treatment	41 per 1000	155 per 1000 (76 to 292)	OR 4.28 (1.91 to 9.6)	387 (1 study)	Low	Poor reporting of study methods, serious imprecision with low event rate
van der Linden 2015 Progesterone versus hCG regimens	126 per 1000	72 per 1000 (31 to 162)	OR 0.54 (0.22 to 1.34)	615 (4 studies)	Low	Poor reporting of study methods, serious imprecision

Table 6. OHSS per woman (*Continued*)

van der Linden 2015 Progesterone compared with progesterone + oestrogen	39 per 1000	22 per 1000 (8 to 62)	OR 0.56 (0.2 to 1.63)	461 (2 studies)	Low	Poor reporting of study methods, serious imprecision
van der Linden 2015 Progesterone compared with progesterone + GnRH agonist	50 per 1000	50 per 1000 (17 to 137)	OR 1.00 (0.33 to 3.01)	300 (1 study)	Very low	Poor reporting of study methods, very serious imprecision
Akhtar 2013 Heparin versus placebo or no treatment	250 per 1000	349 per 1000 (256 to 458)	OR 1.61 (1.03 to 2.53)	386 (3 studies)	Very low	Selection Bias found in one study. High Heterogeneity. Results sensitive to choice of statistical model
11. Prevention of ovarian hyperstimulation syndrome (OHSS)						
Tang 2012 Cabergoline versus placebo/no treatment	312 per 1000	125 per 1000 (62 to 240)	OR 0.40 (0.20 to 0.77)	230 (2 studies)	Low	Lack of details for allocation concealment
D'Angelo 2007 Cryopreservation versus fresh embryo transfer	60 per 1000	8 per 1000 (1 to 128)	OR 1.12 (0.01 to 2.29)	125 (1 study)	Low	Evidence based on a single open label study with insufficient methodological details provided. Evidence of imprecision
D'Angelo 2007 Cryopreservation versus intravenous albumin	77 per 1000	308 per 1000 (41 to 824)	OR 5.33 (0.51 to 56.24)	26 (1 study)	Very low	Evidence based on a single, open label trial with evidence of imprecision
Youssef 2011a Intravenous human albumin	86 per 1000	63 per 1000 (43 to 92)	OR 0.71 (0.47 to 1.07)	1452 (7 studies)	Very low	Outcome is severe OHSS.

Table 6. OHSS per woman (*Continued*)

versus no treatment or placebo						Most studies unblinded. Insufficient methodological details provided. Heterogeneity was 55% (I^2)
Youssef 2011a Intravenous hydroxyethyl starch versus placebo	37 per 1000	5 per 1000 (1 to 28)	OR 0.13 (0.02 to 0.75)	272 (2 studies)	Very low	Outcome is severe OHSS. Studies unblinded. Serious imprecision: findings sensitive to choice of effect estimate, and benefit from HES was no longer evident when a Mantel-Haenszel risk ratio was calculated (RR 0.17, 95% CI 0.02 to 1.39)
D'Angelo 2011 Coasting versus no coasting	265 per 1000	58 per 1000 (11 to 241)	OR 0.17 (0.03 to 0.88)	68 (1 study)	Very low	Evidence is based on a single conference abstract. There are insufficient methodological details provided and there is evidence of imprecision

Table 7. Multiple pregnancy per woman

Outcome Intervention and comparison intervention	Assumed risk with Comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (Studies)	Quality of the evidence (GRADE)	Comments
1. Indication for ART						
Pandian 2012 IVF versus intrauterine insemi-	131 per 1000	88 per 1000 (45 to 163)	OR 0.64 (0.31 to 1.29)	351 (3 studies)	Moderate	The trials lacked ad-

Table 7. Multiple pregnancy per woman (*Continued*)

nation + ovarian stimulation for unexplained subfertility (treatment naïve women)						equate methodological details
2. Pre-ART and adjuvant strategies						
Siristatidis 2011 Aspirin versus placebo or no treatment	59 per 1000	50 per 1000 (27 to 91)	RR 0.74 (0.38 to 1.46)	680 (2 studies)	Moderate	There were some methodological limitations in the two trials
Duffy 2010 Growth hormone compared with placebo	195 per 1000	131 per 1000 (42 to 342)	OR 0.62 (0.18 to 2.15)	80 (2 studies)	Moderate	Some evidence of lack of precision
Cheong 2013 Acupuncture versus no acupuncture on or around the day of embryo transfer	56 per 1000	72 per 1000 (42 to 122)	OR 1.32 (0.74 to 2.35)	795 (2 studies)	Low	Only 1/2 studies described adequate allocation concealment, wide confidence intervals crossed line of no effect
Nastri 2015 Endometrial injury prior to ovulation induction (pipelle induced) versus no endometrial injury	278 per 1000	251 per 1000 (81 to 559)	OR 0.87 (0.23 to 3.3)	46 (1 study)	Very low	Evidence based on a single trial with imprecision
Gutarra-Vilchez 2014 Vasodilator compared with placebo	89 per 1000	79 per 1000 (35 to 180)	RR 0.89 (0.39 to 2.03)	250 (2 studies)	Moderate	Studies had low or unclear risk of bias but serious imprecision
3. Down-regulation with agonists or antagonists						
Albuquerque 2013 GnRHa depot versus daily injection	24 per 100	25 per 100 (13 to 43)	OR 1.1 (0.49 to 2.46)	132 (4 studies)	Low	Most of the studies were classified as at unclear risk of bias for all domains.

Table 7. Multiple pregnancy per woman (*Continued*)

						The total number of events was fewer than 300. There were insufficient studies to assess publication bias.
Boomsma 2012 Peri-implantation glucocorticoids versus no glucocorticoids	38 per 1000	74 per 1000 (31 to 168)	OR 2.02 (0.8 to 5.11)	372 (4 studies)	Moderate	Lacked methodological details
4. Ovarian stimulation						
4.1 Medication type						
Gibreel 2012 Clomiphene citrate (± urinary or recombinant gonadotrophin) versus urinary or recombinant gonadotrophin in either long or short protocols	233 per 1000	211 per 1000 (109 to 372)	OR 0.88 (0.4 to 1.95)	160 (4 studies)	Moderate	The studies lacked methodological details
Smulders 2010 Combined oral contraceptive pill plus antagonist versus antagonist	42 per 1000	92 per 1000 (10 to 507)	OR 2.32 (0.23 to 23.65)	45 (1 study)	Very low	Imprecision, high risk of attrition bias
Smulders 2010 Combined oral contraceptive pill plus antagonist versus agonist	67 per 1000	68 per 1000 (26 to 168)	OR 1.02 (0.37 to 2.82)	238 (2 studies)	Low	Imprecision
4.4 Natural cycle IVF						
Allersma 2013 Natural cycle versus standard IVF	29 per 1000	6 per 1000 (0 to 117)	OR 0.21 (0.01 to 4.38)	132 (1 study)	Very low	Method of sequence generation and allocation conceal-

Table 7. Multiple pregnancy per woman (*Continued*)

						ment not stated, high risk of attrition bias, very serious imprecision
5. Ovulation triggering						
Youssef 2014 GnRH agonist versus HCG	82 per 1000	134 per 1000 (71 to 238)	OR 1.74 (0.86 to 3.5)	342 (3 studies)	Moderate	No evidence of blinding in many of the trials
van Wely 2011 rFSH versus urinary gonadotrophins	85 per 1000	78 per 1000 (66 to 92)	OR 0.91 (0.76 to 1.09)	6329 (25 studies)	Moderate	No evidence of blinding in many of the trials
8. Laboratory phase						
Twisk 2006 Preimplantation genetic screening versus no screening in women with advanced age	200 per 1000	206 per 1000 (113 to 347)	OR 1.04 (0.51 to 2.13)	199 (4 studies)	Low	There were methodological limitations that were not adequately explained and evidence of imprecision
Carney 2012 Assisted hatching versus no assisted hatching	102 per 1000	136 per 1000 (112 to 162)	OR 1.38 (1.11 to 1.7)	3447 (14 studies)	Low	There were methodological limitations or missing information in most trials There was inconsistency between the trials (I square statistic was 57%)
Bontekoe 2012 Embryo culture with low oxygen concentration versus atmospheric oxygen concentration	88 per 1000	113 per 1000 (80 to 158)	OR 1.33 (0.91 to 1.95)	1382 (4 studies)	Low	There were methodological limitations that were not adequately explained and evidence of imprecision

Table 7. Multiple pregnancy per woman (*Continued*)

9. Embryo transfer						
9.1 Developmental stage						
Glujovsky 2012 Cleavage stage transfer versus blastocyst stage transfer	109 per 1000	101 per 1000 (80 to 127)	OR 0.92 (0.71 to 1.19)	2481 (16 studies)	Moderate	Some methodological details were unclear or inadequate
9.2 Number of embryos						
Pandian 2013 Single versus double embryo transfer (one cycle only)	144 per 1000	20 per 1000 (12 to 32)	OR 0.12 (0.07 to 0.20)	1612 (10 studies)	High	Moderate heterogeneity attributable to 36% of women noncompliant with treatment allocation in one study (I^2 = 45%)
Pandian 2013 Repeated single embryo transfer versus double embryo transfer	133 per 1000	5 per 1000 (2 to 19)	OR 0.03 (0.01 to 0.13)	811 (3 studies)	Moderate	Methods poorly described
Pandian 2013 Double embryo transfer versus three embryo transfers	91 per 1000	17 per 1000 (1 to 278)	OR 0.17 (0.01 to 3.85)	45 (1 study)	Very low	Randomisation and blinding were unclear, evidence is based on a single trial with evidence of imprecision
Pandian 2013 Double embryo transfer versus four embryo transfers	214 per 1000	107 per 1000 (27 to 349)	OR 0.44 (0.1 to 1.97)	56 (1 study)	Very low	Randomisation, allocation concealment and blinding were unclear, evidence is based on a single trial with evidence of imprecision
9.3 Transfer techniques						

Table 7. Multiple pregnancy per woman (*Continued*)

Gunby 2004 Day 3 versus Day 2 embryo transfer	136 per 1000	138 per 1000 9114 to 166)	OR 1.02 (0.82 to 1.27)	2780 (8 studies)	Moderate	Trials lacked details on blinding
Bontekoe 2014 Transfer medium enriched with high level of hyaluronic acid versus medium with low level or no hyaluronic acid	20 per 1000	37 per 1000 (240 to 328)	OR 1.86 (1.49 to 2.31)	1951 (5 studies)	Moderate	All studies except one at high risk of bias in one or more domains
Brown 2010 Ultrasound guidance versus clinical touch for embryo transfer	63 per 1000	79 per 1000 (59 to 105)	OR 1.27 (0.93 to 1.75)	2346 (6 studies)	Low	Studies were open label and heterogeneity >60%
Abou-Setta 2014 Less bed rest versus more bed rest	73 per 1000	113 per 1000 (25 to 383)	OR 1.62 (0.33 to 7.9)	542 (2 studies)	Very low	Heterogeneity >70%, wide confidence intervals indicating imprecision, one trial was open
Abou-Setta 2014 Mechanical pressure on cervix versus no intervention	121 per 1000	243 per 1000 (174 to 329)	OR 2.33 (1.53 to 3.56)	639 (1 study)	Very low	Evidence based on a single trial, trial was open label and method of randomisation was unclear
12. Frozen embryo replacement cycles						
Ghobara 2008 Oestrogen + progesterone frozen thawed embryo transfer (FET) versus natural cycle FET	0 per 1000	0 per 1000	OR 2.48 (0.09 to 68.14)	21 (1 study)	Very low	Evidence based on a single trial, evidence of imprecision, very small sample size, open label and insufficient methodological details provided

Table 7. Multiple pregnancy per woman (*Continued*)

Ghobara 2008 Clomiphene + HMG frozen thawed embryo transfer (FET) versus HMG FET	143 per 1000	187 per 1000 (43 to 544)	OR 1.38 (0.27 to 7.15)	44 (1 study)	Very low	Evidence based on a single trial, evidence of imprecision, very small sample size, open label and insufficient methodological details provided
Glujovsky 2010 Intramuscular progesterone versus vaginal progesterone for endometrial preparation for embryo transfer with frozen embryos or donor oocytes	422 per 1000	414 per 1000 (271 to 574)	OR 0.97 (0.51 to 1.85)	153 (1 study)	Very low	Evidence based on a single trial, evidence of imprecision, open label and insufficient methodological details provided

Table 8. Miscarriage per woman

Outcome Intervention and comparison intervention	Assumed risk with Comparator	Corresponding risk with intervention	Relative effect (95%CI)	Number of participants (Studies)	Quality of the evidence (GRADE)	Comments
2. Pre-ART strategies						
Cheong 2013 Acupuncture versus no acupuncture on or around the day of embryo transfer	207 per 1000	233 per 1000 (160 to 303)	OR 1.1 (0.73 to 1.67)	616 (6 studies)	Low	Only 2/6 studies described adequate allocation concealment, imprecision
Cheong 2013 Acupuncture versus no acupuncture around the time of oocyte retrieval	242 per 1000	201 per 1000 (118 to 319)	OR 0.79 (0.42 to 1.47)	262 (4 studies)	Low	Only 1/4 studies described adequate allocation concealment, imprecision

Table 8. Miscarriage per woman (*Continued*)

Siristatidis 2011 Aspirin versus placebo or no treatment	41 per 1000	47 per 1000 (30 to 75)	RR 1.10 (0.68 to 1.77)	1497 (5 studies)	Moderate	There were some methodological limitations in some of the trials
Tso 2014 Metformin versus placebo or no treatment	139 per 1000	110 per 1000 (65 to 182)	OR 0.76 (0.43 to 1.37)	521 (6 studies)	Moderate	Imprecision: total number of events low
Nastri 2015 Endometrial injury performed between day 7 of the previous cycle and day 7 of the ET cycle vs no control	158 per 1000	147 per 1000 (100 to 242)	RR 0.99 (0.63 to 1.53)	500 (8 studies)	Low	Serious imprecision and high risk of bias in included studies
Benschop 2010 Aspiration of endometrioma versus expectant management	100 per 1000	97 per 1000 (25 to 316)	Peto OR 0.97 (0.23 to 4.15)	81 (1 study)	Very low	Evidence was based on a single trial, wide confidence intervals which cross line of no effect
Benschop 2010 GnRH antagonist versus GnRH agonist	30 per 1000	29 per 1000 (2 to 331)	Peto OR 0.97 (0.06 to 15.85)	67 (1 study)	Very low	Evidence was based on a single trial, wide confidence intervals which cross line of no effect
Johnson 2010 Salpingectomy versus no surgical treatment	53 per 1000	46 per 1000 (17 to 117)	OR 0.86 (0.31 to 2.38)	329 (3 studies)	Moderate	Randomisation methods not fully described. Imprecision: wide confidence intervals which cross line of no effect
Johnson 2010 Tubal occlusion versus no surgical treatment	67 per 1000	60 per 1000 (6 to 399)	OR 0.89 (0.09 to 9.28)	65 (1 study)	Very low	Evidence based on a single trial. Evidence of imprecision: wide confidence intervals which cross line of no effect

Table 8. Miscarriage per woman (*Continued*)

Johnson 2010 Aspiration of hydro salpingeal fluid versus no surgical treatment	31 per 1000	63 per 1000 (6 to 436)	OR 2.07 (0.18 to 24.01)	64 (1 study)	Very low	Evidence based on a single trial. Evidence of imprecision: wide confidence intervals which cross line of no effect
Gutarra-Vilchez 2014 Vasodilator compared with placebo	69 per 1000	58 per 1000 (26 to 132)	RR 0.84 (0.37 to 1.91)	350 (3 studies)	Moderate	Studies had low or unclear risk of bias but serious imprecision
3. Down-regulation with agonists or antagonists						
Albuquerque 2013 GnRHa depot versus daily injection	13 per 100	14 per 100 (9 to 22)	OR 1.16 (0.7 to 1.94)	512 (9 studies)	Low	Most of the studies were classified as at unclear risk of bias for all domains. The total number of events was fewer than 300. There were insufficient studies to assess publication bias
Al-Inany 2011 GnRH antagonist versus long course GnRH agonist	118 per 1000	113 per 1000 (85 to 149)	OR 0.96 (0.7 to 1.31)	1647 (27 studies)	Low	Methodological limitations including lack of blinding and there was also evidence of imprecision
Boomsma 2012 Peri-implantation glucocorticoids versus no glucocorticoids	57 per 1000	80 per 1000 (47 to 132)	OR 1.44 (0.82 to 2.51)	832 (7 studies)	Low	Methodological limitations including lack of blinding and there was also evidence of imprecision
4. Ovarian stimulation						
4.1 Type of medication						

Table 8. Miscarriage per woman (*Continued*)

Pandian 2010 Multiple dose GnRH agonist versus mini dose long agonist protocol	22 per 1000	46 per 1000 (4 to 353)	OR 2.1 (0.18 to 23.98)	89 (1 study)	Very low	Single trial with no allocation concealment or blinding and evidence of imprecision
Gibreel 2012 Clomiphene citrate (+/- urinary or recombinant gonadotrophin) versus urinary or recombinant gonadotrophin in either long or short protocols	184 per 1000	199 per 1000 (107 to 337)	OR 1.1 (0.53 to 2.25)	201 (4 studies)	Moderate	Most of the included trials lacked adequate methodological details
Gibreel 2012 Clomiphene citrate (+/- urinary or recombinant gonadotrophin) and mid cycle antagonists versus urinary or recombinant gonadotrophin in either long or short protocols	155 per 1000	115 per 1000 (44 to 268)	OR 0.71 (0.25 to 1.99)	125 (3 studies)	Moderate	Most of the included trials lacked adequate methodological details
Mochtar 2007 Recombinant luteinizing hormone + recombinant follicle stimulating hormone (rFSH) versus rFSH alone for controlled ovarian hyperstimulation	66 per 1000	53 per 1000 (35 to 81)	OR 0.8 (0.51 to 1.26)	1330 (11 studies)	Moderate	Some methodological details were unclear
Martins 2013 FSH replaced by low-dose hCG in the late follicular phase versus	160 per 1000	170 per 1000 (80 to 360)	RR 1.08 (0.50 to 2.31)	127 (4 studies)	Very low	Very serious imprecision, high risk of bias

Table 8. Miscarriage per woman (*Continued*)

continued FSH for assisted reproductive techniques						
Smulders 2010 Combined oral contraceptive pill plus antagonist versus antagonist	68 per 1000	84 per 1000 (52 to 134)	OR 1.26 (0.76 to 2.12)	847 (4 studies)	Low	Imprecision, insufficient reporting of randomisation methods
Smulders 2010 Combined oral contraceptive pill plus antagonist versus agonist	80 per 1000	43 per 1000 (20 to 87)	OR 0.52 (0.24 to 1.1)	472 (3 studies)	Low	Imprecision, insufficient reporting of randomisation methods
5. Ovulation triggering						
Youssef 2014 GnRH agonist versus HCG	67 per 1000	111 per 1000 (73 to 165)	OR 1.74 (1.10 to 2.75)	1198 (11 studies)	Moderate	5/11 studies at high risk of bias because of early termination and/or inadequate allocation concealment. None clearly reported blinded outcome assessment
van Wely 2011 rFSH versus urinary gonadotrophins	50 per 1000	57 per 1000 (46 to 70)	OR 1.16 (0.93 to 1.44)	6663 (30 studies)	Moderate	No evidence of blinding in many of the trials
Youssef 2011 rhCG versus uhCG	63 per 1000	44 per 1000 (27 to 74)	OR 0.69 (0.41 to 1.18)	1106 (7 studies)	Moderate	Some methodological detail was lacking in some of the trials
Youssef 2011 rhLH versus uhCG	66 per 1000	62 per 1000 (25 to 144)	OR 0.94 (0.37 to 2.38)	280 (2 studies)	Low	One of the trials lacked adequate methodological details and there was evidence of

Table 8. Miscarriage per woman (*Continued*)

						imprecision
7. Sperm selection						
McDowell 2014 HA culture dish (PICSI) compared with viscous medium containing HA (SpermSlow) for infertility requiring intracytoplasmic sperm injection	250 per 1000-	190 per 1000 (50 to 510)	RR 0.76 (0.24 to 2.44)	41 pregnancies (1 study)	Low	Serious risk of bias: study methods not reported in adequate detail Serious imprecision: confidence intervals compatible with substantial benefit or harm from the intervention, or with no effect
8. Laboratory phase						
Bontekoe 2012 Embryo culture with low oxygen concentration versus atmospheric oxygen concentration	75 per 1000	94 per 1000 (65 to 133)	OR 1.28 (0.86 to 1.9)	1291 (3 studies)	Low	There were methodological limitations and evidence of imprecision
Carney 2012 Assisted hatching versus no assisted hatching	45 per 1000	46 per 1000 (32 to 68)	OR 1.03 (0.69 to 1.54)	2131 (14 studies)	Moderate	There were methodological limitations or missing information in most of the trials
Twisk 2006 Preimplantation genetic screening versus no screening in women with advanced age	122 per 1000	108 per 1000 (76 to 150)	OR 0.87 (0.59 to 1.27)	1062 (5 studies)	Moderate	Most of the included trials lacked adequate methodological details
Twisk 2006 Preimplantation genetic screening versus no screening in women	89 per 1000	103 per 1000 (54 to 183)	OR 1.17 (0.59 to 2.3)	388 (3 studies)	Very low	Open label studies with evidence of imprecision. Heterogeneity was >60%

Table 8. Miscarriage per woman (*Continued*)

with good prognosis						
Huang 2013 Brief co-incubation versus standard insemination	24 per 1000	47 per 1000 (9 to 217)	OR 1.98 (0.35 to 11.09)	167 (1 study)	Low	One trial only and method of randomization or allocation concealment not stated
Teixeira 2013 Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction	220 per 1000	180 per 1000 (130 to 250)	RR 0.82 (0.59 to 1.14)	552 (6 studies)	Very low	High risk of bias, very serious imprecision
Armstrong 2015 TLS with or without cell-tracking algorithms versus conventional incubation	143 per 1000	105 per 1000 (73 to 143)	OR 0.7 (0.47 to 1.04)	994 (3 RCTs)	Low	Overall high risk of selection, performance, attrition and reporting bias The largest study used donor and autologous oocytes, whereas the remaining two studies used autologous oocytes only. Donor oocytes were generally from young women, which may behave differently to the usual population of oocytes and embryos of couples undergoing ART
9. Embryo transfer						
Glujovsky 2012 Cleavage stage transfer versus blastocyst	80 per 1000	91 per 1000 (68 to 119)	OR 1.14 (0.84 to 1.55)	2127 (14 studies)	Moderate	Some methodological details were unclear

Table 8. Miscarriage per woman (*Continued*)

stage transfer						or inadequate
Gunby 2004 Day 3 versus Day 2 embryo transfer	63 per 1000	66 per 1000 (49 to 89)	OR 1.05 (0.76 to 1.44)	2452 (9 studies)	Low	Evidence of imprecision and lack of details about blinding
Brown 2010 Ultrasound guidance versus clinical touch for embryo transfer	40 per 1000	38 per 1000 (26 to 54)	OR 0.95 (0.65 to 1.38)	2930 (8 studies)	Low	Studies were open label and there was evidence of imprecision
Derks 2009 Cervical dilatation versus no intervention	35 per 1000	23 per 1000	OR 0.64 (0.21 to 1.93)	288 (1 study)	Moderate	Evidence of imprecision and evidence based on a single trial
Abou-Setta 2014 Less bed rest versus more bed rest	47 per 1000	75 per 1000 (38 to 143)	OR 1.63 (0.79 to 3.35)	542 (2 studies)	Moderate	Open label trial
11. Prevention of ovarian hyperstimulation syndrome (OHSS)						
Tang 2012 Cabergoline versus placebo or no treatment	38 per 1000	12 per 1000 (1 to 117)	RR 0.31 (0.03 to 3.07)	163 (1 study)	Low	Lack of details for allocation concealment and evidence based on a single trial
D'Angelo 2011 Coasting versus no coasting	88 per 1000	59 per 1000 (10 to 285)	OR 0.65 (0.1 to 4.13)	68 (1 study)	Very low	Evidence based on a single conference abstract. Insufficient methodological detail and evidence of imprecision
Frozen embryo transfer cycles						
Ghobara 2008 Oestrogen + progesterone frozen thawed embryo transfer (FET) ver-	314 per 1000	256 per 1000 (135 to 436)	OR 0.75 (0.34 to 1.69)	128 (3 studies)	Very low	Insufficient details on methodological detail in some trials, open label

Table 8. Miscarriage per woman (*Continued*)

sus GnRHa, oestrogen and progesterone preparations FET						trials and heterogeneity >73% (I^2)
Ghobara 2008 Clomiphene + HMG frozen thawed embryo transfer (FET) versus HMG FET	179 per 1000	250 per 1000 (71 to 596)	OR 1.53 (0.35 to 6.79)	44 (1 study)	Very low	Insufficient details on methodological detail in some trials, evidence based on a single trial with evidence of imprecision
Glujovsky 2010 GnRH agonists versus control for endometrial preparation for embryo transfer with frozen embryos or donor oocytes	30 per 1000	28 per 1000 (9 to 84)	OR 0.92 (0.29 to 2.96)	415 (2 studies)	Moderate	Insufficient details on methodological detail in some trials
Glujovsky 2010 Intramuscular progesterone versus vaginal progesterone for endometrial preparation for embryo transfer with frozen embryos or donor oocytes	65 per 1000	40 per 1000	OR 0.6 (0.26 to 1.39)	579 (3 studies)	Moderate	Insufficient details on methodological detail in some trials

APPENDICES

Appendix 1. ART protocols and titles

Protocols

The following 11 protocols (published and in authoring phase for full review) were identified. They will be added to the overview when they are published as full reviews and the overview is updated.

Pre-ART or adjuvant strategies:

- Nyachieo 2009 *Nonsteroidal anti-inflammatory drugs for assisted reproductive technology* LMW1121
- Nagels 2012 *Androgens (dehydroepiandrosterone or testosterone) in women undergoing assisted reproduction* HEN1730
- Granne 2010 *Human chorionic gonadotrophin priming for fertility treatment with in vitro maturation* IG1250
- Zhu 2013 *Acupuncture for female subfertility* XZ1550
- Benschop 2012 *Immune therapies for women with history of failed implantation undergoing IVF treatment* KH1670

Ovarian stimulation:

- ElDaly 2006 *Aromatase inhibitors for ovulation induction* AED1161
- Pandian 2004 *Glucocorticoid supplementation during ovarian stimulation for IVF or ICSI* BKT841

Laboratory phase:

- Youssef 2009 *Culture media for human preimplantation embryos in assisted reproductive technology cycles* MM1610

Frozen cycles:

- Chua 2012 *Slow freeze versus vitrification for embryo cryopreservation* CB994
- Wong 2014 *Fresh versus frozen embryo transfers for assisted reproduction KMW1790*

Luteal phase support:

- Abou-Setta 2006 *Soft versus firm embryo transfer catheters for assisted reproductive technology* GG603

Titles

Five titles were identified

- Oocyte activation for women following ICSI (AAS1332)
- Application of seminal plasma to female genital tract prior to embryo transfer in assisted reproductive technology cycles (IVF, ICSI and frozen embryo transfer) (BA1920)
- Metabolomics for improving pregnancy outcomes in women undergoing assisted reproductive technologies (CS1968)
- Luteal phase support after ovulation induction for women undergoing intrauterine insemination, timed intercourse and natural conception (MAC1967)
- Long-term GnRH agonist therapy before in vitro fertilization (IVF) for improving fertility outcomes in women with endometriosis (SHJ881)

WHAT'S NEW

Last assessed as up-to-date: 1 July 2015.

Date	Event	Description
19 April 2016	Amended	Updated declaration of interest

HISTORY

Protocol first published: Issue 5, 2013

Review first published: Issue 8, 2013

Date	Event	Description
23 September 2015	Amended	Corrected minor typos in text
11 September 2015	Amended	Minor corrections to text and data tables
13 August 2015	Amended	Minor correction to data in additional tables
8 July 2015	New citation required but conclusions have not changed	The additional information has not led to a change in the conclusions of this review
1 July 2015	New search has been performed	One new review added: SCA1950 (Armstrong 2015) Three reviews updated: MV263 (van der Linden 2015), AWP1710 (Pouwer 2015 and WM 1504 (Nastri 2015)
22 December 2014	New citation required but conclusions have not changed	Evidence added from four new and six updated reviews
31 October 2014	New search has been performed	Six reviews updated: AAS605 (Abou-Setta 2014); DB552 (Bontekoe 2014); IOK972 (Kwan 2014); MGS1510 (Showell 2014); MM1690 (Youssef 2014) ; LDT 1201(Tso 2014) Four new reviews added: DG1352 (Glujovsky 2014) ; RBG1760 (Gutarra-Vilchez 2014); SMD1810 (McDowell 2014); SH1141 (McDonnell 2014)
13 November 2013	Amended	Minor correction of data in one included review; no effect on findings of this overview
14 October 2013	Amended	Minor amendment to abstract and results.

CONTRIBUTIONS OF AUTHORS

Professor Farquhar, Drs Brown and Nelen, Josephine Rishworth and Jane Marjoribanks have all contributed to the development of this overview.

DECLARATIONS OF INTEREST

Professor Farquhar, Dr Nelen, Dr Brown and Jane Marjoribanks are authors on some of the included reviews. There are no conflicts of interest that relate to commercial funding.

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

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INDEX TERMS

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*Databases, Bibliographic; *Live Birth; *Review Literature as Topic; Abortion, Spontaneous; Infertility [*therapy]; Libraries, Digital; Ovarian Hyperstimulation Syndrome [prevention & control]; Pregnancy, Multiple; Randomized Controlled Trials as Topic; Reproductive Techniques, Assisted [classification; *standards]

MeSH check words

Female; Humans; Pregnancy