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

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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-eight systematic reviews published in *The Cochrane Library* 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 = 3) or possibly ineffective (n=11), and 12 reviews were unable to draw conclusions due to lack of evidence.

An additional 11 protocols and one title 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 58 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 truly 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 12 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 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-eight systematic reviews published in *The Cochrane Library* were included in this overview. See Table 1 for a summary of the

characteristics of the 58 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 one title 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 58 reviews had prespecified their clinical question and inclusion criteria.
- All 58 reviews conducted study selection and data extraction in duplicate.
- All 58 reviews conducted a comprehensive literature search.
- All 58 reviews included searches of grey literature.
- All 58 reviews listed included and excluded studies.
- All 58 reviews described the characteristics of the included studies.
- All 58 reviews assessed study quality.
- All 58 reviews combined the studies using appropriate methods.
- A total of 48/58 reviews addressed the risk of reporting bias, using a statistical test where appropriate.
- All 58 reviews addressed the potential for conflict of interest.

Thirty of the 58 reviews had conducted a literature search within the past three years (to October 2014) 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 41 reviews).
- Table 5: clinical pregnancy per woman (data from 53 reviews).
- Table 6: ovarian hyperstimulation syndrome per woman (data from 21 reviews).
- Table 7: multiple pregnancy per woman (data from 25 reviews).
- Table 8: miscarriage per woman (data from 35 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 2011: '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 2011 reported that endometrial injury performed in the month prior to ovulation induction for ART appeared to increase both the live birth rate and clinical pregnancy rate compared with no endometrial injury. There was a lack of data reported on miscarriage and multiple pregnancy rates in the included trials and the trials did not report on outcomes such as pain or bleeding.

2.1.3 Medical therapy

Antioxidants

Showell 2014 reported that antioxidant supplementation in subfertile males may improve live birth rates for couples attending fertility clinics and that clinical pregnancy rates may increase, based on limited evidence. There was no evidence of increased risk of miscarriage but this was uncertain as the evidence is of very low quality. Data were lacking on other adverse effects.
Showell 2013 reported that antioxidants for females were not associated with a significantly increased live birth rate or clinical pregnancy rate. There did not appear to be any association of antioxidants with adverse effects for women, but data for these outcomes were limited.

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' (A412).
- 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 by four-fold.

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 2012: '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 2012 reported no evidence of an effect on live birth rate in a comparison of long-acting FSH versus daily FSH, 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 effect on live births in the medium dose subgroup. 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 was equally effective compared to daily FSH. The review authors indicated that further research is needed to determine if 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 2011: 'Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology' (MM1690).

- Youssef 2014: 'Recombinant versus urinary human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles' (HA413).

Youssef 2011 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 2014 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

Seven 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).

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 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.

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 2011: '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 2011 reported that progesterone for luteal phase support significantly improved live birth rates compared to placebo or no treatement, favouring synthetic progesterone over micronized progesterone. Overall, the addition of other substances such as estrogen or hCG did not appear to affect the outcomes. There was no evidence favouring a specific route or duration of administration of progesterone. The authors reported that hCG, or hCG plus progesterone, was associated with a higher risk of OHSS. The use of hCG should therefore be avoided. There were significant results showing a benefit from addition of a GnRH agonist to progesterone for the outcomes of live birth, clinical pregnancy and ongoing pregnancy. Progesterone seemed to be the best option for luteal phase support, with better pregnancy results when synthetic progesterone was used.
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.

- 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 2011b: '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 no evidence to suggest any benefit of withholding gonadotrophins (coasting) after ovulation in IVF for the prevention of OHSS or in live births compared with no coasting or other interventions (early unilateral follicular aspiration, GnRH agonist). The evidence was limited by the small number of included trials.
Youssef 2011b reported a borderline statistically significant decrease in the incidence of severe OHSS with administration of human albumin. 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 (natural 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 (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 rate and clinical pregnancy rate (Nastri 2011)
- Growth hormone for IVF: the use of growth hormone in poor responders was associated with a significant improvement in live birth rates (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. However, the use of this insulin-sensitising agent increased clinical pregnancy rates and decreased the risk of OHSS (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 (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 and clinical pregnancy rates, but more evidence is needed (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.

Possibly ineffective interventions (more evidence needed)

- Acupuncture and ART: there was no evidence that acupuncture improves live birth or pregnancy rates in assisted conception (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 (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 (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. 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 found to be higher when GnRHa was used in a long protocol as compared to a short or ultra-short protocol (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 (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 by fourfold (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 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 (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 (van Wely 2011)
- Long-acting FSH versus daily FSH for women undergoing assisted reproduction: the use of a medium dose of long-acting FSH is a safe treatment option and equally as effective as daily FSH (though further research is needed in specific subgroups) (Pouwer 2012)

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 results in more live births than controlled ovarian hyperstimulation (COH) with rFSH alone. Nevertheless, all pooled pregnancy estimates, although not statistically different, pointed towards a beneficial effect of co-treatment with rLH, in particular with respect to pregnancy loss (Mochtar 2007)
- Clomiphene citrate for controlled ovarian stimulation in women undergoing IVF: the results of 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 (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, expending less FSH (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 (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 (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 either 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 (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 (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 both the women and the clinicians, and resource availability (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 (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 is insufficient evidence to recommend any specific sperm retrieval technique for azoospermic men undergoing ICSI (only one RCT) (Proctor 2008)
- Advanced sperm selection techniques for assisted reproduction: there is insufficient evidence to determine whether sperm selected by hyaluronanic 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. (McDowell 2014)

8. Laboratory phase

Effective interventions

- Low oxygen concentrations for embryo culture in ARTs: there is evidence of an increase in live birth rate associated with embryo culture using low oxygen concentrations (Bontekoe 2012)

Promising interventions (more evidence needed)

- Assisted hatching on assisted conception (IVF and ICSI): whilst assisted hatching (AH) appeared to offer a significantly 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 proven to be increased by AH, and multiple pregnancy rates were significantly increased in the AH groups (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 infertile women undergoing IVF cycles, compared to the standard overnight insemination protocol. More RCTs are required (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 (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 (Teixeira 2013)

Ineffective interventions

- Preimplantation genetic screening for abnormal number of chromosomes (aneuploidies) in IVF or ICSI: preimplantation genetic screening as currently performed significantly decreases 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 (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)

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 (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 (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. 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 (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 (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. 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. 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 showed a significant effect in favour of progesterone for luteal phase support, favouring synthetic progesterone over micronized progesterone (van der Linden 2011)

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

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 the clinical outcome (Boomsma 2012)

11. Prevention of ovarian hyperstimulation syndrome (OHSS)

Effective interventions

- Intravenous fluids for the prevention of severe OHSS: hydroxyethyl starch markedly decreased the incidence of severe OHSS. There was limited evidence of borderline benefit for intravenous albumin administration (Youssef 2011b)
- Cabergoline for preventing OHSS: cabergoline appears to reduce the risk of OHSS in high risk women, especially for moderate OHSS. The use of cabergoline does not affect the pregnancy outcome (clinical pregnancy rate, miscarriage rate), nor is there an increased risk of adverse events (Tang 2012)

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 (D'Angelo 2007)

Ineffective interventions

- Coasting (withholding gonadotrophins) for preventing OHSS: there was no evidence to suggest a benefit of using coasting to prevent OHSS compared with no coasting or other interventions (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 truly 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 54 reviews. Nearly 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.
The National Institute for Health and Care Excellence (NICE) recently published clinical guidelines on the assessment and treatment of people with fertility problems (NICE 2013), which used many of our reviews. As the most recent search for NICE 2013 was conducted in November 2011 our overview can be considered the most up to date evidence on ART cycles.

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. 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.

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.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Trial 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 Intra-	Live birth rate Clinical pregnancy rate Multiple pregnancy rate	Some evidence was based on a single trial. There

Table 1. Trial characteristics (*Continued*)

					uterine insemination + ovarian stimulation Clomiphene citrate	OHSS	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-anastamosis	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 subfertile women with polycystic ovarian syndrome undergoing assisted reproduction	17/02/2011	No RCTs	N/A	In vitro maturation	In vitro fertilisation Intra-cytoplasmic sperm injection	Live birth Cycle cancellation Oocyte fertilisation rate OHSS Miscarriage rate Preterm birth Congenital abnormalities	Empty review with no trials. No longer 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 2011 Endometrial in-	14/11/2011	5 RCTs	591 women undergoing ART	Endometrial injury	No endometrial injury Mock proce-	Live birth rate Clinical pregnancy rate	Some evidence was based

Table 1. Trial characteristics (*Continued*)

jury in women undergoing assisted reproductive technology					dure	Multiple pregnancy rate Miscarriage rate Ongoing pregnancy rate Pain/bleeding Implantation rate	on a single trial Adverse events such as miscarriage rate and multiple pregnancy rate were poorly reported Some methodological details were unclear
MGS1510 Showell 2014 Antioxidants for male subfertility	25/08/2014	48 RCTs	4179 male partners of couples undergoing ART.	Antioxidant	Placebo/no treatment Antioxidant	Live birth Pregnancy Adverse events DNA fragmentation Sperm parameters Miscarriage	Lack of a clear description of trial methods and inconsistent, inadequate reporting of live births and clinical pregnancies
JC1630 Showell 2013 Antioxidants for female subfertility	15/4/13	28 RCTs	3548 women attending an ART clinic	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

Table 1. Trial characteristics (*Continued*)

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 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	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 preg-	None of the trials showed evidence of blinding. Live

Table 1. Trial characteristics (*Continued*)

in women due to undergo in vitro fertilisation						nancy Ectopic pregnancy Miscarriage rate	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 treatment before and during IVF or ICSI in women with polycystic ovary syndrome	15/10/2014	9 RCTs	816 women with polycystic ovary syndrome	Metformin	Placebo No treatment	Live birth Clinical pregnancy Miscarriage OHSS Adverse events Number of oocytes retrieved Total dose FSH (IU) Number of days gonadotrophin treatment Cycle cancellation rate Serum E2 level (nmol/l	Half the trials were not blinded 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	Live birth not reported by any of the studies Poor reporting of study methods Imprecision Inconsistency

Table 1. Trial characteristics (*Continued*)

						cancelled cycles	
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	963 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 gonadotrophin treatment Number of oocytes retrieved Abortion rate Ongoing/ delivered pregnancy rates per cycle started Multiple pregnancy rates OHSS	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
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 pi-	20/05/2010	3 RCTs	165 women with	GnRH agonist	No GnRH agonist	Clinical pregnancy	No blinding Unclear allo-

Table 1. Trial characteristics (*Continued*)

tuitary down- regulation before in vitro fertilization (IVF) for women with endometriosis			endometriosis undergoing ART			Dose of FSH/HMG (ampoule) Duration of FSH administration (days) Number of oocytes	cation concealment in all trials and no reporting of live birth
SD265 Maheshwari 2011 Gonadotrophin-releasing hormone agonist protocols for pituitary suppression in assisted reproductive treatment	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 cancellation	Only 3 trials reported live birth Methodology limited by lack of blinding and inadequate reporting of outcome 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 2012 Long-acting FSH versus daily FSH	10/10/2011	4 RCTs	2335 women with subfertility	Long acting FSH	Daily FSH	Live birth rate Ongoing pregnancy rate Clinical pregnancy rate	Two of the trials lacked adequate blinding and one of the trials pro-

Table 1. Trial characteristics (*Continued*)

for women undergoing assisted reproduction						OHSS Multiple pregnancy rate Miscarriage rate Adverse events Satisfaction	vided insufficient details on allocation concealment and randomisation
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 oestrodial used Number of oocytes retrieved	Live birth was reported in 5 of the trials There was a lack of methodological details provided by the review authors with regards to 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 ver-	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 hyper-	Live birth OHSS Ongoing pregnancy Clinical pregnancy	Only two studies reported live birth: both were at high risk of at-

Table 1. Trial characteristics (*Continued*)

sus continued FSH for assisted reproductive techniques					stimulation	Miscarriage Total dose of FSH used Oocytes retrieved	trition bias Low precision due to small overall sample size
DHH752 Smulders 2010 Oral contraceptive pill, progestogen or estrogen pre- treatment for ovarian stimulation protocols for women undergoing assisted reproductive techniques	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 treatment Pregnancy loss Ovarian cyst formation Multiple pregnancies OHSS	Live birth reported in 6 trials Methodological limitations: poor reporting of randomisation procedures, high 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	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	Long protocol GnRHa flare up protocol Spontaneous natural cycle IVF Mini dose long ago-	Live birth rate per woman Clinical pregnancy rate per woman Ongoing pregnancy rate per woman	Live birth rate only reported in one trial Methodological limitations in terms of limited blinding, lack of de-

Table 1. Trial characteristics (*Continued*)

(COH) in in-vitro fertilisation (IVF)				flare up protocol Multiple dose GnRH antagonist Flare up protocol Long protocol	nist protocol Modified long protocol	Miscarriage rate Ectopic pregnancy Cancellation rate Oocytes retrieved Dose of gonadotrophins Total FSH used	tails on addressing incomplete data outcome
4.4 Natural cycle IVF							
TA1860 Allersma 2013 Natural cycle IVF for subfertile couples	5/3/13	5 RCTs	382 subfertile women and couples undertaking IVF treatment	Natural cycle IVF Modified natural cycle IVF	Controlled ovarian hyperstimulation IVF	Live birth OHSS 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	Few studies, live birth only reported in one very small trial Inclusion criteria differed
5. Ovulation triggering							
MM1690 Youssef 2014 Gonadotropin-	8/9/2014	17 RCTs	1847 women undergoing ART	GnRH agonist	HCG	Live birth rate Ongoing pregnancy rate	Risk of bias in included studies. Limita-

Table 1. Trial characteristics (*Continued*)

releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology						Clinical pregnancy rate Multiple pregnancy rate Miscarriage rate OHSS	tions 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 human chorionic gonadotrophin for final oocyte maturation triggering in IVF and ICSI cycles	20/1/2010	14 RCTs	2306 women undergoing ART	Recombinant hCG Recombinant hLH	Urinary hCG	Live birth OHSS Clinical pregnancy rate Miscarriage rate Oocytes retrieved Tolerance	Authors combined ongoing pregnancy and 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 se-	Electro-acupuncture 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

Table 1. Trial characteristics (*Continued*)

				dation Intramuscular pethidine			
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							
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

Table 1. Trial characteristics (*Continued*)

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 to transfer any embryos Embryo damage In vitro blastocyst development	Few studies described adequate allocation concealment. Most failed to report on live birth rates
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	Only three of the trials reported on live birth outcomes There were unclear methodological details

Table 1. Trial characteristics (*Continued*)

						Implantation rate Embryo development Cryopreservation rate	in six of the trials
SMA991 Twisk 2006 Preimplantation genetic screening for abnormal numbers of chromosomes (aneuploidies) in in vitro fertilisation or intracytoplasmic sperm injection	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 abnormalities	Six of the nine trials were open label and other methodological details were unclear
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 re-	8/5/13	9RCTs	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

Table 1. Trial characteristics (*Continued*)

production							oocytes transferred), imprecision and strong suspicion of publication bias
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	17/07/2012	14 RCTs	2165 couples undergoing ART	Single embryo transfer Double em-	Double embryo transfer Three embryo	Live birth rate Pregnancy rate Multiple preg-	Many of the included studies were small,

Table 1. Trial characteristics (*Continued*)

transfer following in vitro fertilisation or intra cytoplasmic sperm injection				bryo transfer	transfer Four embryo transfer	nancy rate Miscarriage rate	with half enrolling fewer than 60 participants. There was considerable 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	17RCTs	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) with any type of subfertility undergoing IVF at embryo transfer stage	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 Antibi-	23/11/2011	1 RCT	350 women attending infertility clinic	Antibiotics	No treatment	Bacterial contamination rate of	Analysis of bacterial contamination

Table 1. Trial characteristics (*Continued*)

otics prior to embryo transfer in ART						catheter Clinical pregnancy rate	was not performed on all participants
JB604 Brown 2010 Ultrasound versus 'clinical touch' for catheter guidance during embryo transfer in women	9/11/2009	20 RCTs	6524 women with any form of infertility	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 2011 Luteal phase support for ART cycles	25/05/2011	69 RCTs	16,327 women with any cause of subfertility	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 preg-	Some of the trials lacked methodological details. There was poor reporting of live birth

Table 1. Trial characteristics (*Continued*)

						nancy rate	outcomes
CMB126 Boomsma 2012 Peri-implantation glucocorticoid administration for assisted reproductive technology cycles	20/09/2011	14 RCTs	1879 couples with any cause of subfertility	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
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

Table 1. Trial characteristics (*Continued*)

ADA 563 D'Angelo 2011 Coasting (withholding gonadotrophins) for preventing ovarian hyperstimulation syndrome	19/07/2010	4 RCTs	340 women with PCOS down-regulated by GnRH-a, undergoing super-ovulation in IVF or ICSI cycles	Coasting when estradiol levels were > 2500 pg/mL or > 9000 pmol/L Coasting when estradiol levels were > 2500 pg/mL or > 9000 pmol/L	Early unilateral follicular aspiration No coasting or other interventions	OHSS Clinical pregnancy Number of oocytes retrieved Multiple pregnancy Miscarriage Live birth	Comparisons based on limited trial data 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 2011b Intra-venous fluids for the prevention of severe ovarian hyperstimulation syndrome	02/11/2010	9 RCTs	2147 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 trans-	11/10/2007	7 RCTs	1120 women Studies included women with a range of causes of subfertility The review	Oestrogen and progesterone GnRHa + day oestrogen + day progesterone	Natural cycle GnRHa + day oestrogen and progesterone FSH Clomiphene Clomiphene	Live birth per woman Clinical pregnancy per woman Ongoing	Of the included studies, randomisation was unclear in six tri-

Table 1. Trial characteristics (*Continued*)

fer (FET)			does not provide details of the mean ages of the women	Clomiphene + HMG	HMG	pregnancy per woman Multiple pregnancy rate Cycle cancellation rate Miscarriage rate Endometrial thickness	als. Allocation concealment was adequately reported 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 a lack of 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	REVIEW TITLE	AMSTAR CRITERIA									
			Pre-specified question and inclusion criteria	Duplicate study selection and data extraction	Comprehensive lit search	Grey lit included	Lists included and excluded studies	Describes characteristics of included studies	Study quality assessed	Studies combined using appropriate methods	Likelihood of publication bias considered/ tested	Potential for conflict of interest addressed
AAS605	Abou-Setta 2014	Post-embryo transfer interventions for assisted reproduction technology cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ADA561	D'Angelo 2007	Embryo freezing for preventing ovarian hyperstimulation syndrome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ADA563	D'Angelo 2011	Coasting (withholding gonadotropl for preventing ovarian hyper-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

		stimulation syndrome										
AM1335	Gibreel 2012	Clomiphe citrate for controlled ovarian stimulation in women undergoing in vitro fertilization	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AMVP61	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	✓	✓	✓	✓	✓	n/a	n/a	n/a	n/a	✓

Table 2. AMSTAR assessment (*Continued*)

		reversal) for subfertility after tubal sterilisation										
AWP171(	Pouwer 2012	Long-acting FSH versus daily FSH for women undergoing assisted reproduction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CMB126	Boomsma 2012	Periimplantation glucocorticoid administration for assisted reproductive technology cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CO266	Gunby 2004	Day three versus day two embryo transfer following in vitro fertil-	✓	✓	✓	✓	✓	✓	✓	✓	x	✓

Table 2. AMSTAR assessment (*Continued*)

		ization or intracytoplasmic sperm injection										
CS1400	Siristatidis 2009	In vitro maturation in sub fertile women with polycystic ovarian syndrome undergoing assisted reproduction	✓	✓	✓	✓	✓	n/a	n/a	n/a	n/a	✓
DB551	Glujovsky 2012	Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DB552	Bontekoe 2014	Adherence compounds in embryo transfer	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

		media for 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	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DHH752	Smulders 2010	Oral contraceptive pill,	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

		progestogen 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	Gonadotropl releasing hormone antagonists for assisted reproductive technology	✓	✓	✓	✓	✓	✓	✓	✓	x	✓
HA413	Youssef 2011	Recombinant versus urinary human chori-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

		onic go-nadotrop for final oocyte matura-tion trigger-ing in IVF/ ICSI cycles										
HNS881	Sallam 2006	Long-term pitu-itary down-regu-lation before in vitro fertil-ization (IVF) for women with en-dometrio-sis	✓	✓	✓	✓	✓	✓	✓	✓	x	✓
IOK971	Kwan 2013	Pain re-lief for women under-going oocyte re-trieval for as-sisted repro-duction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
IOK972	Kwan 2014	Moni-toring of stim-ulated cy-	✓	✓	✓	✓	✓	✓	✓	✓	x	✓

Table 2. AMSTAR assessment (*Continued*)

		cles in assisted reproduction (IVF and ICSI)										
IOK973	van Wely 2011	Recombinant versus urinary gonadotropl 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 embryo transfer in	✓	✓	✓	✓	✓	✓	✓	✓	x	✓

Table 2. AMSTAR assessment (*Continued*)

		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 gonadotropl releasing hormone agonist protocols for pituitary desensitization in assisted reproduction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

		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	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MGS151	Showell 2014	Antioxidants for male subfertility	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MHM93	Mochtar 2007	Recombinant luteinizing hormone (rLH) for controlled ovarian hyperstimulation in assisted reproductive cycles	✓	✓	✓	✓	✓	✓	✓	✓	x	✓

Table 2. AMSTAR assessment (*Continued*)

MM1690	Youssef 2014	Gonadotropi releasing hormone agonist versus HCG for oocyte triggering in antagonist assisted reproductive technology cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MV263	van der Linden 2011	Luteal phase support in ART cycles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
MVR461	Van Rumste 2003	Intracytoplasmic sperm injection versus conventional techniques for oocyte insemination during in vitro fertilisation in patients	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

		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 2011b	Intravenous fluids for the prevention of severe ovarian hyperstimulation syndrome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
RBG176	Gutarra-Vilchez 2014	Vasodilators for women under-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

		going fertility treatment										
RSS791	Pandian 2010	Interventions for 'poor responders' to controlled ovarian hyper stimulation (COH) in in-vitro fertilisation (IVF)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SB1283	Bontekoe 2012	Low oxygen concentrations for embryo culture in assisted reproductive technologies	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
SD265	Maheshwari 2011	Gonadotropi releasing hormone agonist protocols for pitu-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

		itary suppression in assisted reproductive technology cycles										
SG1241	Benschop 2010	Interventions for women with endometrioma 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	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

		of chromosomes (aneuploidies) in in vitro fertilisation or intracytoplasmic sperm injection										
SMD181	McDowell 2014	Advanced sperm 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	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

		tech-niques										
TA1860	Allersma 2013	Natu-ral cycle IVF for subfer-tile cou-ples	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TG691	Gho-bara 2008	Cy-cle regi-mens for frozen-thawed embryo transfer	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TH1338	Tang 2012	Caber-goline for pre-venting ovarian hyper-stimu-lation syn-drome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
VJP951	Sirista-tidis 2011	Aspirin for in vitro fertili-sation	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
WM150	Nastri 2011	En-dome-trial in-jury in women under-going assisted repro-ductive tech-niques	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

WPM17	Martins 2013	FSH replaced by low-dose hCG in the late follicular phase versus FSH alone for assisted reproductive techniques	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
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	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table 2. AMSTAR assessment (*Continued*)

ZP661	Pandian 2013	Number of embryos for transfer following in-vitro fertilisation or intracytoplasmic sperm injection	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
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 Oct 2014) 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

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

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	✓
AWP1710	Pouwer 2012	Long-acting FSH versus daily FSH for women undergoing assisted reproduction	✓
CMB1261	Boomsma 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 intracytoplasmic sperm injection	x
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	✓
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

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

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)	✓
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	✓

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

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 2011	Luteal phase support in ART cycles	x
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 2011b	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	✓
SD265	Maheshwari 2011	Gonadotropin-releasing hormone agonist protocols for pituitary suppression in assisted reproductive technology cycles	x
SG1241	Benschop 2010	Interventions for women with endometrioma prior to assisted reproductive technology	x

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

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
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 2011	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
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 2011 Endometrial injury prior to ovulation induction (pipelle induced) versus no endometrial injury	168 per 1000	332 per 1000 (206 to 489)	OR 2.46 (1.28 to 4.72)	200 (2 studies)	Moderate	Evidence of imprecision and some methodological details were unclear
Showell 2014 Antioxidant versus control	50 per 1000	181 per 1000 (99 to 309)	OR 4.21 (2.08 to 8.51)	277 (4 studies)	Low	Inadequate explanations of methodology, large unexplained drop-

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

						outs in one study No head to head comparisons: comparison in all these studies was placebo or no treatment
Showell 2013 Antioxidant versus placebo or no treatment/standard treatment	367 per 1000	420 per 1000 (99 to 827)	OR 1.25 (0.19 to 8.26)	97 (2 studies)	Very low	Serious imprecision, some methodological details were unclear, types of subfertility and antioxidants used differed across trials
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 2013 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

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

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 treatment	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 = 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	4 per 100	23 per 100 (181 to 292)	OR 0.95 (0.7 to 1.31)	873 (7 studies)	low	No differences in the results were detected on sensitivity analysis for adequate allocation concealment: OR 0.95 (0.64 to 1.41). 514 participants in 4 studies Most of the studies were classified as at unclear risk

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

						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 in ART	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 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	228 per 1000	215 per 1000 (169 to 268)	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

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

IVF and ICSI cycles						
Pouwer 2012 Long acting FSH (low dose) versus daily FSH	288 per 1000	198 per 1000 (142 to 269)	OR 0.61 (0.41 to 0.91)	645 (3 studies)	Low	Open label trials included with evidence of imprecision due to low events
Pouwer 2012 Long acting FSH (medium dose) versus daily FSH	336 per 1000	343 per 1000 (298 to 391)	OR 1.03 (0.84 to 1.27)	1657 (3 studies)	Low	Open label trials included with evidence of imprecision due to low events
Pouwer 2012 Long acting FSH (high dose) versus daily FSH	375 per 1000	161 per 1000 (29 to 533)	OR 0.32 (0.05 to 1.9)	33 (1 study)	Very low	Open label trials included with evidence of imprecision due to low events and evidence based on a single trial
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	245 per 1000	239 per 1000 (220 to 260)	OR 0.97 (0.87 to 1.08)	7339 (28 studies)	High	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 tech-	14 per 100	22 per 100	RR 1.56 (0.75 to 3.25)	130 (2 studies)	V ery low	Very serious imprecision, high risk of bias

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

niques						
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 natural cycle IVF	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 imprecision
4.4 Natural cycle IVF						
Allersma 2013	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 = 59% to 66%.
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

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

						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						
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 (0.84 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	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

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

concentrations versus atmospheric oxygen concentration						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
Teixeira 2013 Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection	38 per 100	44 per 100 (30 to 63)	RR 1.14 (0.79 to 1.64)	168 (1 study)	Low	Serious imprecision
9. Embryo transfer						
9.1 Developmental stage						
Glujovsky 2012 Cleavage stage versus blastocyst 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						

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

Pandian 2013 Double embryo transfer versus single embryo transfer (one cycle only)	292 per 1000	460 per 1000 (409 to 514)	OR 2.07 (1.68 to 2.57)	1564 (9 studies)	High	36% of women noncompliant with treatment allocation in one study: however no heterogeneity detected (I^2 = 0%).
Pandian 2013 Double embryo transfer versus repeated single embryo transfer	374 per 1000	421 per 1000 (354 to 492)	OR 1.22 (0.92 to 1.62)	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	367 per 1000	450 per 1000 (404 to 495)	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

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

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
10. Luteal phase support						
van der Linden 2011 hCG versus placebo/no treatment	120 per 1000	235 per 1000 (48 to 653)	OR 2.25 (0.37 to 13.8)	38 (1 study)	Low	Evidence is based on a single trial. Insufficient methodological details provided. Evidence of imprecision
van der Linden 2011 Progesterone versus placebo/no treatment	38 per 1000	104 per 1000 (39 to 253)	OR 2.95 (1.02 to 8.56)	156 (1 study)	Low	Evidence is based on a single trial. Insufficient methodological details provided. Evidence of imprecision
Boomsma 2012 Peri-implantation glucocorticoids versus no glucocorticoids	115 per 1000	136 per 1000 (80 to 224)	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 (1 to 128)	OR1.03 (0.5 to 2.12)	125 (1 study)	Low	Evidence based on a single open label study

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

						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
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	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 4. Live birth per woman (*Continued*)

oocytes						

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%
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 2011 Endometrial injury prior to ovulation induction (pipelle induced) versus no en-	211 per 1000	411 per 1000 (314 to 515)	OR 2.61 91.71 to 3.97)	435 (4 studies)	Moderate	Some evidence of imprecision and some methodological details were unclear

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

dometrial injury						
Showell 2014 Antioxidant versus control	59 per 1000	177 per 1000 (108 to 277)	3.43 (1.92 to 6.11)	522 (7 studies)	Low	Inadequate explanations of methodology, large unexplained drop-outs in one study No head to head comparisons: comparison in all these studies was placebo or no treatment lack of head to head comparisons
Showell 2013 Antioxidant versus placebo or no treatment/standard treatment	231 per 1000	281 per 1000 (217 to 357)	OR 1.30 (0.92 to 1.85)	2441 (13 studies)	Very low	Serious imprecision, some methodological details were unclear, types of subfertility and antioxidants used differed across trials
Duffy 2010 Growth hormone compared with placebo	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 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 1.18 (1.00 to 1.92)	717 (8 studies)	Low	Studies had low or unclear risk of bias but very serious risk of imprecision

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

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
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 ver-	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

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

sus no surgical treatment						
Benschop 2010 Aspiration of endometrioma versus expectant management prior to ART	200 per 1000	244 per 1000 (101 to 476)	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)	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 agonist versus GnRH antagonist prior to ART	242 per 1000	206 per 1000 (77 to 448)	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)	OR 0.72 (0.25 to 2.08)	65 (1 study)	Very low	Unclear risk of bias related to sequence generation. Single small 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

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

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	No differences in the results were detected on sensitivity analysis for adequate allocation concealment: OR 0.96 (0.68 to 1.37). 574 participants in 5 studies 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 Ultralong GnRH agonist versus conventional stimulation protocols	395 per 1000	516 per 1000 (340 to 687)	OR 1.63 (0.79 to 3.36)	149 (3 studies)	Very low	All of the trials were subject to methodological limitations, the outcome is an intermediate outcome and there was evidence of lack of precision

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

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	231 per 1000	243 per 1000 (203 to 285)	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 luteinizing hormone + recombinant follicle stimulating hormone (rFSH) versus rFSH alone for controlled ovarian hyperstimulation	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 sufficient methodological details
van Wely 2011 rFSH versus uri-	282 per 1000	280 per 1000 (263 to 299)	OR 0.99 (0.91 to	9482 (41 studies)	Moderate	No evidence of blind-

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

nary gonadotrophins			1.09)			ing 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	35 per 100	41 per 100 (32 to 54)	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 concealment, one at high risk of attrition bias
4.2. Monitoring						
Kwan 2014 Ultrasound + estradiol versus ultrasound only	358per 1000	380 per 1000 (306 to 462)	OR 1.1 (0.79 to 1.54)	647 (4 studies)	Low	Methods of allocation concealment inadequately described in the four trials; none

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

						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 GnRH a flare up protocol	163 per 1000	163 per 1000 (62 to 363)	OR 1 (0.34 to 2.92)	98 92 studies)	Low	Lack of methodological details 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

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

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	112 per 1000	86 per 1000 (36 to 194)	OR 0.75 (0.3 to 1.91)	219 (3 studies)	Low	1/3 studie did not report adequate allocaiton concealment, risk of performace 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 = 59% to 66%. 5/11 studies at high risk of bias because of early termination and/or inadequate allocation concealment. None

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

						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 general anaesthesia	375 per 1000	296 per 1000	OR 0.7 (0.22 to 1.26	51 (1 study)	Very low	One small study
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

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

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
McDowell 2014 Conventional sperm selection versus hyaluron 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

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

						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 (0.86 to 9.11)	106 (2 studies)	Moderate	Live birth not reported, wide CIs
Van Rumste 2003 Intracytoplasmic sperm injection versus in vitro fertilisation	252 per 1000	329 per 1000 (243 to 429)	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
Bontekoe 2012 Embryo culture with low oxygen concentrations versus atmospheric	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

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

oxygen concentration						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 0.56 (0.41 to 0.75)	1000 (4 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	33 per 100	43 per 100 (36 to 52)	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
9. Embryo transfer						
9.1 Developmental stage						
Glujovsky 2012 Cleavage stage transfer versus blastocyst stage transfer	388 per 1000	420 per 156)	OR 1.14 (0.99 to 1.32)	3241 (23 studies)	Moderate	Some methodological details were unclear or inadequate. Significant heterogeneity but I2 < 50%
9.2 Number of embryos						

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

Pandian 2013 Double embryo transfer versus single embryo transfer (one cycle only)	357 per 1000	553 per 1000 (500 to 605)	OR 2.23 (1.80 to 2.76)	1505 (7 studies)	Moderate	Most studies do fully describe method of allocation concealment
Pandian 2013 Double embryo transfer versus repeated single embryo transfer	524 per 1000	483 per 1000 (413 to 554)	OR 0.85 (0.64 to 1.13)	752 (2 studies)	Low	Method of allocation concealment not fully described in either trial, some inconsistency (I squared =47%)
Pandian 2013 Double embryo transfer versus three embryo transfers	273 per 1000	305 per 1000 (107 to 614)	OR 1.17 (0.32 to 4.25)	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	607 per 1000	537 per 1000 (287 to 769)	OR 0.75 (0.26 to 2.16)	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						
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 enriched with high level of hyaluronic acid versus medium with low level	412 per 1000	493 per 1000 (459 to 528)	OR 1.39 (1.21 to 1.6)	3542 (14 studies)	Moderate	All studies except one were at high risk of bias in at least one domain, moderate heterogeneity I^2=46%

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

or no hyaluronic acid						
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)	High	Not all of the patients were followed up for one of the outcomes (bacterial contamination)
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 versus no intervention	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, evidence of imprecision and evidence based on a single trial

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

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)	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 Less bed rest versus more bed rest	277 per 1000	303 per 1000 (228 to 391)	OR 1.13 (0.77 to 1.67)	542 (2 studies)	Moderate	One of the trials was open label
10. Luteal phase support						
van der Linden 2011 hCG versus placebo/no treatment	169 per 1000	209 per 1000 (155 to 277)	OR 1.3 (0.9 to 1.88)	746 (5 study)	Low	Insufficient methodological details provided. Evidence of imprecision
van der Linden 2011 Progesterone versus placebo/no treatment	140 per 1000	230 per 1000 (174 to 298)	OR 1.83 (1.29 to 2.61)	841 (7 study)	Low	Insufficient methodological details provided. Evidence of imprecision
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
11. Prevention of ovarian hyperstimulation syndrome (OHSS)						
D'Angelo 2007 Cryopreservation versus fresh embryo transfer	463 per 1000	482 per 1000 (318 to 654)	OR1.08 (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

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

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 2011b Intravenous fluids for the prevention of OHSS versus placebo	69 per 1000	58 per 1000 (40 to 85)	OR 0.84 (0.56 to 1.26)	1522 (7 studies)	Low	Insufficient methodological details provided and evidence of imprecision
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	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 la-

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

thawed embryo transfer (FET) versus GnRHa, oestrogen and progesterone preparations FET						bel trials, some of the trials failed to provide adequate methodological details
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	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

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

preparation for embryo transfer with frozen embryos or donor oocytes						methodological details in many of the studies
Glujovsky 2010 Intramuscular progesterone versus vaginal progesterone for endometrial preparation for embryo transfer with frozen embryos or donor oocytes	261 per 1000	337 per 1000 (257 to 426)	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

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						

Table 6. OHSS per woman (*Continued*)

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 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	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	35 per 1000	8 per 1000 (4 to 19)	OR 0.23 (0.1 to 0.52)	1559 (5 studies)	low	Few participants. Small number

Table 6. OHSS per woman (*Continued*)

(with or without mid-cycle GnRH antagonist) versus gonadotropins with GnRH agonists protocols in IVF and ICSI cycles						of events in outcome. Very wide 95% confidence interval crossing the threshold points of appreciable benefit or harm, which is 25%
Pouwer 2012 Long acting FSH (low dose) versus daily FSH	42 per 1000	51 per 1000 (23 to 110)	OR 1.23 (0.54 to 2.82)	645 (3 studies)	Low	Open label trials included with evidence of imprecision due to low events
Pouwer 2012 Long acting FSH (medium dose) versus daily FSH	62 per 1000	66 per 1000 (45 to 95)	OR 1.07 (0.72 to 1.58)	1657 (3 studies)	Low	Open label trials included with evidence of imprecision due to low events
Pouwer 2012 Long acting FSH (high dose) versus daily FSH	0 per 1000	0 per 1000 (0 to 0)	OR 1.81 (0.08 to 41.62)	33 (1 study)	Very low	Open label trials included with evidence of imprecision due to low events and evidence based on a single trial
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	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*)

continued FSH for assisted reproductive techniques						
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	37 per 1000	38 per 1000 (18 to 78)	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

Table 6. OHSS per woman (*Continued*)

4.4 Natural cycle IVF						
Allersma 2013	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 reported, 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 (9 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 2011 hCG versus placebo/no treatment	41 per 1000	134 per 1000 (73 to 232)	OR 3.62 (1.85 to 7.06)	387 (1 study)	Low	Evidence is based on a single trial. Insufficient methodological details provided. Evidence of imprecision

Table 6. OHSS per woman (*Continued*)

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	60per 1000	8 per 1000 (318 1 to 128)	OR1.12 (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 2011b Intravenous human albumin for prevention of OHSS versus placebo	83 per 1000	57 per 1000	OR 0.67 (0.45 to 0.99)	1660 (8 studies)	Low	Insufficient methodological details provided. Heterogeneity was >60% (I2)
Youssef 2011b Intravenous hydroxyethyl starch for prevention of OHSS versus placebo	46 per 1000	6 per 1000 (2 to 19)	OR 0.12 (0.04 to 0.4)	487 (3 studies)	Moderate	Insufficient methodological details provided in some of the trials
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.

Table 6. OHSS per woman (*Continued*)

						There are insufficient methodolog- ical 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 insemination + ovarian stimulation for unexplained subfertility (treatment naïve women)	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- 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
Showell 2013 Antioxidant versus placebo or no treatment/standard treatment	67 per 1000	48 per 1000 (29 to 80)	OR 0.7 (0.41 to 1.21)	1022 (2 studies)	Very low	Im- precision, some methodological details were unclear
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	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

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

or around the day of embryo transfer						concealment, wide confidence intervals crossed line of no effect
Nastri 2011 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. 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 go-	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

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

nadotrophin) versus urinary or recombinant gonadotrophin in either long or short protocols						
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	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 generatin and allocation concealment not stated, high risk of attrition bias, very serious imprecisikon
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	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

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

versus no screening in women with advanced age						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
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 (1.71 to 1.19)	2481 (16 studies)	Moderate	Some methodological details were unclear or inadequate
9.2 Number of embryos						
Pandian 2013 Double embryo transfer versus single embryo transfer (one cycle only)	293 per 1000	24 per 1000 (8 to 62)	OR 0.06 (0.02 to 0.16)	468 (8 studies)	Moderate	Some methodological details such as randomisation and blinding were unclear
Pandian 2013 Double embryo transfer ver-	17 per 1000	130 per 1000 (81 to 203)	OR 8.47 (4.97 to 14.43)	1612 (10 studies)	High	Heterogeneity (I^2 = 45%) : attributable to

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

sus repeated single embryo transfer						36% of women noncompliant with treatment allocation in one study
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						
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	175 per 1000	282 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%

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

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
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 em-	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 7. Multiple pregnancy per woman (*Continued*)

bryos or donor oocytes						

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
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
Showell 2014 Antioxidant versus control	19 per 1000	33 per 1000 (8 to 29)	OR 1.74 (0. 40 to 7.60)	247 (3 studies)	Very low	Inadequate explanations of methodol- ogy, large unexplained dropouts in one study, low event rate No head to head comparisons:

Table 8. Miscarriage per woman (*Continued*)

						comparison in all these studies was placebo or no treatment
Showell 2013 Antioxidant versus placebo or no treatment/standard treatment	63 per 1000	56 per 1000 (37 to 84)	OR 0.88 (0.57 to 1.36)	1456 (8 studies)	Low	Imprecision, some methodological details were unclear, types of subfertility and antioxidants used differed across trials
Nastri 2011 Endometrial injury prior to ovulation induction (pipelle induced) versus no endometrial injury	286 per 1000	12 per 1000 (-179 to 147)	OR 0.03 (-0.38 to 0.43)	23 (1 study)	Very low	Evidence of imprecision and evidence based on a single trial
Benschop 2010 Aspiration of endometrioma versus expectant management	100 per 1000	97 per 1000 (25 to 316)	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 agonist versus GnRH antagonist	30 per 1000	29 per 1000 (2 to 331)	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 im-

Table 8. Miscarriage per woman (*Continued*)

						precision: wide confidence intervals which cross line of no effect
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 (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	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

Table 8. Miscarriage per woman (*Continued*)

4. Ovarian stimulation						
4.1 Type of medication						
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

Table 8. Miscarriage per woman (*Continued*)

Martins 2013 FSH replaced by low-dose hCG in the late follicular phase versus continued FSH for assisted reproductive techniques	16 per 100	17 per 1000	RR 1.08 (0.50 to 2.31)	127 (4 studies)	Very low	Very serious imprecision, high risk of bias
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	111per 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

Table 8. Miscarriage per woman (*Continued*)

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 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

Table 8. Miscarriage per woman (*Continued*)

Twisk 2006 Preimplantation genetic screening versus no screening in women with good prognosis	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%
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
9. Embryo transfer						
Glujovsky 2012 Cleavage stage transfer versus blastocyst stage transfer	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 or inadequate
Pandian 2013 Double embryo transfer versus single embryo transfer (one cycle only)	67 per 1000	78 per 1000 (51 to 118)	OR 1.18 (0.75 to 1.86)	1097 (3 studies)	Low	Some methodological details such as randomisation and blinding were unclear. INconsistency (I squared =61%)
Pandian 2013 Double embryo transfer versus repeated single embryo transfer	94 per 1000	148 per 1000 (50 to 363)	OR 1.67 (0.51 to 5.48)	107 (1 study)	Very low	Method of allocation concealment not fully described, very serious imprecision
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 impre-

Table 8. Miscarriage per woman (*Continued*)

						cision
Derks 2009 Straightening the utero-cervical angle versus no intervention	156 per 1000	0 per 1000 (0 to 0)	OR 0 (0 to 0)	131 (1 study)	Low	Evidence based on a single trial, evidence of imprecision and study lacked blinding
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) versus GnRHa, oestrogen and progesterone preparations FET	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 trials and heterogeneity >73% (I2)

Table 8. Miscarriage per woman (*Continued*)

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 (dehydroepiandosterone 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

One title was identified

- Oocyte activation for women following ICSI AAS1332

WHAT'S NEW

Last assessed as up-to-date: 19 December 2014.

Date	Event	Description
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)

(*Continued*)

		; RBG1760 (Gutarra-Vilchez 2014); SMD1810 (McDowell 2014); SH1141 (McDonnell 2014)

HISTORY

Protocol first published: Issue 5, 2013

Review first published: Issue 8, 2013

Date	Event	Description
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.

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- None, Other.

INDEX TERMS

Medical Subject Headings (MeSH)

*Databases, Bibliographic; *Review Literature as Topic; Infertility [*therapy]; Libraries, Digital; Reproductive Techniques, Assisted [*standards]

MeSH check words

Humans